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(54) Titre : METHODE D'IDENTIFICATION DU RISQUE DE MELANOME ET TRAITEMENTS ASSOCIES
(54) Title: METHOD FOR IDENTIFYING RISK OF MELANOMA AND TREATMENTS THEREOF

4A

>gi|32528262|ref|NM_003674.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 1, mRNA

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TCTGAAGTGTATTCGTAAGGAGGGCTTCTTCACGGTGCCTCCGGAACACAGGGTGAGCCACCGCCCCCAGCCTGGC
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4B

>gi|32528264|ref|NM_052987.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 2, mRNA

GTCTGCGCCTGCGCGCAAGAGAGGCGGGGCCAGCGCTCGGCATGGCGGAGCCAGATCTGGAGTGCGAGCAGATCCG
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AAAAGCTTTTTTAACAGAAAAAAAAAAAAAAAAAAAA

(57) Abrégé/Abstract:
Provided herein are methods for identifying risk of melanoma in a subject and/or subjects at risk of melanoma, reagents and kits for carrying out the methods, methods for identifying candidate therapeutics for treating melanoma, therapeutic methods for treating melanoma in a subject and compositions comprising one or more melanoma cells and one or more CDK10, FPGT, PCLO or REPS2 directed agents. These embodiments are based upon an analysis of polymorphic variations in a CDK10, FPGT, PCLO or REPS2 nucleic acid, exemplified by nucleotide sequences of SEQ ID NO: 1, 2, 3 or 4.

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60/489,703 23 July 2003 (23.07.2003) US

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(54) Title: METHOD FOR IDENTIFYING RISK OF MELANOMA AND TREATMENTS THEREOF

(57) Abstract: Provided herein are methods for identifying risk of melanoma in a subject and/or subjects at risk of melanoma, reagents and kits for carrying out the methods, methods for identifying candidate therapeutics for treating melanoma, therapeutic methods for treating melanoma in a subject and compositions comprising one or more melanoma cells and one or more *CDK10, FPGT, PCLO* or *REPS2* directed agents. These embodiments are based upon an analysis of polymorphic variations in a *CDK10*, *FPGT*, *PCLO* or *REPS2* nucleic acid, exemplified by nucleotide sequences of SEQ ID NO: 1, 2, 3 or 4.

4A

>gi|32528262|ref|NM_003674.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 1, mRNA

GTCTGCGCCTGCGCGCAAGAGAGGCGGGGCCAGCGCTCGGCATGGCGGAGCCAGATCTGGAGTGCGAGCAGATCCG
TCTGAAGTGTATTCGTAAGGAGGGCTTCTTCACGGTGCCTCCGGAACACAGGGTGAGCCACCGCCCCCAGCCTGGC
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4B

>gi|32528264|ref|NM_052987.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 2, mRNA

GTCTGCGCCTGCGCGCAAGAGAGGCGGGGCCAGCGCTCGGCATGGCGGAGCCAGATCTGGAGTGCGAGCAGATCCG
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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS FOR IDENTIFYING RISK OF MELANOMA AND TREATMENTS THEREOF

Field of the Invention

[0001] The invention relates to genetic methods for identifying risk of melanoma and treatments that specifically target the disease.

Background

[0002] In some parts of the world, especially among western countries, the number of people who develop melanoma is increasing faster than any other cancer. In the United States, for example, the number of new cases of melanoma has more than doubled in the past twenty years. The probability of developing melanoma increases with age, but this disease effects people of all age groups. Melanoma is one of the most common cancers in young adults.

[0003] Melanoma occurs when melanocytes (pigment cells) become malignant. Most pigment cells are in skin, and when melanoma begins its etiology in the skin it is referred to as coetaneous melanoma. Melanoma may also occur in the eye and is called ocular melanoma or intraocular melanoma. Rarely, melanoma arises in the meninges, the digestive tract, lymph nodes or other areas where melanocytes are found. Within the skin, melanocytes are located throughout the lower part of the epidermis, the latter being the surface layer of the skin. Melanocytes produce melanin, which is the pigment that gives skin its natural color. When skin is exposed to the sun, melanocytes produce more pigment, causing the skin to tan or darken.

[0004] Sometimes, clusters of melanocytes and surrounding tissue form benign growths referred to as moles or nevi (singular form is nevus). Cells in or near the nevi can divide without control or order and form malignant tumors. When melanoma spreads, cancer cells often are found in the lymph nodes. If the cancer has reached the lymph nodes, it may mean that cancer cells have spread to other parts of the body such as the liver, lungs or brain, giving rise to metastatic melanoma.

[0005] Melanoma is currently diagnosed by assessing risk factors and by performing biopsies. Risk factors for melanoma are a family history of melanoma, the presence of dysplastic nevi, patient history of melanoma, weakened immune system, many ordinary nevi, exposure levels to ultraviolet radiation, exposure to severe sunburns especially as a child or teenager, and fair skin. In a biopsy, a pathologist typically examines the biopsied tissue under a microscope to identify cancer cells. Depending upon the thickness of a tumor, if one exists, a physician may order chest x-ray, blood tests, liver scans, bone scans, and brain scans to determine whether the cancer spread to other tissues. Also, a test that identifies p16 nucleotide sequences is sold.

[0006] Upon a diagnosis of melanoma, the standard treatment is surgery. Side effects of surgery typically are pain and scarring. Surgery is generally not effective, however, in controlling melanoma that is known to have spread to other parts of the body. In such cases, physicians may utilize other methods of treatment, such as chemotherapy, biological therapy, radiation therapy, or a combination of these methods. Chemotherapy agents for treating melanoma include cisplatin, vinblastine, and dacarbazine. Chemotherapy can lead to side effects such as an increased probability of infection, bruising and bleeding, weakness and fatigue, hair loss, poor appetite, nausea and vomiting, and mouth and lip sores. Side effects of radiation therapy include fatigue and hair loss in the treated area. Biological therapies currently utilized for treatment of melanoma include interferon and interleuken-2. Side effects caused by biological therapies include flu-like symptoms, such as chills, fever, muscle aches, weakness, loss of appetite, nausea, vomiting, and diarrhea; bleeding and bruising skin; rashes, and swelling.

[0007] Certain melanoma therapeutics are in clinical trials. For example, canvaxin, which is a whole cell allogenic vaccine developed by irradiating tumor cells from two different patients, is under study. In addition, MAGE-1 and 3 minigenes and peptides and gp100 peptides are being tested. Upcoming studies include testing of agents such as dacarbazine with a bcl-2 antisense oligonucleotide, and paclitaxel in combination with a matrix metalloprotease inhibitor.

Summary

[0008] It has been discovered that polymorphic variations of *CDK10, FPGT, PCLO* and *REPS2* loci in human genomic DNA are associated with occurrence of melanoma. Thus, featured herein are methods for identifying a subject at risk of melanoma and/or determining risk of melanoma in a subject, which comprise detecting the presence or absence of one or more polymorphic variations associated with melanoma in a nucleic acid sample from the subject. The one or more polymorphic variations of ten are detected in or near the *CDK10, FPGT, PCLO* and/or *REPS2* nucleotide sequence, which are set forth as SEQ ID NOs: 1, 2, 3 and 4 respectively, or a substantially identical nucleotide sequence thereof.

[0009] Also featured are nucleic acids that encode a *CDK10, FPGT, PCLO* or *REPS2* polypeptide, and include one or more polymorphic variations associated with melanoma, and oligonucleotides which hybridize to those nucleic acids. Also provided are polypeptides encoded by nucleic acids having a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence, which include the full-length polypeptide, isoforms and fragments thereof. In addition, featured are methods for identifying candidate therapeutic molecules for treating melanoma and related disorders, as well as methods of treating melanoma in a subject by administering a therapeutic molecule.

[0010] Also provided are compositions comprising a melanoma cell and/or a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid, or a fragment or substantially identical nucleic acid thereof, with a RNAi, siRNA, antisense DNA or RNA, or ribozyme nucleic acid designed from a *CDK10, FPGT, PCLO* or

REPS2 nucleotide sequence. In an embodiment, the nucleic acid is designed from a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence that includes one or more melanoma associated polymorphic variations, and in some instances, specifically interacts with such a nucleotide sequence. Further, provided are arrays of nucleic acids bound to a solid surface, in which one or more nucleic acid molecules of the array are *CDK10, FPGT, PCLO* or *REPS2* nucleic acids, or a fragment or substantially identical nucleic acid thereof, or a complementary nucleic acid of the foregoing. Featured also are compositions comprising a melanoma cell and/or a protein, polypeptide or peptide encoded by a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid with an antibody that specifically binds to the protien, polypeptide or peptide. In an embodiment, the antibody specifically binds to an epitope in a *CDK10, FPGT, PCLO* or *REPS2* protein, polypeptide or peptide that includes a non-synonymous amino acid modification associated with melanoma.

Brief Description Of The Drawings

[0011] Figures 1A to 1Z show a genomic sequence of cyclin-dependent kinase 10 (CDK10) with the polymorphic variants in IUPAC format. The genomic sequence set forth in Figures 1A to 1Z correspond to SEQ ID NO: 1. Figures 2A to 2X show a genomic sequence of presynaptic cytomatrix protein (PCLO) with the polymorphic variants in IUPAC format. The genomic sequence set forth in Figures 2A to 2X correspond to SEQ ID NO: 2. Figures 3A to 3Z show a genomic sequence of a region near cardiac ankyrin repeat kinase (CARK) and fucose-1-phosphate guanylyltransferase (FPGT) with the polymorphic variants in IUPAC format. The genomic sequence set forth in Figures 3A to 3Z correspond to SEQ ID NO: 3. The following nucleotide representations are used throughout the specification and figures: "A" or "a" is adenosine, adenine, or adenylic acid; "C" or "c" is cytidine, cytosine, or cytidylic acid; "G" or "g" is guanosine, guanine, or guanylic acid; "T" or "t" is thymidine, thymine, or thymidylic acid; and "I" or "i" is inosine, hypoxanthine, or inosinic acid. SNPs are designated by the following convention: "R" represents A or G, "M" represents A or C; "W" represents A or T; "Y" represents C or T; "S" represents C or G; "K" represents G or T; "V" represents A, C or G; "H" represents A, C, or T; "D" represents A, G, or T; "B" represents C, G, or T; and "N" represents A, G, C, or T.

[0012] Figures 4A-4C show human cDNA structures for three isoforms of CDK10.

[0013] Figure 5 shows a human cDNA structure for PCLO.

[0014] Figure 6A shows a human cDNA structure for FPGT. Figure 6B shows a human cDNA structure for CARK.

[0015] Figure 7 shows a human cDNA structure for REPS2.

[0016] Figures 8A-8C show human polypeptide sequences for three isoforms of CDK10.

[0017] Figure 9 shows a human polypeptide sequence for PCLO.

[0018] Figures 10A-10B show human polypeptide sequences for FPGT and CARK.

[0019] Figure 11 shows a human polypeptide sequence for REPS2.

[0020] Figures 12, 13 and 14 show proximal SNPs in and around the CDK10 gene for males and females combined, females alone, and males alone, respectively. The position of each SNP on the chromosome is shown on the x-axis and the y-axis provides the negative logarithm of the p-value comparing the estimated allele to that of the control group. Also shown in Figures 12-14 are the exons and introns of the genes in the approximate chromosomal positions.

[0021] Figures 15, 16 and 17 show proximal SNPs in and around the PCLO gene for males and females combined, females alone, and males alone, respectively. The position of each SNP on the chromosome is shown on the x-axis and the y-axis provides the negative logarithm of the p-value comparing the estimated allele to that of the control group. Also shown in Figures 15-17 are the exons and introns of the genes in the approximate chromosomal positions.

[0022] Figures 18, 19 and 20 show proximal SNPs in and around the FPGT/CARK genes for males and females combined, females alone, and males alone, respectively. The position of each SNP on the chromosome is shown on the x-axis and the y-axis provides the negative logarithm of the p-value comparing the estimated allele to that of the control group. Also shown in Figures 18-20 are the exons and introns of the genes in the approximate chromosomal positions.

[0023] Figure 21 depicts effects of CDK10_siRNA on melanoma A375 cell line proliferation according to a Wst-1 assay.

[0024] Figures 22A to 22UU show a genomic sequence of presynaptic cytomatrix protein (REPS2) with the polymorphic variants in IUPAC format. The genomic sequence set forth in Figures 22A-22UU correspond to SEQ ID NO: 4. The following nucleotide representations are used throughout the specification and figures: "A" or "a" is adenosine, adenine, or adenylic acid; "C" or "c" is cytidine, cytosine, or cytidylic acid; "G" or "g" is guanosine, guanine, or guanylic acid; "T" or "t" is thymidine, thymine, or thymidylic acid; and "I" or "i" is inosine, hypoxanthine, or inosinic acid. SNPs are designated by the following convention: "R" represents A or G, "M" represents A or C; "W" represents A or T; "Y" represents C or T; "S" represents C or G; "K" represents G or T; "V" represents A, C or G; "H" represents A, C, or T; "D" represents A, G, or T; "B" represents C, G, or T; and "N" represents A, G, C, or T. The SNP designated as rs1904528 herein is located at position 38753 in these figures.

Detailed Description

[0025] It has been discovered that polymorphic variants in and around *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences are associated with occurrence of melanoma in subjects. Thus, detecting genetic determinants associated with an increased risk of melanoma occurrence can lead to early identification of melanoma or susceptibility to melanoma and early prescription of preventative measures

and treatments. Also, associating *CDK10, FPGT, PCLO* and *REPS2* polymorphic variants with melanoma has provided new targets for screening molecules useful in melanoma prognostics/diagnostics and melanoma treatments.

Melanoma and Sample Selection

[0026] Melanoma is typically described as a malignant neoplasm derived from cells capable of forming melanin. Melanomas arise most commonly in the skin of any part of the body, or in the eye, and rarely, in the mucous membranes of the genitalia, anus, oral cavity, or other sites. Melanoma occurs mostly in adults and may originate de novo or from a pigmented nevus or lentigo maligna. Melanomas frequently metastasize widely to regions such as lymph-nodes, skin, liver, lungs, and brain.

[0027] In the early phases, the cutaneous form is characterized by proliferation of cells at the dermal-epidermal junction that soon invade adjacent tissues. The cells vary in amount and pigmentation of cytoplasm; the nuclei are relatively large and irregular in shape, with prominent acidophilic nucleoli; and mitotic figures tend to be numerous. Other criteria for melanomas are asymmetry, irregular borders, heterogeneous color, large diameter, and a recent change in shape, size or pigmentation. Excised melanoma skin samples are often subjected to the following analyses: diagnosis of the melanocytic nature of the lesion and confirmation of its malignancy; maximum tumor thickness in millimeters (according to Breslow's method); assessment of completeness of excision of invasive and in situ components and microscopic measurements of the shortest extent of clearance; level of invasion (Clark); presence and extent of regression; presence and extent of ulceration; histological type and special variants; pre-existing lesion; mitotic rate; vascular invasion; neurotropism; cell type; tumor lymphocyte infiltration; and growth phase, vertical or radial.

[0028] Based in part upon selection criteria set forth above, individuals having melanoma can be selected for genetic studies. Also, individuals having no history of cancer or melanoma often are selected for genetic studies. Other selection criteria can include: a tissue or fluid sample is derived from an individual characterized as Caucasian; a sample is derived from an individual of German paternal and maternal descent; and relevant phenotype information is available for the individual. Phenotype information corresponding to each individual can include sex of the individual, number of nevi (*e.g.*, actual number or relative number (*e.g.*, few, moderate, numerous)), hair color (*e.g.*, black, brown, blond, red), diagnosis of melanoma (*e.g.*, tumor thickness, date of primary diagnosis, age of individual as of primary diagnosis, post-operative tumor classification, presence of nodes, occurrence of metastases, subtype, location), country or origin of mother and father, presence of certain conditions for each individual (*e.g.*, coronary heart disease, cardiomyopathy, arteriosclerosis, abnormal blood clotting/thrombosis, emphysema, asthma, diabetes type 1, diabetes type 2, Alzheimer's disease, epilepsy, schizophrenia, manic depression/bipolar disorder, autoimmune disease, thyroid disorder, and

hypertension), presence of cancer in the donor individual or blood relative (*e.g.*, melanoma, basaliom/spinaliom/lentigo malignant/mycosis fungoides, breast cancer, colon cancer, rectum cancer, lung cancer, lung cancer, bronchus cancer, prostate cancer, stomach cancer, leukemia, lymphoma, or other cancer in donor, donor parent, donor aunt or uncle, donor offspring or donor grandparent).

[0029] Provided herein is a set of blood samples and a set of corresponding nucleic acid samples isolated from the blood samples, where the blood samples are donated from individuals diagnosed with melanoma. The sample set often includes blood samples or nucleic acid samples from 100 or more, 150 or more, or 200 or more individuals having melanoma, and sometimes from 250 or more, 300 or more, 400 or more, or 500 or more individuals. The individuals can have parents from any place of origin, and in an embodiment, the set of samples are extracted from individuals of German paternal and German maternal ancestry. The samples in each set may be selected based upon five or more criteria and/or phenotypes set forth above.

Polymorphic Variants Associated with Melanoma

[0030] A genetic analysis described hereafter linked melanoma with polymorphic variants of *CDK10, FPGT, PCLO* and *REPS2* from human subjects. Nucleotide sequences representative of *CDK10, FPGT, PCLO* and *REPS2* nucleic acids are set forth in Figures 1A-1Z (SEQ ID NO: 1), Figures 2A-2X (SEQ ID NO: 2), Figures 3A-3Z (SEQ ID NO: 3), and Figures 22A-22UU (SEQ ID NO: 4), respectively, and are incorporated herein by reference from published database entries (*see* Examples section and http address at www.ncbi.nlm.nih.gov/LocusLink/). The following is a description of *CDK10, FPGT, PCLO* and *REPS2* molecules.

CDK10

[0031] The protein CDK10 (cyclin-dependent kinase (CDC2-like) 10) is also known as cyclin-dependent kinase 10 isoform 1 (331 amino acids); cyclin-dependent kinase 10 isoform 2 (314 amino acids); cyclin-dependent kinase 10 isoform 3 (123 amino acids); CDC2-related protein kinase; cell division protein kinase 10; cyclin-dependent kinase related protein; serine/threonine protein kinase and PISSLRE. CDK10 has been mapped to chromosomal position 16q24.

[0032] The protein encoded by CDK10 belongs to the CDK subfamily of the Ser/Thr protein kinase family. The CDK subfamily members are highly similar to the gene products of S. cerevisiae cdc28, and S. pombe cdc2, and are known to be essential for cell cycle progression. This kinase has been shown to play a role in cellular proliferation. Its function is limited to cell cycle G2-M phase. At least three alternatively spliced transcript variants encoding different isoforms have been reported, two of which contain multiple non-AUG translation initiation sites. Cyclin-dependent kinases (CDKs) are CDC2 (NCBI MIM 116940)-related kinases that bind to cyclin to form active holoenzymes that play a

pivotal role in the regulation of the eukaryotic cell cycle. A 360-amino acid protein PISSLRE was predicted based on the amino acid sequence of the region corresponding to the conserved CDC2 PSTAIRE motif. PISSLRE contains all the structural elements characteristic of CDKs and unique extensions at both ends. Sequence comparisons revealed that it shares 41% and 50% protein sequence identity with CDC2 and CDC2L1 (NCBI MIM 176873), respectively. It was determined that PISSLRE was expressed broadly in human tissues as a 2-kb mRNA. An additional 3.5-kb transcript was observed in some tissues (Brambilla et al., Molecular cloning of PISSLRE, a novel putative member of the cdk family of protein serine/threonine kinases. Oncogene 9: 3037-3041, 1994).

FPGT

[0033] The protein FPGT (fucose-1-phosphate guanylyltransferase) is also known as GFPP and GDP-beta-L-fucose pyrophosphorylase. FPGT contains about 594 amino acids. FPGT has been mapped to chromosomal position 1p31.1

[0034] L-fucose is a key sugar in glycoproteins and other complex carbohydrates since it may be involved in many of the functional roles of these macromolecules, such as in cell-cell recognition. The fucosyl donor for these fucosylated oligosaccharides is GDP-beta-L-fucose. There are two alternate pathways for the biosynthesis of GDP-fucose; the major pathway converts GDP-alpha-D-mannose to GDP-beta-L-fucose. FPGT participates in an alternate pathway that is present in certain mammalian tissues, such as liver and kidney, and appears to function as a salvage pathway to reutilize L-fucose arising from the turnover of glycoproteins and glycolipids. This pathway involves the phosphorylation of L-fucose to form beta-L-fucose-1-phosphate, and then condensation of the beta-L-fucose-1-phosphate with GTP by fucose-1-phosphate guanylyltransferase to form GDP-beta-L-fucose.

[0035] GFPP was purified from pig kidney and a partial protein sequence was determined. Human cDNAs encoding a region similar to one of the pig GFPP peptides also were identified. Using a PCR strategy with primers based on one of the ESTs, a cDNA corresponding to the entire human GFPP coding region was cloned. The predicted GFPP protein contains 594 amino acids. When expressed in mammalian cells, the human enzyme exhibited high levels of GFPP activity. Northern blot analysis indicated that the 3.5-kb GFPP mRNA is expressed in several human tissues (Pastuszak et al., GDP-L-fucose pyrophosphorylase: purification, cDNA cloning, and properties of the enzyme. *J. Biol. Chem.* 273: 30165-30174, 1998).

PCLO

[0036] The protein PCLO is also known as piccolo (presynaptic cytomatrix protein), ACZ, KIAA0559 and aczonin. PCLO contains about 1225 amino acids. PCLO has been mapped to chromosomal position 7q11.23-q21.1.

[0037] Synaptic vesicles dock and fuse in the active zone of the plasma membrane at chemical synapses. The presynaptic cytoskeletal matrix (PCM), which is associated with the active zone and is situated between synaptic vesicles, is thought to be involved in maintaining the neurotransmitter release site in register with the postsynaptic reception apparatus. The cycling of synaptic vesicles is a multistep process involving a number of proteins (see NCBI MIM 603215). Among the components of the PCM that orchestrate these events are Bassoon (BSN; NCBI MIM 604020), RIM (RBBP8; NCBI MIM 604124), Oboe, and Piccolo.

[0038] By screening human brain cDNAs for those encoding proteins larger than 50 kD, a partial cDNA encoding PCLO, referred to as KIAA0559, was identified. RT-PCR analysis detected PCLO expression in kidney, with little or no expression in all other tissues tested (Nagase *et al.*, Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro. *DNA Res.* 5: 31-39, 1998).

[0039] By searching EST and genome databases with a murine Pclo cDNA probe, genomic sequences and a brain-specific EST (KIAA0559) encoding human PCLO were identified. Sequence analysis indicated that the deduced 4,880-amino acid rat Pclo protein is 86% identical to human PCLO. In addition, PCLO shares significant amino acid sequence homology with BSN. BSN and PCLO share 10 homology regions, or PBH regions. PBH1 and PBH2 contain 2 double-zinc finger motifs. PBH4, PBH6, and PBH8 are likely to form coiled-coil structures. At the C terminus, unlike BSN but like RIM and Oboe, PCLO contains a PDZ domain and a C2 domain. The PCLO C2 domain contains all the asp residues required for calcium binding. PCLO also contains multiple proline-rich segments. Confocal microscopy analysis of cultured hippocampal neurons showed colocalization of BSN and PCLO at identical GABAergic and glutamergic synapses, of synaptotagmin (see SYT1; NCBI MIM 185605) and PCLO along dendritic profiles, and of PCLO zinc fingers and PRA1 (NCBI MIM 604925) at nerve terminals (Fenster *et al.*, Piccolo, a presynaptic zinc finger protein structurally related to Bassoon. *Neuron* 25: 203-214, 2000).

[0040] Using cAMP-GEFII (NCBI MIM 606058) as bait in a yeast 2-hybrid screen, mouse piccolo was cloned from an insulin-secreting cell line cDNA library. Northern blot analysis of mouse tissues revealed high levels in cerebrum and cerebellum and moderate levels in pituitary gland, pancreatic islets, and a pheochromocytoma-derived mouse cell line. In situ hybridization of mouse brain revealed piccolo mRNA expressed in cerebral cortex, hippocampus, olfactory bulb, cerebellar cortex, and pituitary gland. The distribution of piccolo mRNA largely overlapped that of cAMP-GEFII and Rim2 (NCBI MIM 606630) mRNA in tissues, cell lines, and mouse brain. Mouse piccolo interacts with both cAMP-GefII and Rim2. In the presence of Ca(2+), the C2A domain of piccolo could homodimerize, it could interact with the C2A domain of Rim2, or it could bind the cAMP GefII-Rim2 complex. It did not bind cAMP-GefII directly. Treatment of pancreatic islets with antisense piccolo oligonucleotides inhibited insulin

secretion induced by a cAMP analog and high glucose stimulation. Piccolo serves as a Ca(2+) sensor in exocytosis in pancreatic beta cells and that the formation of a cAMP-GEFII-RIM2 piccolo complex is required (Fujimoto *et al.*, Piccolo, a Ca(2+) sensor in pancreatic beta-cells: involvement of cAMP-GEFII-Rim2-piccolo complex in cAMP-dependent exocytosis. *J. Biol. Chem.* 277: 50497-50502, 2002).

[0041] By comparing the human PCLO genomic sequence with the rat Pclo cDNA, it was determined that the human PCLO gene contains at least 19 exons and spans over 350 kb.

REPS2

[0042] The protein REPS2 (RALBP1 associated Eps domain containing 2) is also known as POB1 and partner of Ral-binding protein 1. REPS2 contains about 521 amino acids. REPS2 has been mapped to chromosomal position Xp22.22.

[0043] Small G proteins have GDP-bound inactive and GTP-bound active forms; RAL proteins (e.g., RALA; NCBI MIM 179550) shift from the inactive to the active state through the actions of RALGDS (NCBI MIM 601619). RALGDS interacts with the active form of RAS (see HRAS; NCBI MIM 190020).

[0044] Using RALA-binding protein-1 (RALBP1; NCBI MIM 605801) as bait in a yeast 2-hybrid screen of a brain cDNA library, cDNAs encoding REPS2, which is designated POB1, were identified (Ikeda et al., Identification and characterization of a novel protein interacting with Ral-binding protein 1, a putative effector protein of Ral. *J. Biol. Chem.* 273: 814-821, 1998). Sequence analysis predicted that the 521-amino acid protein has 2 potential initiator methionines in its N terminus, a central EPS15 (NCBI MIM 600051)-like domain, and 2 proline-rich regions and a putative coiled-coil structure in its C terminus. Northern blot analysis revealed strong expression in rat cerebrum, cerebellum, lung, and testis, with weak expression in kidney and no expression in heart, thymus, liver, spleen, or adrenal gland. Immunoprecipitation and immunoblot analyses confirmed that the C-terminal 146 amino acids of REPS2 and the C-terminal 147 residues of RALBP1 interact in intact cells. RAL interacts with a distinct region of RALBP1, just N terminal of the REPS2-binding domain, and both proteins can interact simultaneously with RALBP1. Immunoblot analysis established that REPS2 is tyrosine phosphorylated in response to epidermal growth factor (EGF; NCBI MIM 131530) and interacts with the EGF receptor (EGFR; NCBI MIM 131550), possibly through the adaptor protein GRB2 (NCBI MIM 108355), with which REPS2 interacts specifically.

[0045] Using nuclear magnetic resonance spectroscopy, it was shown that the EPS15 homology domain of REPS2 consists of 2 EF-hand structures, the second of which binds calcium (Koshiba et al., Solution structure of the Eps15 homology domain of a human POB1 (partner of RalBP1). *FEBS Lett.* 442: 138-142, 1999).

[0046] As used herein, "polymorphic site" refers to a region in a nucleic acid at which two or more alternative nucleotide sequences are observed in a significant number of nucleic acid samples from a population of individuals. A polymorphic site may be a nucleotide sequence of two or more nucleotides, an inserted nucleotide or nucleotide sequence, a deleted nucleotide or nucleotide sequence, or a microsatellite, for example. A polymorphic site that is two or more nucleotides in length may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more, 20 or more, 30 or more, 50 or more, 75 or more, 100 or more, 500 or more, or about 1000 nucleotides in length, where all or some of the nucleotide sequences differ within the region. A polymorphic site is often one nucleotide in length, which is referred to herein as a "single nucleotide polymorphism" or a "SNP."

[0047] Where there are two, three, or four alternative nucleotide sequences at a polymorphic site, each nucleotide sequence is referred to as a "polymorphic variant." Where two polymorphic variants exist, for example, the polymorphic variant represented in a minority of samples from a population is sometimes referred to as a "minor allele" and the polymorphic variant that is more prevalently represented is sometimes referred to as a "major allele." Many organisms possess a copy of each chromosome (*e.g.*, humans), and those individuals who possess two major alleles or two minor alleles are often referred to as being "homozygous" with respect to the polymorphism, and those individuals who possess one major allele and one minor allele are normally referred to as being "heterozygous" with respect to the polymorphism. Individuals who are homozygous with respect to one allele are sometimes predisposed to a different phenotype as compared to individuals who are heterozygous or homozygous with respect to another allele. As shown hereafter, certain polymorphic variants of *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences are associated with melanoma.

[0048] A genotype or polymorphic variant may be expressed in terms of a "haplotype," which as used herein refers to two or more polymorphic variants occurring within genomic DNA in a group of individuals within a population. For example, two SNPs may exist within a gene where each SNP position includes a cytosine variation and an adenine variation. Certain individuals in a population may carry one allele (heterozygous) or two alleles (homozygous) having the gene with a cytosine at each SNP position. As the two cytosines corresponding to each SNP in the gene travel together on one or both alleles in these individuals, the individuals can be characterized as having a cytosine/cytosine haplotype with respect to the two SNPs in the gene.

[0049] As used herein, "phenotype" refers to a trait which can be compared between individuals, such as presence or absence of a condition, a visually observable difference in appearance between individuals, metabolic variations, physiological variations, variations in the function of biological molecules, and the like. An example of a phenotype is occurrence of melanoma.

[0050] Researchers sometimes report a polymorphic variant in a database without determining whether the variant is represented in a significant fraction of a population. Because a subset of these

reported polymorphic variants are not represented in a statistically significant portion of the population, some of them are sequencing errors and/or not biologically relevant. Thus, it often is not known whether a reported polymorphic variant is statistically significant or biologically relevant until the presence of the variant is detected in a population of individuals and the frequency of the variant is determined. Methods for detecting a polymorphic variant in a population are described herein, such as in Example 2. A polymorphic variant is statistically significant and often biologically relevant if it is represented in 5% or more of a population, sometimes 10% or more, 15% or more, or 20% or more of a population, and often 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, or 50% or more of a population.

[0051] A polymorphic variant may be detected on either or both strands of a double-stranded nucleic acid. Also, a polymorphic variant may be located within an intron or exon of a gene or within a portion of a regulatory region such as a promoter, a 5′ untranslated region (UTR), a 3′ UTR, and in DNA (*e.g.*, genomic DNA (gDNA) and complementary DNA (cDNA)), RNA (*e.g.*, mRNA, tRNA, and rRNA), or a polypeptide. Polymorphic variations may or may not result in detectable differences in gene expression, polypeptide structure, or polypeptide function.

[0052] For duplex DNA, a polymorphic variation may be reported from one strand or its complementary strand. For example, a thymine at a particular position in SEQ ID NO: 1, 2, 3 or 4 can be reported as an adenine from the complementary strand. Also, while polymorphic variations at all positions within a haplotype often are reported from the same strand orientation, polymorphic variations at certain positions within a haplotype sometimes are reported from one strand orientation while others are reported from the other. The latter sometimes occurs even though it is understood by the person of ordinary skill in the art that polymorphic variants in a haplotype occur within one strand in a nucleic acid. Where a haplotype is reported from mixed strand orientations, a person of ordinary skill in the art can determine the orientation of each polymorphic variation in the haplotype by analyzing the orientation of each extension oligonucleotide utilized to identify each polymorphic variation.

[0053] In the genetic analyses that associated polymorphic variations in *CDK10, FPGT, PCLO* or *REPS2* with melanoma, samples from individuals having melanoma and individuals not having cancer were allelotyped and genotyped. The term "allelotype" as used herein refers to a process for determining the allele frequency for a polymorphic variant in pooled DNA samples from cases and controls. By pooling DNA from each group, an allele frequency for each SNP in each group is calculated. These allele frequencies are then compared to one another. Particular SNPs are considered as being associated with a particular disease when allele frequency differences calculated between case and control pools are statistically significant. The term "genotyped" as used herein refers to a process for determining a genotype of one or more individuals, where a "genotype" is a representation of one or more polymorphic variants in a population. It was determined that polymorphic variations associated with an increased risk of melanoma existed in *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences. In specific

embodiments, polymorphic variants at the following positions in SEQ ID NO: 1 were associated with an increased risk of melanoma: 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523. Of these, variations at postitions 139, 3525, 9640, 21338, 85666, 88389 and 92523 were in particular associated with an increased risk of melanoma in females, and variations at positions 7960, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, and 83831 were in particular associated with an increased risk of melanoma in males. Polymorphic variants at the following positions in SEQ ID NO: 2 were associated with an increased risk of melanoma: 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870. Of these, variations at postitions 17207, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 50015, 50442, 51203, 57523, 60557, 60645, 64531 and 83870 were in particular associated with an increased risk of melanoma in females, and variations at positions 19057, 32252, 33887, 42857, 46643, 47007, 51983, 60557, 60645, and 83870 were in particular associated with an increased risk of melanoma in males. Polymorphic variants at the following positions in SEQ ID NO: 3 were associated with an increased risk of melanoma: 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488. Of these, variations at postitions 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 46972, 48524 and 72488 were in particular associated with an increased risk of melanoma in females, and variations at positions 21583 and 38293 were in particular associated with an increased risk of melanoma in males. A polymorphic variant at position 38753 in SEQ ID NO: 4 was associated with increased risk of melanoma. At these positions in SEQ ID NOs: 1, 2, 3, and 4, a cytosine at position 139 in SEQ ID NO: 1, a guanine at position 3525 in SEQ ID NO: 1, a thymine at position 7960 in SEQ ID NO: 1, a guanine at position 9640 in SEQ ID NO: 1, a thymine at position 14845 in SEQ ID NO: 1, a cytosine at position 19300 in SEQ ID NO: 1, a cytosine at position 21338 in SEQ ID NO: 1, a thymine at position 21343 in SEQ ID NO: 1, a guanine at position 42477 in SEQ ID NO: 1, a thymine at position 43164 in SEQ ID NO: 1, a thymine at position 43734 in SEQ ID NO: 1, an adenine at position 44029 in SEQ ID NO: 1, a thymine at position 44986 in SEQ ID NO: 1, a guanine at position 53410 in SEQ ID NO: 1, a cytosine at position 83831 in SEQ ID NO: 1, a cytosine at position 85666 in SEQ ID NO: 1, a cytosine at position 88389 in SEQ ID NO: 1, a guanine at position 92523 in SEQ ID NO: 1, a thymine at position 17207 in SEQ ID NO: 2, a guanine at position 19057 in SEQ ID NO: 2, a guanine at position 32252 in SEQ ID NO: 2, a thymine at position 33887 in SEQ ID NO: 2, a cytosine at position 36394 in SEQ ID NO: 2, an adenine at position 39184 in SEQ ID NO: 2, a thymine at position 40707 in SEQ ID NO: 2, an adenine at position 42857 in SEQ ID NO: 2, a cytosine at position 45812 in SEQ ID NO: 2, a thymine at position 46643 in SEQ ID NO: 2, a cytosine at position 47007 in SEQ ID NO: 2, a guanine at position 50015 in SEQ ID NO: 2, a guanine at position 50442 in SEQ ID NO: 2, an adenine at position 51203 in SEQ ID NO: 2, a guanine at position 51983 in SEQ ID NO: 2, an adenine at position 57523 in SEQ ID NO: 2, an adenine at position 60557 in

SEQ ID NO: 2, a thymine at position 60645 in SEQ ID NO: 2, an adenine at position 64531 in SEQ ID NO: 2, a thymine at position 83870 in SEQ ID NO: 2, a cytosine at position 4029 in SEQ ID NO: 3, an adenine at position 5343 in SEQ ID NO: 3, an adenine at position 8817 in SEQ ID NO: 3, a thymine at position 18596 in SEQ ID NO: 3, an adenine at position 18602 in SEQ ID NO: 3, a cytosine at position 21583 in SEQ ID NO: 3, a thymine at position 36594 in SEQ ID NO: 3, a thymine at position 37994 in SEQ ID NO: 3, an adenine at position 38293 in SEQ ID NO: 3, a cytosine at position 46972 in SEQ ID NO: 3, an adenine at position 48524 in SEQ ID NO: 3, a thymine at position 72488 in SEQ ID NO: 3 and a cytosine at position 38753 in SEQ ID NO: 4 were in particular associated with an increased risk of melanoma.

Additional Polymorphic Variants Associated with Melanoma

[0054] Also provided is a method for identifying polymorphic variants proximal to an incident, founder polymorphic variant associated with melanoma. Thus, featured herein are methods for identifying a polymorphic variation associated with melanoma that is proximal to an incident polymorphic variation associated with melanoma, which comprises identifying a polymorphic variant proximal to the incident polymorphic variant associated with melanoma, where the incident polymorphic variant is in a nucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4. The nucleotide sequence often comprises a polynucleotide sequence selected from the group consisting of (a) a polynucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4; (b) a polynucleotide sequence that encodes a polypeptide having an amino acid sequence encoded by a nucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4; and (c) a polynucleotide sequence that encodes a polypeptide having an amino acid sequence that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4 or a polynucleotide sequence 90% or more identical to the polynucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4. The presence or absence of an association of the proximal polymorphic variant with NIDDM then is determined using a known association method, such as a method described in the Examples hereafter. In an embodiment, the incident polymorphic variant is described in SEQ ID NO: 1, 2, 3 or 4 or in the Examples below. In another embodiment, the proximal polymorphic variant identified sometimes is a publicly disclosed polymorphic variant, which for example, sometimes is published in a publicly available database. In other embodiments, the polymorphic variant identified is not publicly disclosed and is discovered using a known method, including, but not limited to, sequencing a region surrounding the incident polymorphic variant in a group of nucleic samples. Thus, multiple polymorphic variants proximal to an incident polymorphic variant are associated with melanoma using this method.

[0055] The proximal polymorphic variant often is identified in a region surrounding the incident polymorphic variant. In certain embodiments, this surrounding region is about 50 kb flanking the first polymorphic variant (*e.g.* about 50 kb 5' of the first polymorphic variant and about 50 kb 3' of the first

polymorphic variant), and the region sometimes is composed of shorter flanking sequences, such as flanking sequences of about 40 kb, about 30 kb, about 25 kb, about 20 kb, about 15 kb, about 10 kb, about 7 kb, about 5 kb, or about 2 kb 5' and 3' of the incident polymorphic variant. In other embodiments, the region is composed of longer flanking sequences, such as flanking sequences of about 55 kb, about 60 kb, about 65 kb, about 70 kb, about 75 kb, about 80 kb, about 85 kb, about 90 kb, about 95 kb, or about 100 kb 5' and 3' of the incident polymorphic variant.

[0056] In certain embodiments, polymorphic variants associated with melanoma are identified iteratively. For example, a first proximal polymorphic variant is associated with melanoma using the methods described above and then another polymorphic variant proximal to the first proximal polymorphic variant is identified (*e.g.*, publicly disclosed or discovered) and the presence or absence of an association of one or more other polymorphic variants proximal to the first proximal polymorphic variant with melanoma is determined.

[0057] The methods described herein are useful for identifying or discovering additional polymorphic variants that may be used to further characterize a gene, region or loci associated with a condition, a disease (*e.g.*, melanoma), or a disorder. For example, allelotyping or genotyping data from the additional polymorphic variants may be used to identify a functional mutation or a region of linkage disequilibrium. In certain embodiments, polymorphic variants identified or discovered within a region comprising the first polymorphic variant associated with melanoma are genotyped using the genetic methods and sample selection techniques described herein, and it can be determined whether those polymorphic variants are in linkage disequilibrium with the first polymorphic variant. The size of the region in linkage disequilibrium with the first polymorphic variant also can be assessed using these genotyping methods. Thus, provided herein are methods for determining whether a polymorphic variant is in linkage disequilibrium with a first polymorphic variant associated with melanoma, and such information can be used in prognosis methods described herein.

Isolated Nucleic Acids and Variants Thereof

[0058] Featured herein are isolated *CDK10, FPGT, PCLO* or *REPS2* nucleic acids, which include the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4, *CDK10, FPGT, PCLO* or *REPS2* nucleic acid variants, and substantially identical nucleic acids and fragments of the foregoing. Nucleotide sequences of *CDK10, FPGT, PCLO* or *REPS2* nucleic acids sometimes are referred to herein as "*CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences." A "*CDK10, FPGT, PCLO* or *REPS2* nucleic acid variant" refers to one allele that may have different polymorphic variations as compared to another allele in another subject or the same subject. A polymorphic variation in the *CDK10, FPGT, PCLO* or *REPS2* nucleic acid variant may be represented on one or both strands in a double-stranded nucleic acid or on one chromosomal complement (heterozygous) or both chromosomal complements (homozygous). A

CDK10, FPGT, PCLO or *REPS2* nucleic acid may comprise one or more polymorphic variations associated with melanoma described herein.

[0059] As used herein, the term "nucleic acid" includes DNA molecules (*e.g.*, a complementary DNA (cDNA) and genomic DNA (gDNA)) and RNA molecules (*e.g.*, mRNA, rRNA, siRNA and tRNA) and analogs of DNA or RNA, for example, by use of nucleotide analogs. The nucleic acid molecule can be single-stranded and it is often double-stranded. The term "isolated or purified nucleic acid" refers to nucleic acids that are separated from other nucleic acids present in the natural source of the nucleic acid. For example, with regard to genomic DNA, the term "isolated" includes nucleic acids which are separated from the chromosome with which the genomic DNA is naturally associated. An "isolated" nucleic acid is often free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and/or 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of 5' and/or 3' nucleotide sequences which flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. As used herein, the term "*CDK10, FPGT, PCLO* or *REPS2* gene" refers to a nucleotide sequence that encodes a *CDK10, FPGT, PCLO* or *REPS2* polypeptide.

[0060] Also included herein are nucleic acid fragments. These fragments are typically a nucleotide sequence identical to a nucleotide sequence in SEQ ID NO: 1, 2, 3 or 4, a nucleotide sequence substantially identical to a nucleotide sequence in SEQ ID NO: 1, 2, 3 or 4, or a nucleotide sequence that is complementary to the foregoing. The nucleic acid fragment may be identical, substantially identical or homologous to a nucleotide sequence in an exon or an intron in SEQ ID NO: 1, 2, 3 or 4 and may encode a full-length or mature polypeptide, or may encode a domain or part of a domain of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Sometimes, the fragment will comprises one or more of the polymorphic variations described herein as being associated with melanoma. The nucleic acid fragment is often 50, 100, or 200 or fewer base pairs in length, and is sometimes about 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, or 1400 base pairs in length. A nucleic acid fragment that is complementary to a nucleotide sequence identical or substantially identical to the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4 and hybridizes to such a nucleotide sequence under stringent conditions is often referred to as a "probe." Nucleic acid fragments often include one or more polymorphic sites, or sometimes have an end that is adjacent to a polymorphic site as described hereafter.

[0061] An example of a nucleic acid fragment is an oligonucleotide. As used herein, the term "oligonucleotide" refers to a nucleic acid comprising about 8 to about 50 covalently linked nucleotides,

often comprising from about 8 to about 35 nucleotides, and more often from about 10 to about 25 nucleotides. The backbone and nucleotides within an oligonucleotide may be the same as those of naturally occurring nucleic acids, or analogs or derivatives of naturally occurring nucleic acids, provided that oligonucleotides having such analogs or derivatives retain the ability to hybridize specifically to a nucleic acid comprising a targeted polymorphism. Oligonucleotides described herein may be used as hybridization probes or as components of prognostic or diagnostic assays, for example, as described herein.

[0062] Oligonucleotides are typically synthesized using standard methods and equipment, such as the ABI™3900 High Throughput DNA Synthesizer and the EXPEDITE™ 8909 Nucleic Acid Synthesizer, both of which are available from Applied Biosystems (Foster City, CA). Analogs and derivatives are exemplified in U.S. Pat. Nos. 4,469,863; 5,536,821; 5,541,306; 5,637,683; 5,637,684; 5,700,922; 5,717,083; 5,719,262; 5,739,308; 5,773,601; 5,886,165; 5,929,226; 5,977,296; 6,140,482; WO 00/56746; WO 01/14398, and related publications. Methods for synthesizing oligonucleotides comprising such analogs or derivatives are disclosed, for example, in the patent publications cited above and in U.S. Pat. Nos. 5,614,622; 5,739,314; 5,955,599; 5,962,674; 6,117,992; in WO 00/75372; and in related publications.

[0063] Oligonucleotides may also be linked to a second moiety. The second moiety may be an additional nucleotide sequence such as a tail sequence (*e.g.*, a polyadenosine tail), an adapter sequence (*e.g.*, phage M13 universal tail sequence), and others. Alternatively, the second moiety may be a non-nucleotide moiety such as a moiety which facilitates linkage to a solid support or a label to facilitate detection of the oligonucleotide. Such labels include, without limitation, a radioactive label, a fluorescent label, a chemiluminescent label, a paramagnetic label, and the like. The second moiety may be attached to any position of the oligonucleotide, provided the oligonucleotide can hybridize to the nucleic acid comprising the polymorphism.

Uses for Nucleic Acids

[0064] Nucleic acid coding sequences depicted in SEQ ID NO: 1, 2, 3 or 4, or substantially identical sequences thereof, may be used for diagnostic purposes for detection and control of polypeptide expression. Also, included are oligonucleotide sequences such as antisense nucleic acids (*e.g.*, DNA, RNA or PNA), inhibitory RNA and small-interfering RNA (siRNA), and ribozymes that function to inhibit translation of a polypeptide. Antisense techniques and RNA interference techniques are known in the art and are described herein.

[0065] Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example,

hammerhead motif ribozyme molecules may be engineered that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences encoded by a nucleotide sequence set forth in SEQ ID NO: 1. 2 or 3 or a substantially identical sequence thereof. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites which include the following sequences, GUA, GUU and GUC. Once identified, short RNA sequences of between fifteen (15) and twenty (20) ribonucleotides corresponding to the region of the target gene containing the cleavage site may be evaluated for predicted structural features such as secondary structure that may render the oligonucleotide sequence unsuitable. The suitability of candidate targets may also be evaluated by testing their accessibility to hybridization with complementary oligonucleotides, using ribonuclease protection assays.

[0066] Antisense RNA and DNA molecules, siRNA and ribozymes may be prepared by any method known in the art for the synthesis of RNA molecules. These include techniques for chemically synthesizing oligodeoxyribonucleotides well known in the art such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors which incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

[0067] DNA encoding a polypeptide also may have a number of uses for the diagnosis of diseases, including melanoma, resulting from aberrant expression of a target gene described herein. For example, the nucleic acid sequence may be used in hybridization assays of biopsies or autopsies to diagnose abnormalities of expression or function (*e.g.*, Southern or Northern blot analysis, in situ hybridization assays).

[0068] In addition, the expression of a polypeptide during embryonic development may also be determined using nucleic acid encoding the polypeptide. As addressed, *infra*, production of functionally impaired polypeptide is the cause of various disease states, melanoma. *In situ* hybridizations using polypeptide as a probe may be employed to predict problems related to melanoma. Further, as indicated, *infra*, administration of human active polypeptide, recombinantly produced as described herein, may be used to treat disease states related to functionally impaired polypeptide. Alternatively, gene therapy approaches may be employed to remedy deficiencies of functional polypeptide or to replace or compete with dysfunctional polypeptide.

Expression Vectors, Host Cells, and Genetically Engineered Cells

[0069] Provided herein are nucleic acid vectors, often expression vectors, which contain a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid. As used herein, the term "vector" refers to a nucleic acid

molecule capable of transporting another nucleic acid to which it has been linked and can include a plasmid, cosmid, or viral vector. The vector can be capable of autonomous replication or it can integrate into a host DNA. Viral vectors may include replication defective retroviruses, adenoviruses and adeno-associated viruses for example.

[0070] A vector can include a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid in a form suitable for expression of the nucleic acid in a host cell. The recombinant expression vector typically includes one or more regulatory sequences operatively linked to the nucleic acid sequence to be expressed. The term "regulatory sequence" includes promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence, as well as tissue-specific regulatory and/or inducible sequences. The design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of polypeptide desired, and the like. Expression vectors can be introduced into host cells to produce *CDK10, FPGT, PCLO* or *REPS2* polypeptides, including fusion polypeptides, encoded by *CDK10, FPGT, PCLO* or *REPS2* nucleic acids.

[0071] Recombinant expression vectors can be designed for expression of *CDK10, FPGT, PCLO* or *REPS2* polypeptides in prokaryotic or eukaryotic cells. For example, *CDK10, FPGT, PCLO* or *REPS2* polypeptides can be expressed in *E. coli*, insect cells (*e.g.*, using baculovirus expression vectors), yeast cells, or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology 185*, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[0072] Expression of polypeptides in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion polypeptides. Fusion vectors add a number of amino acids to a polypeptide encoded therein, usually to the amino terminus of the recombinant polypeptide. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant polypeptide; 2) to increase the solubility of the recombinant polypeptide; and 3) to aid in the purification of the recombinant polypeptide by acting as a ligand in affinity purification. Often, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant polypeptide to enable separation of the recombinant polypeptide from the fusion moiety subsequent to purification of the fusion polypeptide. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith & Johnson, *Gene 67:* 31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding polypeptide, or polypeptide A, respectively, to the target recombinant polypeptide.

[0073] Purified fusion polypeptides can be used in screening assays and to generate antibodies specific for *CDK10, FPGT, PCLO* or *REPS2* polypeptides. In a therapeutic embodiment, fusion polypeptide expressed in a retroviral expression vector is used to infect bone marrow cells that are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six (6) weeks).

[0074] Expressing the polypeptide in host bacteria with an impaired capacity to proteolytically cleave the recombinant polypeptide is often used to maximize recombinant polypeptide expression (Gottesman, S., *Gene Expression Technology: Methods in Enzymology, Academic Press, San Diego, California 185:* 119-128 (1990)). Another strategy is to alter the nucleotide sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al., Nucleic Acids Res. 20:* 2111-2118 (1992)). Such alteration of nucleotide sequences can be carried out by standard DNA synthesis techniques.

[0075] When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. Recombinant mammalian expression vectors are often capable of directing expression of the nucleic acid in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Non-limiting examples of suitable tissue-specific promoters include an albumin promoter (liver-specific; Pinkert *et al., Genes Dev. 1:* 268-277 (1987)), lymphoid-specific promoters (Calame & Eaton, *Adv. Immunol. 43:* 235-275 (1988)), promoters of T cell receptors (Winoto & Baltimore, *EMBO J. 8:* 729-733 (1989)) promoters of immunoglobulins (Banerji *et al., Cell 33:* 729-740 (1983); Queen & Baltimore, *Cell 33:* 741-748 (1983)), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne & Ruddle, *Proc. Natl. Acad. Sci. USA 86:* 5473-5477 (1989)), pancreas-specific promoters (Edlund *et al., Science 230:* 912-916 (1985)), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are sometimes utilized, for example, the murine hox promoters (Kessel & Gruss, *Science 249:* 374-379 (1990)) and the a-fetopolypeptide promoter (Campes & Tilghman, *Genes Dev. 3:* 537-546 (1989)).

[0076] A *CDK10, FPGT, PCLO* or *REPS2* nucleic acid may also be cloned into an expression vector in an antisense orientation. Regulatory sequences (*e.g.*, viral promoters and/or enhancers) operatively linked to a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid cloned in the antisense orientation can be chosen for directing constitutive, tissue specific or cell type specific expression of antisense RNA in a variety of cell types. Antisense expression vectors can be in the form of a recombinant plasmid, phagemid or attenuated virus. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.,* Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) (1986).

[0077] Also provided herein are host cells that include a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid within a recombinant expression vector or *CDK10, FPGT, PCLO* or *REPS2* nucleic acid sequence fragments which allow it to homologously recombine into a specific site of the host cell genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. Such terms refer not only to the particular subject cell but rather also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein. A host cell can be any prokaryotic or eukaryotic cell. For example, a *CDK10, FPGT, PCLO* or *REPS2* polypeptide can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[0078] Vectors can be introduced into host cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, transduction/infection, DEAE-dextran-mediated transfection, lipofection, or electroporation.

[0079] A host cell provided herein can be used to produce (*i.e.*, express) a *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Accordingly, further provided are methods for producing a *CDK10, FPGT, PCLO* or *REPS2* polypeptide using the host cells described herein. In one embodiment, the method includes culturing host cells into which a recombinant expression vector encoding a *CDK10, FPGT, PCLO* or *REPS2* polypeptide has been introduced in a suitable medium such that a *CDK10, FPGT, PCLO* or *REPS2* polypeptide is produced. In another embodiment, the method further includes isolating a *CDK10, FPGT, PCLO* or *REPS2* polypeptide from the medium or the host cell.

[0080] Also provided are cells or purified preparations of cells which include a *CDK10, FPGT, PCLO* or *REPS2* transgene, or which otherwise misexpress *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Cell preparations can consist of human or non-human cells, *e.g.*, rodent cells, *e.g.*, mouse or rat cells, rabbit cells, or pig cells. In embodiments, the cell or cells include a *CDK10, FPGT, PCLO* or *REPS2* transgene (*e.g.*, a heterologous form of a *CDK10, FPGT, PCLO* or *REPS2* such as a human gene expressed in non-human cells). The *CDK10, FPGT, PCLO* or *REPS2* transgene can be misexpressed, *e.g.*, overexpressed or underexpressed. In other embodiments, the cell or cells include a gene which misexpress an endogenous *CDK10, FPGT, PCLO* or *REPS2* polypeptide (*e.g.*, expression of a gene is disrupted, also known as a knockout). Such cells can serve as a model for studying disorders which are related to mutated or mis-expressed *CDK10, FPGT, PCLO* or *REPS2* alleles or for use in drug screening. Also provided are human cells (*e.g.*, a hematopoietic stem cells) transformed with a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid.

[0081] Also provided are cells or a purified preparation thereof (*e.g.*, human cells) in which an endogenous *CDK10, FPGT, PCLO* or *REPS2* nucleic acid is under the control of a regulatory sequence that does not normally control the expression of the endogenous *CDK10, FPGT, PCLO* or *REPS2* gene. The expression characteristics of an endogenous gene within a cell (*e.g.*, a cell line or microorganism) can be modified by inserting a heterologous DNA regulatory element into the genome of the cell such that the inserted regulatory element is operably linked to the endogenous *CDK10, FPGT, PCLO* or *REPS2* gene. For example, an endogenous *CDK10, FPGT, PCLO* or *REPS2* gene (*e.g.*, a gene which is "transcriptionally silent," not normally expressed, or expressed only at very low levels) may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed gene product in that cell. Techniques such as targeted homologous recombinations, can be used to insert the heterologous DNA as described in, *e.g.*, Chappel, US 5,272,071; WO 91/06667, published on May 16, 1991.

Transgenic Animals

[0082] Non-human transgenic animals that express a heterologous *CDK10, FPGT, PCLO* or *REPS2* polypeptide (*e.g.*, expressed from a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid isolated from another organism) can be generated. Such animals are useful for studying the function and/or activity of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide and for identifying and/or evaluating modulators of *CDK10, FPGT, PCLO* or *REPS2* nucleic acid and *CDK10, FPGT, PCLO* or *REPS2* polypeptide activity. As used herein, a "transgenic animal" is a non-human animal such as a mammal (*e.g.*, a non-human primate such as chimpanzee, baboon, or macaque; an ungulate such as an equine, bovine, or caprine; or a rodent such as a rat, a mouse, or an Israeli sand rat), a bird (*e.g.*, a chicken or a turkey), an amphibian (*e.g.*, a frog, salamander, or newt), or an insect (*e.g.*, *Drosophila melanogaster*), in which one or more of the cells of the animal includes a *CDK10, FPGT, PCLO* or *REPS2* transgene. A transgene is exogenous DNA or a rearrangement (*e.g.*, a deletion of endogenous chromosomal DNA) that is often integrated into or occurs in the genome of cells in a transgenic animal. A transgene can direct expression of an encoded gene product in one or more cell types or tissues of the transgenic animal, and other transgenes can reduce expression (*e.g.*, a knockout). Thus, a transgenic animal can be one in which an endogenous *CDK10, FPGT, PCLO* or *REPS2* gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal (*e.g.*, an embryonic cell of the animal) prior to development of the animal.

[0083] Intronic sequences and polyadenylation signals can also be included in the transgene to increase expression efficiency of the transgene. One or more tissue-specific regulatory sequences can be operably linked to a *CDK10, FPGT, PCLO* or *REPS2* transgene to direct expression of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide to particular cells. A transgenic founder animal can be identified based

upon the presence of a *CDK10, FPGT, PCLO* or *REPS2* transgene in its genome and/or expression of *CDK10, FPGT, PCLO* or *REPS2* mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a *CDK10, FPGT, PCLO* or *REPS2* polypeptide can further be bred to other transgenic animals carrying other transgenes.

[0084] *CDK10, FPGT, PCLO* or *REPS2* polypeptides can be expressed in transgenic animals or plants by introducing, for example, a nucleic acid encoding the polypeptide into the genome of an animal. In embodiments the nucleic acid is placed under the control of a tissue specific promoter, *e.g.*, a milk or egg specific promoter, and recovered from the milk or eggs produced by the animal. Also included is a population of cells from a transgenic animal.

CDK10, FPGT, PCLO or *REPS2* Polypeptides

[0085] Also featured herein are isolated *CDK10, FPGT, PCLO* or *REPS2* polypeptides, including proteins and peptides, that include an amino acid sequence set forth in Figures 8A-8C, 9, 10A-10B and 11, respectively, or a substantially identical sequence thereof or variant thereof. Isolated *CDK10, FPGT, PCLO* or *REPS2* polypeptides featured herein include both the full-length polypeptide and the mature polypeptide (*i.e.*, the polypeptide minus the signal sequence or propeptide domain). A *CDK10, FPGT, PCLO* or *REPS2* polypeptide is a polypeptide encoded by a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid, where one nucleic acid can encode one or more different polypeptides. An "isolated" or "purified" polypeptide or protein is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. In one embodiment, the language "substantially free" means preparation of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or *CDK10, FPGT, PCLO* or *REPS2* polypeptide variant having less than about 30%, 20%, 10% and more preferably 5% (by dry weight), of non-*CDK10, FPGT, PCLO* or *REPS2* polypeptide (also referred to herein as a "contaminating protein"), or of chemical precursors or non-*CDK10, FPGT, PCLO* or *REPS2* chemicals. When the *CDK10, FPGT, PCLO* or *REPS2* polypeptide or a biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, specifically, where culture medium represents less than about 20%, sometimes less than about 10%, and often less than about 5% of the volume of the polypeptide preparation. Isolated or purified *CDK10, FPGT, PCLO* or *REPS2* polypeptide preparations are sometimes 0.01 milligrams or more or 0.1 milligrams or more, and often 1.0 milligrams or more and 10 milligrams or more in dry weight.

[0086] Further included herein are *CDK10, FPGT, PCLO* or *REPS2* polypeptide fragments. The polypeptide fragment may be a domain or part of a domain of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide. The polypeptide fragment may have increased, decreased or unexpected biological activity.

The polypeptide fragment is often 50 or fewer, 100 or fewer, or 200 or fewer amino acids in length, and is sometimes 300, 400, 500, 600, or 700, or fewer amino acids in length.

[0087] Substantially identical polypeptides may depart from the amino acid sequences set forth in Figures 8A-8C, 9, 10A-10B and 11 in different manners. For example, conservative amino acid modifications may be introduced at one or more positions in the amino acid sequences of Figures 8A-8C, 9, 10A-10B and 11. A "conservative amino acid substitution" is one in which the amino acid is replaced by another amino acid having a similar structure and/or chemical function. Families of amino acid residues having similar structures and functions are well known. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Also, essential and non-essential amino acids may be replaced. A "non-essential" amino acid is one that can be altered without abolishing or substantially altering the biological function of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide, whereas altering an "essential" amino acid abolishes or substantially alters the biological function of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Amino acids that are conserved among *CDK10, FPGT, PCLO* or *REPS2* polypeptides are typically essential amino acids.

[0088] Also, *CDK10, FPGT, PCLO* or *REPS2* polypeptides and polypeptide variants may exist as chimeric or fusion polypeptides. As used herein, a *CDK10, FPGT, PCLO* or *REPS2* "chimeric polypeptide" or "fusion polypeptide" includes a *CDK10, FPGT, PCLO* or *REPS2* polypeptide linked to a non-*CDK10, FPGT, PCLO* or *REPS2* polypeptide. A "non-*CDK10, FPGT, PCLO* or *REPS2* polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a polypeptide which is not substantially identical to the *CDK10, FPGT, PCLO* or *REPS2* polypeptide, which includes, for example, a polypeptide that is different from the *CDK10, FPGT, PCLO* or *REPS2* polypeptide and derived from the same or a different organism. The *CDK10, FPGT, PCLO* or *REPS2* polypeptide in the fusion polypeptide can correspond to an entire or nearly entire *CDK10, FPGT, PCLO* or *REPS2* polypeptide or a fragment thereof. The non-*CDK10, FPGT, PCLO* or *REPS2* polypeptide can be fused to the N-terminus or C-terminus of the *CDK10, FPGT, PCLO* or *REPS2* polypeptide.

[0089] Fusion polypeptides can include a moiety having high affinity for a ligand. For example, the fusion polypeptide can be a GST-*CDK10, FPGT, PCLO* or *REPS2* fusion polypeptide in which the *CDK10, FPGT, PCLO* or *REPS2* sequences are fused to the C-terminus of the GST sequences, or a polyhistidine-*CDK10, FPGT, PCLO* or *REPS2* fusion polypeptide in which the *CDK10, FPGT, PCLO* or *REPS2* polypeptide is fused at the N- or C-terminus to a string of histidine residues. Such fusion polypeptides can facilitate purification of recombinant *CDK10, FPGT, PCLO* or *REPS2*. Expression

vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide), and a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid can be cloned into an expression vector such that the fusion moiety is linked in-frame to the *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Further, the fusion polypeptide can be a *CDK10, FPGT, PCLO* or *REPS2* polypeptide containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression, secretion, cellular internalization, and cellular localization of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide can be increased through use of a heterologous signal sequence. Fusion polypeptides can also include all or a part of a serum polypeptide (*e.g.*, an IgG constant region or human serum albumin).

[0090] *CDK10, FPGT, PCLO* or *REPS2* polypeptides or fragments thereof can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. Administration of these *CDK10, FPGT, PCLO* or *REPS2* polypeptides can be used to affect the bioavailability of a *CDK10, FPGT, PCLO* or *REPS2* substrate and may effectively increase *CDK10, FPGT, PCLO* or *REPS2* biological activity in a cell. *CDK10, FPGT, PCLO* or *REPS2* fusion polypeptides may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a *CDK10, FPGT, PCLO* or *REPS2* polypeptide; (ii) mis-regulation of the *CDK10, FPGT, PCLO* or *REPS2* gene; and (iii) aberrant post-translational modification of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Also, *CDK10, FPGT, PCLO* or *REPS2* polypeptides can be used as immunogens to produce anti-*CDK10, FPGT, PCLO* or *REPS2* antibodies in a subject, to purify *CDK10, FPGT, PCLO* or *REPS2* ligands or binding partners, and in screening assays to identify molecules which inhibit or enhance the interaction of *CDK10, FPGT, PCLO* or *REPS2* with a *CDK10, FPGT, PCLO* or *REPS2* substrate.

[0091] In addition, polypeptides can be chemically synthesized using techniques known in the art (See, *e.g.*, Creighton, 1983 Proteins. New York, N.Y.: W. H. Freeman and Company; and Hunkapiller *et al.*, (1984) *Nature* July 12 -18;310(5973):105-11). For example, a relative short fragment can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the fragment sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoroamino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0092] Polypeptides and polypeptide fragments sometimes are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand,

etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH4; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; and the like. Additional post-translational modifications include, for example, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptide fragments may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the polypeptide.

[0093] Also provided are chemically modified derivatives of polypeptides that can provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (*see e.g.*, U.S. Pat. No: 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0094] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the molecular weight often utilized is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (*e.g.*, the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog).

[0095] The polymers should be attached to the polypeptide with consideration of effects on functional or antigenic domains of the polypeptide. There are a number of attachment methods available to those skilled in the art (*e.g.*, EP 0 401 384 (coupling PEG to G-CSF) and Malik *et al.* (1992) Exp Hematol. September;20(8):1028-35 (pegylation of GM-CSF using tresyl chloride)). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. For therapeutic purposes, the attachment sometimes is at an amino group, such as attachment at the N-terminus or lysine group.

[0096] Proteins can be chemically modified at the N-terminus. Using polyethylene glycol as an illustration of such a composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (*i.e.*, separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus may be accomplished by reductive alkylation, which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

Substantially Identical *CDK10, FPGT, PCLO* or *REPS2* Nucleic Acids and Polypeptides

[0097] *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences and *CDK10, FPGT, PCLO* or *REPS2* polypeptide sequences that are substantially identical to the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4 and the polypeptide sequences of Figures 8A-8C, 9, 10A-10B and 11, respectively, are included herein. The term "substantially identical" as used herein refers to two or more nucleic acids or polypeptides sharing one or more identical nucleotide sequences or polypeptide sequences, respectively. Included are nucleotide sequences or polypeptide sequences that are 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more (each often within a 1%, 2%, 3% or 4% variability) identical to the *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence in SEQ ID NO: 1, 2, 3 or 4 or the *CDK10, FPGT, PCLO* or *REPS2* polypeptide sequences of Figures 8A-8C, 9, 10A-10B and 11. One test for determining whether two nucleic acids are substantially identical is to determine the percent of identical nucleotide sequences or polypeptide sequences shared between the nucleic acids or polypeptides.

[0098] Calculations of sequence identity are often performed as follows. Sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). The length of a reference sequence aligned for comparison purposes is sometimes 30% or more, 40% or more, 50% or more, often 60% or more, and more often 70%, 80%, 90%, 100% of the length of the reference sequence. The nucleotides or amino acids at corresponding nucleotide or polypeptide positions, respectively, are then compared among the two sequences. When a position in the first sequence is occupied by the same nucleotide or amino acid as the corresponding position in the second sequence, the nucleotides or amino acids are deemed to be identical at that position. The percent identity between the two sequences is a function of the number of identical

positions shared by the sequences, taking into account the number of gaps, and the length of each gap, introduced for optimal alignment of the two sequences.

[0099] Comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. Percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of Meyers & Miller, *CABIOS 4:* 11-17 (1989), which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. Also, percent identity between two amino acid sequences can be determined using the Needleman & Wunsch, *J. Mol. Biol. 48:* 444-453 (1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at the http address www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. Percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at http address www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A set of parameters often used is a Blossum 62 scoring matrix with a gap open penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

[0100] Another manner for determining if two nucleic acids are substantially identical is to assess whether a polynucleotide homologous to one nucleic acid will hybridize to the other nucleic acid under stringent conditions. As use herein, the term "stringent conditions" refers to conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. , 6.3.1-6.3.6 (1989). Aqueous and non-aqueous methods are described in that reference and either can be used. An example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50°C. Another example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 55°C. A further example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C. Often, stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C. More often, stringency conditions are 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C.

[0101] An example of a substantially identical nucleotide sequence to SEQ ID NO: 1, 2, 3 or 4 is one that has a different nucleotide sequence and still encodes a polypeptide sequence set forth in Figures 8A-8C, 9, 10A-10B and 11. Another example is a nucleotide sequence that encodes a polypeptide having

a polypeptide sequence that is more than 70% identical to, sometimes more than 75%, 80%, or 85% identical to, and often more than 90% and 95% or more identical to the polypeptide sequences set forth in Figures 8A-8C, 9, 10A-10B and 11.

[0102] *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences and polypeptide sequences can be used as "query sequences" to perform a search against public databases to identify other family members or related sequences, for example. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul *et al., J. Mol. Biol. 215:* 403-10 (1990). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to *CDK10, FPGT, PCLO* or *REPS2* nucleic acid molecules. BLAST polypeptide searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to *CDK10, FPGT, PCLO* or *REPS2* polypeptides. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al., Nucleic Acids Res. 25(17):* 3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used (*see* the http address www.ncbi.nlm.nih.gov).

[0103] A nucleic acid that is substantially identical to the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4 may include polymorphic sites at positions equivalent to those described herein (*e.g.*, position 146311 in SEQ ID NO: 1, 2, 3 or 4) when the sequences are aligned. For example, using the alignment procedures described herein, SNPs in a sequence substantially identical to the sequence of SEQ ID NO: 1, 2, 3 or 4 can be identified at nucleotide positions that match (*i.e.*, align) with nucleotides at SNP positions in SEQ ID NO: 1, 2, 3 or 4. Also, where a polymorphic variation is an insertion or deletion, insertion or deletion of a nucleotide sequence from a reference sequence can change the relative positions of other polymorphic sites in the nucleotide sequence.

[0104] Substantially identical *CDK10, FPGT, PCLO* or *REPS2* nucleotide and polypeptide sequences include those that are naturally occurring, such as allelic variants (same locus), splice variants, homologs (different locus), and orthologs (different organism) or can be non-naturally occurring. Non-naturally occurring variants can be generated by mutagenesis techniques, including those applied to polynucleotides, cells, or organisms. The variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions (as compared in the encoded product). Orthologs, homologs, allelic variants, and splice variants can be identified using methods known in the art. These variants normally comprise a nucleotide sequence encoding a polypeptide that is 50%, about 55% or more, often about 70-75% or more, more often about 80-85% or more, and typically about 90-95% or more identical to the amino acid sequences shown in Figures 8A-8C, 9, 10A-10B and 11 or a fragment thereof. Such nucleic acid molecules can readily be identified as being able to hybridize under

stringent conditions to the nucleotide sequence shown in SEQ ID NO: 1, 2, 3 or 4 or a fragment of this sequence. Nucleic acid molecules corresponding to orthologs, homologs, and allelic variants of the *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence can further be identified by mapping the sequence to the same chromosome or locus as the *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence or variant.

[0105] Also, substantially identical *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequences may include codons that are altered with respect to the naturally occurring sequence for enhancing expression of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or polypeptide variant in a particular expression system. For example, the nucleic acid can be one in which one or more codons are altered, and often 10% or more or 20% or more of the codons are altered for optimized expression in bacteria (*e.g.*, *E. coli.*), yeast (*e.g.*, *S. cervesiae*), human (*e.g.*, 293 cells), insect, or rodent (*e.g.*, hamster) cells.

Methods for Identifying Subjects at Risk of Melanoma and Risk of Melanoma

[0106] Methods for determining whether a subject is at risk of melanoma are provided herein. These methods include detecting the presence or absence of one or more polymorphic variations associated with melanoma in a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence, or substantially identical sequence thereof, in a sample from a subject, where the presence of such a polymorphic variation is indicative of the subject being at risk of melanoma. These genetic tests are useful for prognosing and/or diagnosing melanoma and often are useful for determining whether an individual is at an increased, intermediate or decreased risk of developing or having melanoma.

[0107] Thus, featured herein is a method for identifying a subject at risk of melanoma, which comprises detecting in a nucleic acid sample from the subject the presence or absence of a polymorphic variation associated with melanoma at a polymorphic site in a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence. The nucleotide sequence often is selected from the group consisting of: (a) a nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; (b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; (c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and (d) a fragment of a nucleotide sequence of (a), (b), or (c), where the fragment often comprises a polymorphic site; whereby the presence of the polymorphic variation is indicative of the subject being at risk of melanoma. A polymorphic variation assayed in the genetic test often is located in an intron, sometimes in a region surrounding the *CDK10, FPGT, PCLO* or *REPS2* open reading frame (*e.g.*, within 50 kilobases (kb), 40 kb, 30 kb, 20 kb, 15, kb, 10 kb, 5 kb, 4 kb, 3 kb, 2 kb, or 1 kb of the open reading frame initiation site or termination site), and sometimes in an exon. Sometimes the polymorphic variation is not located in an exon (*e.g.*, it sometimes is located in an intron or region upstream or downstream of a terminal intron or exon).

[0108] Results from such genetic tests may be combined with other test results to diagnose melanoma. For example, genetic test results may be gathered, a patient sample may be ordered based on a determined predisposition to melanoma (*e.g.*, a skin biopsy), the patient sample is analyzed, and the results of the analysis may be utilized to diagnose melanoma. Also, melanoma diagnostic tests are generated by stratifying populations into subpopulations having different progressions of melanoma and detecting polymorphic variations associated with different progressions of the melanoma, as described in further detail hereafter. In another embodiment, genetic test results are gathered, a patient's risk factors for developing melanoma are analyzed (*e.g.*, exposure to sun and skin pigmentation), and a patient sample may be ordered based on a determined risk of melanoma.

[0109] Risk of melanoma sometimes is expressed as a probability, such as an odds ratio, percentage, or risk factor. The risk assessment is based upon the presence or absence of one or more polymorphic variants described herein, and also may be based in part upon phenotypic traits of the individual being tested. Methods for calculating risks based upon patient data are well known (*see, e.g.*, Agresti, *Categorical Data Analysis*, 2nd Ed. 2002. Wiley). Allelotyping and genotyping analyses may be carried out in populations other than those exemplified herein to enhance the predictive power of the prognostic method. These further analyses are executed in view of the exemplified procedures described herein, and may be based upon the same polymorphic variations or additional polymorphic variations.

[0110] The nucleic acid sample typically is isolated from a biological sample obtained from a subject. For example, nucleic acid can be isolated from blood, saliva, sputum, urine, cell scrapings, and biopsy tissue. The nucleic acid sample can be isolated from a biological sample using standard techniques, such as the technique described in Example 2. As used herein, the term "subject" refers primarily to humans but also refers to other mammals such as dogs, cats, and ungulates (*e.g.*, cattle, sheep, and swine). Subjects also include avians (*e.g.*, chickens and turkeys), reptiles, and fish (*e.g.*, salmon), as embodiments described herein can be adapted to nucleic acid samples isolated from any of these organisms. The nucleic acid sample may be isolated from the subject and then directly utilized in a method for determining the presence of a polymorphic variant, or alternatively, the sample may be isolated and then stored (*e.g.*, frozen) for a period of time before being subjected to analysis.

[0111] The presence or absence of a polymorphic variant is determined using one or both chromosomal complements represented in the nucleic acid sample. Determining the presence or absence of a polymorphic variant in both chromosomal complements represented in a nucleic acid sample from a subject having a copy of each chromosome is useful for determining the zygosity of an individual for the polymorphic variant (*i.e.*, whether the individual is homozygous or heterozygous for the polymorphic variant). Any oligonucleotide-based diagnostic may be utilized to determine whether a sample includes the presence or absence of a polymorphic variant in a sample. For example, primer extension methods, ligase sequence determination methods (*e.g.*, U.S. Pat. Nos. 5,679,524 and 5,952,174, and WO

01/27326), mismatch sequence determination methods (*e.g.*, U.S. Pat. Nos. 5,851,770; 5,958,692; 6,110,684; and 6,183,958), microarray sequence determination methods, restriction fragment length polymorphism (RFLP), single strand conformation polymorphism detection (SSCP) (*e.g.*, U.S. Pat. Nos. 5,891,625 and 6,013,499), PCR-based assays (*e.g.*, TAQMAN® PCR System (Applied Biosystems)), and nucleotide sequencing methods may be used.

[0112] Oligonucleotide extension methods typically involve providing a pair of oligonucleotide primers in a polymerase chain reaction (PCR) or in other nucleic acid amplification methods for the purpose of amplifying a region from the nucleic acid sample that comprises the polymorphic variation. One oligonucleotide primer is complementary to a region 3' of the polymorphism and the other is complementary to a region 5' of the polymorphism. A PCR primer pair may be used in methods disclosed in U.S. Pat. Nos. 4,683,195; 4,683,202, 4,965,188; 5,656,493; 5,998,143; 6,140,054; WO 01/27327; and WO 01/27329 for example. PCR primer pairs may also be used in any commercially available machines that perform PCR, such as any of the GENEAMP® Systems available from Applied Biosystems. Also, those of ordinary skill in the art will be able to design oligonucleotide primers based upon the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4 without undue experimentation using knowledge readily available in the art.

[0113] Also provided are extension oligonucleotides that hybridize to the amplified fragment adjacent to the polymorphic variation. As used herein, the term "adjacent" refers to the 3' end of the extension oligonucleotide being sometimes 1 nucleotide from the 5' end of the polymorphic site, often 2 or 3, and at times 4, 5, 6, 7, 8, 9, or 10 nucleotides from the 5' end of the polymorphic site, in the nucleic acid when the extension oligonucleotide is hybridized to the nucleic acid. The extension oligonucleotide then is extended by one or more nucleotides, often 2 or 3 nucleotides, and the number and/or type of nucleotides that are added to the extension oligonucleotide determine whether the polymorphic variant is present. Oligonucleotide extension methods are disclosed, for example, in U.S. Pat. Nos. 4,656,127; 4,851,331; 5,679,524; 5,834,189; 5,876,934; 5,908,755; 5,912,118; 5,976,802; 5,981,186; 6,004,744; 6,013,431; 6,017,702; 6,046,005; 6,087,095; 6,210,891; and WO 01/20039. Oligonucleotide extension methods using mass spectrometry are described, for example, in U.S. Pat. Nos. 5,547,835; 5,605,798; 5,691,141; 5,849,542; 5,869,242; 5,928,906; 6,043,031; and 6,194,144, and a method often utilized is described herein in Example 2.

[0114] A microarray can be utilized for determining whether a polymorphic variant is present or absent in a nucleic acid sample. A microarray sometimes includes an oligonucleotides described herein, and methods for making and using oligonucleotide microarrays suitable for prognostic use are disclosed in U.S. Pat. Nos. 5,492,806; 5,525,464; 5,589,330; 5,695,940; 5,849,483; 6,018,041; 6,045,996; 6,136,541; 6,142,681; 6,156,501; 6,197,506; 6,223,127; 6,225,625; 6,229,911; 6,239,273; WO 00/52625; WO 01/25485; and WO 01/29259. The microarray typically comprises a solid support and the

oligonucleotides sometimes are linked to the solid support by covalent or non-covalent interactions. The oligonucleotides sometimes are linked to the solid support directly or by a spacer molecule. A microarray sometimes comprise one or more oligonucleotides complementary to a portion of SEQ ID NO: 1, 2, 3 or 4, or complementary to a variant described herein.

[0115] A kit may also be utilized for determining whether a polymorphic variant is present or absent in a nucleic acid sample. A kit often comprises one or more pairs of oligonucleotide primers useful for amplifying a fragment of SEQ ID NO: 1, 2, 3 or 4 or a substantially identical sequence thereof, where the fragment includes a polymorphic site. The kit sometimes comprises a polymerizing agent, for example, a thermostable nucleic acid polymerase such as one disclosed in U.S. Pat. Nos. 4,889,818 or 6,077,664. Also, the kit often comprises an elongation oligonucleotide that hybridizes to a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid in a nucleic acid sample adjacent to the polymorphic site. Where the kit includes an elongation oligonucleotide, it also often comprises chain elongating nucleotides, such as dATP, dTTP, dGTP, dCTP, and dITP, including analogs of dATP, dTTP, dGTP, dCTP and dITP, provided that such analogs are substrates for a thermostable nucleic acid polymerase and can be incorporated into a nucleic acid chain elongated from the extension oligonucleotide. Along with chain elongating nucleotides would be one or more chain terminating nucleotides such as ddATP, ddTTP, ddGTP, ddCTP, and the like. In an embodiment, the kit comprises one or more oligonucleotide primer pairs, a polymerizing agent, chain elongating nucleotides, at least one elongation oligonucleotide, and one or more chain terminating nucleotides. Kits optionally include buffers, vials, microtitre plates, and instructions for use. *CDK10, FPGT, PCLO* or *REPS2* directed hits may be utilized to prognose or diagnose melanoma for a significant fraction of melanoma occurrences, such as in 50% or more melanoma occurrences, or sometimes 60% or more, 70% or more, 80% or more, 90% or more, or 95% or more melanoma occurrences.

[0116] Using a polymorphism detection technology (*e.g.*, a technique described above or below in Example 2), mutations and polymorphisms in or around the *CDK10, FPGT, PCLO* or *REPS2* locus may be detected in melanocytic lesions, which include nevi, radial growth phase (RGP) melanomas, vertical growth phase (VGP) melanomas, and melanoma metastases. The mutations can be detected within 50 kilobases (kb), 40 kb, 30 kb, 20 kb, 15, kb, 10 kb, 5 kb, 4 kb, 3 kb, 2 kb, or 1 kb from the *CDK10, FPGT, PCLO* or *REPS2* open reading frame initiation or termination site. Therefore, provided herein are methods for genotyping *CDK10, FPGT, PCLO* or *REPS2* mutations in melanocytic lesions and metastases (*e.g.*, described in Example 2). Mutations in or around the *CDK10, FPGT, PCLO* or *REPS2* loci present in later stage melanomas, such as VGP melanomas and melanoma metastases, are indicative of melanomas particularly likely to continue to progress and/or metastasize (*e.g.*, from RGP to VGP melanoma or melanoma metastases), *i.e.*, aggressive melanomas. Thus, provided herein are methods for identifying subjects at risk of a progressive or aggressive melanoma by determining the presence or

absence of one or more *CDK10, FPGT, PCLO* or *REPS2* mutations in the DNA sample of a subject that exist in melanocytic lesions and/or metastases. Identifying the presence of one or more of these mutations is useful for identifying subjects in need of aggressive treatments of melanoma, and once identified using such methods, a subject often is given information concerning preventions and treatments of the disease, and sometimes is treated with an aggressive melanoma treatment method (*e.g.*, surgery or administration of drugs), as described in more detail hereafter.

[0117] Determining the presence of a polymorphic variant, or a combination of two or more polymorphic variants, in a nucleic acid set forth in SEQ ID NOs: 1, 2, 3 and/or 4 of the sample often is indicative of a predisposition to melanoma. In certain embodiments, nucleic acid variants of other loci, such as the *BRAF* locus described in U.S. application no. 10/661,966 filed September 11, 2003 and any loci described in the concurrently filed applications directed to melanoma (*e.g., NRP1, NID2* and *ENDO180*), are detected in combination with one or more nucleic acid variants in the *CDK10, FPGT, PCLO* or *REPS2* loci.

[0118] As noted above, a cytosine at position 139 in SEQ ID NO: 1, a guanine at position 3525 in SEQ ID NO: 1, a thymine at position 7960 in SEQ ID NO: 1, a guanine at position 9640 in SEQ ID NO: 1, a thymine at position 14845 in SEQ ID NO: 1, a cytosine at position 19300 in SEQ ID NO: 1, a cytosine at position 21338 in SEQ ID NO: 1, a thymine at position 21343 in SEQ ID NO: 1, a guanine at position 42477 in SEQ ID NO: 1, a thymine at position 43164 in SEQ ID NO: 1, a thymine at position 43734 in SEQ ID NO: 1, an adenine at position 44029 in SEQ ID NO: 1, a thymine at position 44986 in SEQ ID NO: 1, a guanine at position 53410 in SEQ ID NO: 1, a cytosine at position 83831 in SEQ ID NO: 1, a cytosine at position 85666 in SEQ ID NO: 1, a cytosine at position 88389 in SEQ ID NO: 1, a guanine at position 92523 in SEQ ID NO: 1, a thymine at position 17207 in SEQ ID NO: 2, a guanine at position 19057 in SEQ ID NO: 2, a guanine at position 32252 in SEQ ID NO: 2, a thymine at position 33887 in SEQ ID NO: 2, a cytosine at position 36394 in SEQ ID NO: 2, an adenine at position 39184 in SEQ ID NO: 2, a thymine at position 40707 in SEQ ID NO: 2, an adenine at position 42857 in SEQ ID NO: 2, a cytosine at position 45812 in SEQ ID NO: 2, a thymine at position 46643 in SEQ ID NO: 2, a cytosine at position 47007 in SEQ ID NO: 2, a guanine at position 50015 in SEQ ID NO: 2, a guanine at position 50442 in SEQ ID NO: 2, an adenine at position 51203 in SEQ ID NO: 2, a guanine at position 51983 in SEQ ID NO: 2, an adenine at position 57523 in SEQ ID NO: 2, an adenine at position 60557 in SEQ ID NO: 2, a thymine at position 60645 in SEQ ID NO: 2, an adenine at position 64531 in SEQ ID NO: 2, a thymine at position 83870 in SEQ ID NO: 2, a cytosine at position 4029 in SEQ ID NO: 3, an adenine at position 5343 in SEQ ID NO: 3, an adenine at position 8817 in SEQ ID NO: 3, a thymine at position 18596 in SEQ ID NO: 3, an adenine at position 18602 in SEQ ID NO: 3, a cytosine at position 21583 in SEQ ID NO: 3, a thymine at position 36594 in SEQ ID NO: 3, a thymine at position 37994 in SEQ ID NO: 3, an adenine at position 38293 in SEQ ID NO: 3, a cytosine at position 46972 in SEQ ID

NO: 3, an adenine at position 48524 in SEQ ID NO: 3, a thymine at position 72488 in SEQ ID NO: 3 and a cytosine at position 38753 in SEQ ID NO: 4 are in particular associated with an increased risk of melanoma. An individual identified as having a predisposition to melanoma may be heterozygous or homozygous with respect to the allele associated with melanoma. A subject homozygous for an allele associated with an increased risk of melanoma (e.g., a thymine at position 7960 in SEQ ID NO: 1) is at a comparatively high risk of melanoma, a subject heterozygous for an allele associated with an increased risk of melanoma is at a comparatively intermediate risk of melanoma, and a subject homozygous for an allele associated with a decreased risk of melanoma (*e.g.*, an adenine at position 7960 in a SEQ ID NO: 1, see Examples section below) is at a comparatively low risk of melanoma. A genotype may be assessed for a complementary strand, such that the complementary nucleotide at a particular position is detected (*e.g.*, if a thymine or adenine is detected at position 7960 in SEQ ID NO: 1, the complementary strand would yield an adenine or thymine, respectively, where the adenine is associated with increased risk of melanoma).

[0119] Also featured are methods for determining risk of melanoma and/or identifying a subject at risk of melanoma by contacting a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or protein from a subject with an antibody that specifically binds to an epitope associated with increased risk of melanoma in the polypeptide.

Applications of Genomic Information to Pharmacogenomics

[0120] Pharmacogenomics is a discipline that involves tailoring a treatment for a subject according to the subject's genotype as a particular treatment regimen may exert a differential effect depending upon the subject's genotype. Based upon the outcome of a prognostic test described herein, a clinician or physician may target pertinent information and preventative or therapeutic treatments to a subject who would be benefited by the information or treatment and avoid directing such information and treatments to a subject who would not be benefited (*e.g.*, the treatment has no therapeutic effect and/or the subject experiences adverse side effects).

[0121] For example, where a candidate therapeutic exhibits a significant interaction with a major allele and a comparatively weak interaction with a minor allele (*e.g.*, an order of magnitude or greater difference in the interaction), such a therapeutic typically would not be administered to a subject genotyped as being homozygous for the minor allele, and sometimes not administered to a subject genotyped as being heterozygous for the minor allele. In another example, where a candidate therapeutic is not significantly toxic when administered to subjects who are homozygous for a major allele but is comparatively toxic when administered to subjects heterozygous or homozygous for a minor allele, the candidate therapeutic is not typically administered to subjects who are genotyped as being heterozygous or homozygous with respect to the minor allele.

[0122] The prognostic methods described herein are applicable to general pharmacogenomic approaches towards addressing melanoma. For example, a nucleic acid sample from an individual may be subjected to a prognostic test described herein. Where one or more polymorphic variations associated with increased risk of melanoma are identified in a subject, one or more melanoma treatments or prophylactic regimens may be prescribed to that subject. Subjects genotyped as having one or more of the alleles described herein that are associated with increased risk of melanoma often are prescribed a prophylactic regimen designed to minimize the occurance of melanoma. An example of a prophylactic regimen often prescribed is directed towards minimizing ultraviolet (UV) light exposure. Such a regimen may include, for example, prescription of a lotion applied to the skin that minimizes UV penetration and/or counseling individuals of other practices for reducing UV exposure, such as by wearing protective clothing and minimizing sun exposure.

[0123] In certain embodiments, a treatment regimen is specifically prescribed and/or administered to individuals who will most benefit from it based upon their risk of developing melanoma assessed by the prognostic methods described herein. Thus, provided are methods for identifying a subject predisposed to melanoma and then prescribing a therapeutic or preventative regimen to individuals identified as having a predisposition. Thus, certain embodiments are directed to a method for reducing melanoma in a subject, which comprises: detecting the presence or absence of a polymorphic variant associated with melanoma in a nucleotide sequence set forth in Figure 1 in a nucleic acid sample from a subject, where the nucleotide sequence comprises a polynucleotide sequence selected from the group consisting of: (a) a nucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4; (b) a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; (c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4 or a nucleotide sequence about 90% or more identical to the nucleotide sequence in SEQ ID NO: 1, 2, 3 or 4; and (d) a fragment of a polynucleotide sequence of (a), (b), or (c); and prescribing or administering a treatment regimen to a subject from whom the sample originated where the presence of a polymorphic variation associated with melanoma is detected in the nucleotide sequence. In these methods, predisposition results may be utilized in combination with other test results to diagnose melanoma.

[0124] The treatment sometimes is preventative (*e.g.*, is prescribed or administered to reduce the probability that a melanoma associated condition arises or progresses), sometimes is therapeutic, and sometimes delays, alleviates or halts the progression of a melanoma associated condition. Any known preventative or therapeutic treatment for alleviating or preventing the occurrence of a melanoma associated disorder is prescribed and/or administered. For example, the treatment sometimes is or includes a drug that reduces melanoma, including, for example, cisplatin, carmustine (BCNU), vinblastine, vincristine, and bleomycin, and/or a molecule that interacts with a nucleic acid or

polypeptide described hereafter. In another example, the melanoma treatment is surgery. Surgery to remove (excise) a melanoma is the standard treatment for this disease. It is necessary to remove not only the tumor but also some normal tissue around it in order to minimize the chance that any cancer will be left in the area. It is common for lymph nodes near the tumor to be removed during surgery because cancer can spread through the lymphatic system. Surgery is generally not effective in controlling melanoma that is known to have spread to other parts of the body. In such cases, doctors may use other methods of treatment, such as chemotherapy, biological therapy, radiation therapy, or a combination of these methods.

[0125] As therapeutic approaches for melanoma continue to evolve and improve, the goal of treatments for melanoma related disorders is to intervene even before clinical signs (*e.g.*, identification of irregular nevi based on A- asymmetry, B- border irregularity, C- color variation, D- diameter of > 6 mm as described by Friedman RJ, *et al.* in *CA Cancer J Clin.* 1985 May-Jun;35(3):130-51) first manifest. Thus, genetic markers associated with susceptibility to melanoma prove useful for early diagnosis, prevention and treatment of melanoma.

[0126] As melanoma preventative and treatment information can be specifically targeted to subjects in need thereof (*e.g.*, those at risk of developing melanoma or those that have early signs of melanoma), provided herein is a method for preventing or reducing the risk of developing melanoma in a subject, which comprises: (a) detecting the presence or absence of a polymorphic variation associated with melanoma at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject; (b) identifying a subject with a predisposition to melanoma, whereby the presence of the polymorphic variation is indicative of a predisposition to melanoma in the subject; and (c) if such a predisposition is identified, providing the subject with information about methods or products to prevent or reduce melanoma or to delay the onset of melanoma. Also provided is a method of targeting information or advertising to a subpopulation of a human population based on the subpopulation being genetically predisposed to a disease or condition, which comprises: (a) detecting the presence or absence of a polymorphic variation associated with melanoma at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject; (b) identifying the subpopulation of subjects in which the polymorphic variation is associated with melanoma; and (c) providing information only to the subpopulation of subjects about a particular product which may be obtained and consumed or applied by the subject to help prevent or delay onset of the disease or condition.

[0127] Pharmacogenomics methods also may be used to analyze and predict a response to a melanoma treatment or a drug. For example, if pharmacogenomics analysis indicates a likelihood that an individual will respond positively to a melanoma treatment with a particular drug, the drug may be administered to the individual. Conversely, if the analysis indicates that an individual is likely to respond negatively to treatment with a particular drug, an alternative course of treatment may be prescribed. A

negative response may be defined as either the absence of an efficacious response or the presence of toxic side effects. The response to a therapeutic treatment can be predicted in a background study in which subjects in any of the following populations are genotyped: a population that responds favorably to a treatment regimen, a population that does not respond significantly to a treatment regimen, and a population that responds adversely to a treatment regiment (*e.g.*, exhibits one or more side effects). These populations are provided as examples and other populations and subpopulations may be analyzed. Based upon the results of these analyses, a subject is genotyped to predict whether he or she will respond favorably to a treatment regimen, not respond significantly to a treatment regimen, or respond adversely to a treatment regimen.

[0128] The prognostic tests described herein also are applicable to clinical drug trials. One or more polymorphic variants indicative of response to an agent for treating melanoma or to side effects to an agent for treating melanoma may be identified using the methods described herein. Thereafter, potential participants in clinical trials of such an agent may be screened to identify those individuals most likely to respond favorably to the drug and exclude those likely to experience side effects. In that way, the effectiveness of drug treatment may be measured in individuals who respond positively to the drug, without lowering the measurement as a result of the inclusion of individuals who are unlikely to respond positively in the study and without risking undesirable safety problems.

[0129] Thus, another embodiment is a method of selecting an individual for inclusion in a clinical trial of a treatment or drug comprising the steps of: (a) obtaining a nucleic acid sample from an individual; (b) determining the identity of a polymorphic variation which is associated with a positive response to the treatment or the drug, or at least one polymorphic variation which is associated with a negative response to the treatment or the drug in the nucleic acid sample, and (c) including the individual in the clinical trial if the nucleic acid sample contains said polymorphic variation associated with a positive response to the treatment or the drug or if the nucleic acid sample lacks said polymorphic variation associated with a negative response to the treatment or the drug. In addition, the methods for selecting an individual for inclusion in a clinical trial of a treatment or drug encompass methods with any further limitation described in this disclosure, or those following, specified alone or in any combination. The polymorphic variation may be in a sequence selected individually or in any combination from the group consisting of (i) a polynucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4; (ii) a polynucleotide sequence that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; (iii) a polynucleotide sequence that encodes a polypeptide having an amino acid sequence identical to or 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and (iv) a fragment of a polynucleotide sequence of (i), (ii), or (iii) comprising the polymorphic site. The including step (c) optionally comprises administering the drug or the treatment to the individual if the nucleic acid sample

contains the polymorphic variation associated with a positive response to the treatment or the drug and the nucleic acid sample lacks said biallelic marker associated with a negative response to the treatment or the drug.

[0130] Also provided herein is a method of partnering between a diagnostic/prognostic testing provider and a provider of a consumable product, which comprises: (a) the diagnostic/prognostic testing provider detects the presence or absence of a polymorphic variation associated with melanoma at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject; (b) the diagnostic/prognostic testing provider identifies the subpopulation of subjects in which the polymorphic variation is associated with melanoma; (c) the diagnostic/prognostic testing provider forwards information to the subpopulation of subjects about a particular product which may be obtained and consumed or applied by the subject to help prevent or delay onset of the disease or condition; and (d) the provider of a consumable product forwards to the diagnostic test provider a fee every time the diagnostic/prognostic test provider forwards information to the subject as set forth in step (c) above.

Compositions Comprising a *CDK10, FPGT, PCLO* or *REPS2* Directed Molecule

[0131] Featured herein is a composition comprising a melanoma cell and one or more *CDK10, FPGT, PCLO* or *REPS2* directed molecules. *CDK10, FPGT, PCLO* or *REPS2* directed molecules include, but are not limited to, a compound that binds to a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or polypeptide; an RNAi or siRNA molecule having a strand complementary to a *CDK10, FPGT, PCLO* or *REPS2* DNA sequence; an antisense nucleic acid complementary to an RNA encoded by a *CDK10, FPGT, PCLO* or *REPS2* DNA sequence; a ribozyme that hybridizes to a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence; an *CDK10, FPGT, PCLO* or *REPS2* polypeptide, protein or fragment thereof, or a nucleic acid that encodes the foregoing; a nucleic acid aptamer that specifically binds a *CDK10, FPGT, PCLO* or *REPS2* polypeptide, protein, nucleic acid or variant thereof; and an antibody or fragment thereof that specifically binds to a *CDK10, FPGT, PCLO* or *REPS2* polypeptide, protein, nucleic acid or variant thereof. Compositions comprising an anitbody often include an adjuvant known in the art. The melanoma cell may be in a group of melanoma cells and/or other types of cells cultured *in vitro* or in a tissue having melanoma cells (*e.g.*, a melanocytic lesion) maintained *in vitro* or present in an animal in vivo (*e.g.*, a rat, mouse, ape or human). In certain embodiments, a composition comprises a component from a melanoma cell or from a subject having a melanoma cell instead of the melanoma cell or in addition to the melanoma cell, where the component sometimes is a nucleic acid molecule (*e.g.*, genomic DNA), a protein mixture or isolated protein, for example. The aforementioned compositions have utility in diagnostic, prognostic and pharmacogenomic methods described previously and in melanoma therapeutics described hereafter. Certain *CDK10, FPGT, PCLO* or *REPS2* directed molecules are described in greater detail below.

Compounds

[0132] Compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive (see, *e.g.*, Zuckermann *et al., J. Med. Chem.37:* 2678-85 (1994)); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; "one-bead one-compound" library methods; and synthetic library methods using affinity chromatography selection. Biological library and peptoid library approaches are typically limited to peptide libraries, while the other approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, *Anticancer Drug Des. 12:* 145, (1997)). Examples of methods for synthesizing molecular libraries are described, for example, in DeWitt *et al., Proc. Natl. Acad. Sci. U.S.A. 90:* 6909 (1993); Erb *et al., Proc. Natl. Acad. Sci. USA 91:* 11422 (1994); Zuckermann *et al., J. Med. Chem. 37:* 2678 (1994); Cho *et al., Science 261:* 1303 (1993); Carrell *et al., Angew. Chem. Int. Ed. Engl. 33:* 2059 (1994); Carell *et al., Angew. Chem. Int. Ed. Engl. 33:* 2061 (1994); and in Gallop *et al., J. Med. Chem. 37:* 1233 (1994).

[0133] Libraries of compounds may be presented in solution (*e.g.*, Houghten, *Biotechniques 13:* 412-421 (1992)), or on beads (Lam, *Nature 354:* 82-84 (1991)), chips (Fodor, *Nature 364:* 555-556 (1993)), bacteria or spores (Ladner, United States Patent No. 5,223,409), plasmids (Cull *et al., Proc. Natl. Acad. Sci. USA 89:* 1865-1869 (1992)) or on phage (Scott and Smith, *Science 249:* 386-390 (1990); Devlin, *Science 249:* 404-406 (1990); Cwirla *et al., Proc. Natl. Acad. Sci. 87:* 6378-6382 (1990); Felici, *J. Mol. Biol. 222:* 301-310 (1991); Ladner *supra.*).

[0134] A compound may alter expression or activity of *CDK10, FPGT, PCLO* or *REPS2* polypeptides and may be a small molecule. Small molecules include, but are not limited to, peptides, peptidomimetics (*e.g.*, peptoids), amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e.*, including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

Antisense Nucleic Acid Molecules, Ribozymes, RNAi, siRNA and Modified *CDK10, FPGT, PCLO* or *REPS2* Nucleic Acid Molecules

[0135] An "antisense" nucleic acid refers to a nucleotide sequence complementary to a "sense" nucleic acid encoding a polypeptide, *e.g.*, complementary to the coding strand of a double-stranded

cDNA molecule or complementary to an mRNA sequence. The antisense nucleic acid can be complementary to an entire *CDK10, FPGT, PCLO* or *REPS2* coding strand or to only a portion thereof (*e.g.*, the coding region of human *CDK10, FPGT, PCLO* or *REPS2* in SEQ ID NO: 1, 2, 3 or 4). In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding *CDK10, FPGT, PCLO* or *REPS2* (*e.g.*, 5' and 3' untranslated regions).

[0136] An antisense nucleic acid can be designed such that it is complementary to the entire coding region of *CDK10, FPGT, PCLO* or *REPS2* mRNA, and often the antisense nucleic acid is an oligonucleotide antisense to only a portion of a coding or noncoding region of *CDK10, FPGT, PCLO* or *REPS2* mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of *CDK10, FPGT, PCLO* or *REPS2* mRNA, *e.g.*, between the -10 and +10 regions of the target gene nucleotide sequence of interest. An antisense oligonucleotide can be, for example, about 7, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or more nucleotides in length. The antisense nucleic acids, which include the ribozymes described hereafter, can be designed to target *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or *CDK10, FPGT, PCLO* or *REPS2* nucleic acid variants. Among the variants, minor alleles and major alleles can be targeted, and those associated with a higher risk of melanoma are often designed, tested, and administered to subjects.

[0137] An antisense nucleic acid can be constructed using chemical synthesis and enzymatic ligation reactions using standard procedures. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Antisense nucleic acid also can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

[0138] When utilized as therapeutics, antisense nucleic acids typically are administered to a subject (*e.g.*, by direct injection at a tissue site) or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a *CDK10, FPGT, PCLO* or *REPS2* polypeptide and thereby inhibit expression of the polypeptide, for example, by inhibiting transcription and/or translation. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then are administered systemically. For systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, for example, by linking antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. Antisense nucleic acid molecules can also be delivered to cells using the vectors described

herein. Sufficient intracellular concentrations of antisense molecules are achieved by incorporating a strong promoter, such as a pol II or pol III promoter, in the vector construct.

[0139] Antisense nucleic acid molecules sometimes are α-anomeric nucleic acid molecules. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al., Nucleic Acids. Res. 15:* 6625-6641 (1987)). Antisense nucleic acid molecules can also comprise a 2'-o-methylribonucleotide (Inoue *et al., Nucleic Acids Res. 15:* 6131-6148 (1987)) or a chimeric RNA-DNA analogue (Inoue *et al., FEBS Lett. 215:* 327-330 (1987)). Antisense nucleic acids sometimes are composed of DNA or PNA or any other nucleic acid derivatives described previously.

[0140] In another embodiment, an antisense nucleic acid is a ribozyme. A ribozyme having specificity for a *CDK10, FPGT, PCLO* or *REPS2* encoding nucleic acid can include one or more sequences complementary to the nucleotide sequence of a *CDK10, FPGT, PCLO* or *REPS2* DNA sequence disclosed herein (*e.g.*, SEQ ID NO: 1, 2, 3 or 4), and a sequence having a known catalytic region responsible for mRNA cleavage (*see e.g.*, U.S. Pat. No. 5,093,246 or Haselhoff and Gerlach, *Nature 334:* 585-591 (1988)). For example, a derivative of a *Tetrahymena* L-19 IVS RNA is sometimes utilized in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a *CDK10, FPGT, PCLO* or *REPS2* encoding mRNA (*see e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Also, *CDK10, FPGT, PCLO* or *REPS2* mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (*see e.g.*, Bartel & Szostak, *Science 261:* 1411-1418 (1993)).

[0141] *CDK10, FPGT, PCLO* or *REPS2* directed molecules include in certain embodiments nucleic acids that can form triple helix structures with a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence, especially one that includes a regulatory region that controls *CDK10, FPGT, PCLO* or *REPS2* expression. *CDK10, FPGT, PCLO* or *REPS2* gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the *CDK10, FPGT, PCLO* or *REPS2* (*e.g.*, *CDK10, FPGT, PCLO* or *REPS2* promoter and/or enhancers) to form triple helical structures that prevent transcription of the *CDK10, FPGT, PCLO* or *REPS2* gene in target cells (*see e.g.*, Helene, *Anticancer Drug* Des. 6(6): 569-84 (1991); Helene *et al., Ann. N.Y. Acad. Sci. 660:* 27-36 (1992); and Maher, *Bioassays 14(12):* 807-15 (1992). Potential sequences that can be targeted for triple helix formation can be increased by creating a so-called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5'-3', 3'-5' manner, such that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch of either purines or pyrimidines to be present on one strand of a duplex.

[0142] *CDK10, FPGT, PCLO* or *REPS2* directed molecules include RNAi and siRNA nucleic acids. Gene expression may be inhibited by the introduction of double-stranded RNA (dsRNA), which

induces potent and specific gene silencing, a phenomenon called RNA interference or RNAi. See, *e.g.*, Fire *et al.*, US Patent Number 6,506,559; Tuschl *et al.* PCT International Publication No. WO 01/75164; Kay *et al.* PCT International Publication No. WO 03/010180A1; or Bosher JM, Labouesse, *Nat Cell Biol* 2000 Feb;2(2):E31-6. This process has been improved by decreasing the size of the double-stranded RNA to 20-24 base pairs (to create small-interfering RNAs or siRNAs) that "switched off" genes in mammalian cells without initiating an acute phase response, *i.e.*, a host defense mechanism that often results in cell death (*see, e.g.*, Caplen *et al. Proc Natl Acad Sci* U S A. 2001 Aug 14;98(17):9742-7 and Elbashir *et al. Methods* 2002 Feb;26(2):199-213). There is increasing evidence of post-transcriptional gene silencing by RNA interference (RNAi) for inhibiting targeted expression in mammalian cells at the mRNA level, in human cells. There is additional evidence of effective methods for inhibiting the proliferation and migration of tumor cells in human patients, and for inhibiting metastatic cancer development (*see, e.g.*, U.S. Patent Application No. US2001000993183; Caplen *et al. Proc Natl Acad Sci* U S A; and Abderrahmani *et al. Mol Cell Biol* 2001 Nov21(21):7256-67).

[0143] An "siRNA" or "RNAi" refers to a nucleic acid that forms a double stranded RNA and has the ability to reduce or inhibit expression of a gene or target gene when the siRNA is delivered to or expressed in the same cell as the gene or target gene. "siRNA" refers to short double-stranded RNA formed by the complementary strands. Complementary portions of the siRNA that hybridize to form the double stranded molecule often have substantial or complete identity to the target molecule sequence. In one embodiment, an siRNA refers to a nucleic acid that has substantial or complete identity to a target gene and forms a double stranded siRNA, such as a nucleotide sequence set forth in SEQ ID NO: 1, 2, 3 or 4, for example.

[0144] When designing the siRNA molecules, the targeted region often is selected from a given DNA sequence beginning 50 to 100 nucleotides downstream of the start codon. *See, e.g.*, Elbashir *et al,. Methods 26*:199-213 (2002). Initially, 5' or 3' UTRs and regions nearby the start codon were avoided assuming that UTR-binding proteins and/or translation initiation complexes may interfere with binding of the siRNP or RISC endonuclease complex. Sometimes regions of the target 23 nucleotides in length conforming to the sequence motif AA(N19)TT (N, an nucleotide), and regions with approximately 30% to 70% G/C-content (often about 50% G/C-content) often are selected. If no suitable sequences are found, the search often is extended using the motif NA(N21). The sequence of the sense siRNA sometimes corresponds to (N19) TT or N21 (position 3 to 23 of the 23-nt motif), respectively. In the latter case, the 3' end of the sense siRNA often is converted to TT. The rationale for this sequence conversion is to generate a symmetric duplex with respect to the sequence composition of the sense and antisense 3' overhangs. The antisense siRNA is synthesized as the complement to position 1 to 21 of the 23-nt motif. Because position 1 of the 23-nt motif is not recognized sequence-specifically by the antisense siRNA, the 3'-most nucleotide residue of the antisense siRNA can be chosen deliberately.

However, the penultimate nucleotide of the antisense siRNA (complementary to position 2 of the 23-nt motif) often is complementary to the targeted sequence. For simplifying chemical synthesis, TT often is utilized. siRNAs corresponding to the target motif NAR(N17)YNN, where R is purine (A,G) and Y is pyrimidine (C,U), often are selected. Respective 21 nucleotide sense and antisense siRNAs often begin with a purine nucleotide and can also be expressed from pol III expression vectors without a change in targeting site. Expression of RNAs from pol III promoters often is efficient when the first transcribed nucleotide is a purine.

[0145] The sequence of the siRNA can correspond to the full length target gene, or a subsequence thereof. Often, the siRNA is about 15 to about 50 nucleotides in length (*e.g.*, each complementary sequence of the double stranded siRNA is 15-50 nucleotides in length, and the double stranded siRNA is about 15-50 base pairs in length, somtimes about 20-30 nucleotides in length or about 20-25 nucleotides in length, *e.g.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. The siRNA sometimes is about 21 nucleotides in length. Methods of using siRNA are well known in the art, and specific siRNA molecules may be purchased from a number of companies including Dharmacon Research, Inc.

[0146] Antisense, ribozyme, RNAi and siRNA nucleic acids can be altered to form modified *CDK10, FPGT, PCLO* or *REPS2* nucleic acid molecules. The nucleic acids can be altered at base moieties, sugar moieties or phosphate backbone moieties to improve stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup *et al., Bioorganic & Medicinal Chemistry 4 (1):* 5-23 (1996)). As used herein, the terms "peptide nucleic acid" or "PNA" refers to a nucleic acid mimic such as a DNA mimic, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of a PNA can allow for specific hybridization to DNA and RNA under conditions of low ionic strength. Synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described, for example, in Hyrup *et al.,* (1996) *supra* and Perry-O'Keefe *et al., Proc. Natl. Acad. Sci. 93:* 14670-675 (1996).

[0147] PNAs of *CDK10, FPGT, PCLO* or *REPS2* nucleic acids can be used in prognostic, diagnostic, and therapeutic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of *CDK10, FPGT, PCLO* or *REPS2* nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as "artificial restriction enzymes" when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup *et al.,* (1996) *supra*; Perry-O'Keefe *supra*).

[0148] In other embodiments, oligonucleotides may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across cell membranes (*see e.g.*, Letsinger *et al., Proc. Natl. Acad. Sci. USA 86:* 6553-6556 (1989); Lemaitre *et al., Proc. Natl. Acad. Sci. USA 84:* 648-652 (1987); PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al., Bio-Techniques 6:* 958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, *Pharm. Res. 5:* 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

[0149] Also included herein are molecular beacon oligonucleotide primer and probe molecules having one or more regions complementary to a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid, two complementary regions one having a fluorophore and one a quencher such that the molecular beacon is useful for quantifying the presence of the *CDK10, FPGT, PCLO* or *REPS2* nucleic acid in a sample. Molecular beacon nucleic acids are described, for example, in Lizardi *et al.,* U.S. Patent No. 5,854,033; Nazarenko *et al.,* U.S. Patent No. 5,866,336, and Livak *et al.,* U.S. Patent 5,876,930.

Anti-*CDK10, FPGT, PCLO* or *REPS2* Antibodies

[0150] The term "antibody" as used herein refers to an immunoglobulin molecule or immunologically active portion thereof, *i.e.*, an antigen-binding portion. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. An antibody sometimes is a polyclonal, monoclonal, recombinant (*e.g.*, a chimeric or humanized), fully human, non-human (*e.g.*, murine), or a single chain antibody. An antibody may have effector function and can fix complement, and is sometimes coupled to a toxin or imaging agent.

[0151] A full-length *CDK10, FPGT, PCLO* or *REPS2* polypeptide or antigenic peptide fragment can be used as an immunogen or can be used to identify anti-*CDK10, FPGT, PCLO* or *REPS2* antibodies made with other immunogens, *e.g.*, cells, membrane preparations, and the like. An antigenic peptide of *CDK10, FPGT, PCLO* or *REPS2* often includes at least 8 amino acid residues of the amino acid sequences set forth in Figures 5A-5B, 6A-6B or 7A-7B and encompasses an epitope of *CDK10, FPGT, PCLO* or *REPS2*. Antigenic peptides sometimes include 10 or more amino acids, 15 or more amino acids, 20 or more amino acids, or 30 or more amino acids. Hydrophilic and hydrophobic fragments of *CDK10, FPGT, PCLO* or *REPS2* polypeptides sometimes are used as immunogens.

[0152] Epitopes encompassed by the antigenic peptide are regions of *CDK10, FPGT, PCLO* or *REPS2* located on the surface of the polypeptide (*e.g.*, hydrophilic regions) as well as regions with high antigenicity. For example, an Emini surface probability analysis of the human *CDK10, FPGT, PCLO* or

REPS2 polypeptide sequence can be used to indicate the regions that have a particularly high probability of being localized to the surface of the *CDK10, FPGT, PCLO* or *REPS2* polypeptide and are thus likely to constitute surface residues useful for targeting antibody production. The antibody may bind an epitope on any domain or region on *CDK10, FPGT, PCLO* or *REPS2* polypeptides described herein.

[0153] Also, chimeric, humanized, and completely human antibodies are useful for applications which include repeated administration to subjects. Chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, can be made using standard recombinant DNA techniques. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al* International Application No. PCT/US86/02269; Akira, *et al* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al* European Patent Application 173,494; Neuberger *et al* PCT International Publication No. WO 86/01533; Cabilly *et al* U.S. Patent No. 4,816,567; Cabilly *et al* European Patent Application 125,023; Better *et al., Science 240:* 1041-1043 (1988); Liu *et al., Proc. Natl. Acad. Sci. USA 84:* 3439-3443 (1987); Liu *et al., J. Immunol. 139:* 3521-3526 (1987); Sun *et al., Proc. Natl. Acad. Sci. USA 84:* 214-218 (1987); Nishimura *et al., Canc. Res. 47:* 999-1005 (1987); Wood *et al., Nature 314:* 446-449 (1985); and Shaw *et al., J. Natl. Cancer Inst. 80:* 1553-1559 (1988); Morrison, S. L., *Science 229:* 1202-1207 (1985); Oi *et al., BioTechniques 4:* 214 (1986); Winter U.S. Patent 5,225,539; Jones *et al., Nature 321:* 552-525 (1986); Verhoeyan *et al., Science 239:* 1534; and Beidler *et al., J. Immunol. 141:* 4053-4060 (1988).

[0154] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced using transgenic mice that are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. *See*, for example, Lonberg and Huszar, *Int. Rev. Immunol. 13*: 65-93 (1995); and U.S. Patent Nos. 5,625,126; 5,633,425; 5,569,825; 5,661,016; and 5,545,806. In addition, companies such as Abgenix, Inc. (Fremont, CA) and Medarex, Inc. (Princeton, NJ), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above. Completely human antibodies that recognize a selected epitope also can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody (*e.g.*, a murine antibody) is used to guide the selection of a completely human antibody recognizing the same epitope. This technology is described for example by Jespers *et al., Bio/Technology 12:* 899-903 (1994).

[0155] An anti-*CDK10, FPGT, PCLO* or *REPS2* antibody can be a single chain antibody. A single chain antibody (scFV) can be engineered (see, *e.g.*, Colcher *et al., Ann. N Y Acad. Sci. 880:* 263-80 (1999); and Reiter, *Clin. Cancer Res. 2:* 245-52 (1996)). Single chain antibodies can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target *CDK10, FPGT, PCLO* or *REPS2* polypeptide.

[0156] Antibodies also may be selected or modified so that they exhibit reduced or no ability to bind an Fc receptor. For example, an antibody may be an isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor (*e.g.*, it has a mutagenized or deleted Fc receptor binding region).

[0157] Also, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thiotepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[0158] Antibody conjugates can be used for modifying a given biological response. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a polypeptide such as tumor necrosis factor, ?-interferon, a-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors. Also, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, for example.

[0159] An anti-*CDK10, FPGT, PCLO* or *REPS2* antibody (*e.g.*, monoclonal antibody) can be used to isolate *CDK10, FPGT, PCLO* or *REPS2* polypeptides by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, an anti-*CDK10, FPGT, PCLO* or *REPS2* antibody can be used to detect a *CDK10, FPGT, PCLO* or *REPS2* polypeptide (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the polypeptide. Anti-*CDK10, FPGT, PCLO* or *REPS2* antibodies can be used diagnostically to monitor polypeptide levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance (*i.e.*, antibody labeling). Examples of detectable substances include various enzymes, prosthetic groups,

fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, ß-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H. Also, an anti-*CDK10, FPGT, PCLO* or *REPS2* antibody can be utilized as a test molecule for determining whether it can treat melanoma, and as a therapeutic for administration to a subject for treating melanoma.

[0160] An antibody can be made by immunizing with a purified *CDK10, FPGT, PCLO* or *REPS2* antigen, or a fragment thereof, *e.g.*, a fragment described herein, a membrane associated antigen, tissues, *e.g.*, crude tissue preparations, whole cells, preferably living cells, lysed cells, or cell fractions.

[0161] Included herein are antibodies which bind only a native *CDK10, FPGT, PCLO* or *REPS2* polypeptide, only denatured or otherwise non-native *CDK10, FPGT, PCLO* or *REPS2* polypeptide, or which bind both, as well as those having linear or conformational epitopes. Conformational epitopes sometimes can be identified by selecting antibodies that bind to native but not denatured *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Also featured are antibodies that specifically bind to a *CDK10, FPGT, PCLO* or *REPS2* protein or polypeptide variant associated with melanoma.

Screening Assays

[0162] Featured herein are methods for identifying a candidate therapeutic for treating melanoma and detecting occurance of melanoma. The methods comprise contacting a test molecule with a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid, substantially identical nucleic acid, polypeptide, substantially identical polypeptide, or fragment of the foregoing in a system. The nucleic acid often is a *CDK10, FPGT, PCLO* or *REPS2* nucleotide sequence represented by SEQ ID NO: 1, 2, 3 or 4, respectively; sometimes is a nucleotide sequence substantially identical to the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4 or sometimes a fragment thereof; and the *CDK10, FPGT, PCLO* or *REPS2* polypeptide or fragment thereof is a polypeptide encoded by any of these nucleic acids. The method also comprises determining the presence or absence of an interaction between the test molecule and the *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or polypeptide, where the presence of an interaction between the test molecule and the *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or polypeptide identifies the test molecule as a candidate melanoma therapeutic.

[0163] As used herein, the term "test molecule" and "candidate therapeutic" refers to modulators of regulation of transcription and translation of *CDK10, FPGT, PCLO* or *REPS2* nucleic acids and

modulations of expression and activity of *CDK10, FPGT, PCLO* or *REPS2* polypeptides. The term "modulator" as used herein refers to a molecule which agonizes or antagonizes *CDK10, FPGT, PCLO* or *REPS2* DNA replication and/or DNA processing (*e.g.*, methylation), *CDK10, FPGT, PCLO* or *REPS2* RNA transcription and/or RNA processing (*e.g.*, removal of intronic sequences and/or translocation from the nucleus), *CDK10, FPGT, PCLO* or *REPS2* polypeptide production (*e.g.*, translation of the polypeptide from mRNA, and/or post-translational modification such as glycosylation, phosphorylation, and proteolysis of pro-polypeptides), and/or *CDK10, FPGT, PCLO* or *REPS2* function (*e.g.*, conformational changes, binding of nucleotides or nucleotide analogs, interaction with binding partners, effect on phosphorylation, and/or effect on occurrence of melanoma). Test molecules and candidate therapeutics include, but are not limited to, compounds, RNAi or siRNA molecules, antisense nucleic acids, ribozymes, *CDK10, FPGT, PCLO* or *REPS2* polypeptides or fragments thereof, and immunotherapeutics (*e.g.*, antibodies and HLA-presented polypeptide fragments).

[0164] As used herein, the term "system" refers to a cell free *in vitro* environment and a cell-based environment such as a collection of cells, a tissue, an organ, or an organism. A system is "contacted" with a test molecule in a variety of manners, including adding molecules in solution and allowing them to interact with one another by diffusion, cell injection, and any administration routes in an animal. As used herein, the term "interaction" refers to an effect of a test molecule on a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid, polypeptide, or variant thereof (collectively referred to as a "*CDK10, FPGT, PCLO* or *REPS2* molecule"), where the effect is sometimes binding between the test molecule and the nucleic acid or polypeptide, and is often an observable change in cells, tissue, or organism.

[0165] There are many standard methods for detecting the presence or absence of interaction between a test molecule and a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or polypeptide. For example, titrametric, acidimetric, radiometric, NMR, monolayer, polarographic, spectrophotometric, fluorescent, and ESR assays probative of *CDK10, FPGT, PCLO* or *REPS2* function may be utilized.

[0166] *CDK10, FPGT, PCLO* or *REPS2* activity and/or *CDK10, FPGT, PCLO* or *REPS2* interactions can be detected and quantified using assays known in the art and described in Examples hereafter.

[0167] An interaction can be determined by labeling the test molecule and/or the *CDK10, FPGT, PCLO* or *REPS2* molecule, where the label is covalently or non-covalently attached to the test molecule or *CDK10, FPGT, PCLO* or *REPS2* molecule. The label is sometimes a radioactive molecule such as ^{125}I, ^{131}I, ^{35}S or ^{3}H, which can be detected by direct counting of radioemission or by scintillation counting. Also, enzymatic labels such as horseradish peroxidase, alkaline phosphatase, or luciferase may be utilized where the enzymatic label can be detected by determining conversion of an appropriate substrate to product. Also, presence or absence of an interaction can be determined without labeling. For example, a microphysiometer (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at

which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indication of an interaction between a test molecule and *CDK10, FPGT, PCLO* or *REPS2* (McConnell, H. M. *et al., Science 257:* 1906-1912 (1992)).

[0168] In cell-based systems, cells typically include a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or polypeptide or variants thereof and are often of mammalian origin, although the cell can be of any origin. Whole cells, cell homogenates, and cell fractions (*e.g.*, cell membrane fractions) can be subjected to analysis. Where interactions between a test molecule with a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or variant thereof are monitored, soluble and/or membrane bound forms of the polypeptide or variant may be utilized. Where membrane-bound forms of the polypeptide are used, it may be desirable to utilize a solubilizing agent. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)$_n$, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate.

[0169] An interaction between two molecules can also be detected by monitoring fluorescence energy transfer (FET) (see, for example, Lakowicz *et al.,* U.S. Patent No. 5,631,169; Stavrianopoulos *et al.* U.S. Patent No. 4,868,103). A fluorophore label on a first, "donor" molecule is selected such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, "acceptor" molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the "donor" polypeptide molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the "acceptor" molecule label may be differentiated from that of the "donor". Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, the spatial relationship between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the "acceptor" molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

[0170] In another embodiment, determining the presence or absence of an interaction between a test molecule and a *CDK10, FPGT, PCLO* or *REPS2* molecule can be effected by using real-time Biomolecular Interaction Analysis (BIA) (see, *e.g.*, Sjolander & Urbaniczk, *Anal. Chem. 63:* 2338-2345 (1991) and Szabo *et al., Curr. Opin. Struct. Biol. 5:* 699-705 (1995)). "Surface plasmon resonance" or "BIA" detects biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance

(SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

[0171] In another embodiment, the *CDK10, FPGT, PCLO* or *REPS2* molecule or test molecules are anchored to a solid phase. The *CDK10, FPGT, PCLO* or *REPS2* molecule/test molecule complexes anchored to the solid phase can be detected at the end of the reaction. The target *CDK10, FPGT, PCLO* or *REPS2* molecule is often anchored to a solid surface, and the test molecule, which is not anchored, can be labeled, either directly or indirectly, with detectable labels discussed herein.

[0172] It may be desirable to immobilize a *CDK10, FPGT, PCLO* or *REPS2* molecule, an anti-*CDK10, FPGT, PCLO* or *REPS2* antibody, or test molecules to facilitate separation of complexed from uncomplexed forms of *CDK10, FPGT, PCLO* or *REPS2* molecules and test molecules, as well as to accommodate automation of the assay. Binding of a test molecule to a *CDK10, FPGT, PCLO* or *REPS2* molecule can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion polypeptide can be provided which adds a domain that allows a *CDK10, FPGT, PCLO* or *REPS2* molecule to be bound to a matrix. For example, glutathione-S-transferase/*CDK10, FPGT, PCLO* or *REPS2* fusion polypeptides or glutathione-S-transferase/target fusion polypeptides can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target polypeptide or *CDK10, FPGT, PCLO* or *REPS2* polypeptide, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of *CDK10, FPGT, PCLO* or *REPS2* binding or activity determined using standard techniques.

[0173] Other techniques for immobilizing a *CDK10, FPGT, PCLO* or *REPS2* molecule on matrices include using biotin and streptavidin. For example, biotinylated *CDK10, FPGT, PCLO* or *REPS2* polypeptide or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical).

[0174] In order to conduct the assay, the non-immobilized component is added to the coated surface containing the anchored component. After the reaction is complete, unreacted components are removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the previously non-immobilized component is pre-labeled, the detection of label

immobilized on the surface indicates that complexes were formed. Where the previously non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the immobilized component (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody).

[0175] In one embodiment, this assay is performed utilizing antibodies reactive with *CDK10, FPGT, PCLO* or *REPS2* polypeptide or test molecules but which do not interfere with binding of the *CDK10, FPGT, PCLO* or *REPS2* polypeptide to its test molecule. Such antibodies can be derivatized to the wells of the plate, and unbound target or *CDK10, FPGT, PCLO* or *REPS2* polypeptide trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the *CDK10, FPGT, PCLO* or *REPS2* polypeptide or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the *CDK10, FPGT, PCLO* or *REPS2* polypeptide or test molecule.

[0176] Alternatively, cell free assays can be conducted in a liquid phase. In such an assay, the reaction products are separated from unreacted components, by any of a number of standard techniques, including but not limited to: differential centrifugation (see, for example, Rivas, G., and Minton, A. P., *Trends Biochem Sci Aug;18(8):* 284-7 (1993)); chromatography (gel filtration chromatography, ion-exchange chromatography); electrophoresis (see, *e.g.*, Ausubel *et al., eds. Current Protocols in Molecular Biology , J. Wiley:* New York (1999)); and immunoprecipitation (see, for example, Ausubel, F. *et al., eds. Current Protocols in Molecular Biology , J. Wiley:* New York (1999)). Such resins and chromatographic techniques are known to one skilled in the art (*see, e.g.*, Heegaard, *J Mol. Recognit. Winter; 11(1-6):* 141-8 (1998); Hage & Tweed, *J. Chromatogr. B Biomed. Sci. Appl. Oct 10; 699 (1-2): 499-525* (1997)). Further, fluorescence energy transfer may also be conveniently utilized, as described herein, to detect binding without further purification of the complex from solution.

[0177] In another embodiment, modulators of *CDK10, FPGT, PCLO* or *REPS2* expression are identified. For example, a cell or cell free mixture is contacted with a candidate compound and the expression of *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide evaluated relative to the level of expression of *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide in the absence of the candidate compound. When expression of *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide is greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide expression. Alternatively, when expression of *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide expression. The level of

CDK10, FPGT, PCLO or *REPS2* mRNA or polypeptide expression can be determined by methods described herein for detecting *CDK10, FPGT, PCLO* or *REPS2* mRNA or polypeptide.

[0178] In an embodiment, binding partners that interact with a *CDK10, FPGT, PCLO* or *REPS2* molecule are detected. The *CDK10, FPGT, PCLO* or *REPS2* molecules can interact with one or more cellular or extracellular macromolecules, such as polypeptides, in vivo, and these molecules that interact with *CDK10, FPGT, PCLO* or *REPS2* molecules are referred to herein as "binding partners." Molecules that disrupt such interactions can be useful in regulating the activity of the target gene product. Such molecules can include, but are not limited to molecules such as antibodies, peptides, and small molecules (*e.g.*, siRNA). The preferred target genes/products for use in this embodiment are the *CDK10, FPGT, PCLO* or *REPS2* genes herein identified. In an alternative embodiment, provided are methods for determining the ability of the test compound to modulate the activity of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide through modulation of the activity of a downstream effector of a *CDK10, FPGT, PCLO* or *REPS2* target molecule. For example, the activity of the effector molecule on an appropriate target can be determined, or the binding of the effector to an appropriate target can be determined, as previously described.

[0179] To identify compounds that interfere with the interaction between the target gene product and its cellular or extracellular binding partner(s), *e.g.*, a substrate, a reaction mixture containing the target gene product and the binding partner is prepared, under conditions and for a time sufficient, to allow the two products to form complex. In order to test an inhibitory agent, the reaction mixture is provided in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the target gene and its cellular or extracellular binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the target gene product and the cellular or extracellular binding partner is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the target gene product and the interactive binding partner. Additionally, complex formation within reaction mixtures containing the test compound and normal target gene product can also be compared to complex formation within reaction mixtures containing the test compound and mutant target gene product. This comparison can be important in those cases wherein it is desirable to identify compounds that disrupt interactions of mutant but not normal target gene products.

[0180] These assays can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the target gene product or the binding partner onto a solid phase, and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of

reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the target gene products and the binding partners, *e.g.*, by competition, can be identified by conducting the reaction in the presence of the test substance. Alternatively, test compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

[0181] In a heterogeneous assay system, either the target gene product or the interactive cellular or extracellular binding partner, is anchored onto a solid surface (*e.g.*, a microtitre plate), while the non-anchored species is labeled, either directly or indirectly. The anchored species can be immobilized by non-covalent or covalent attachments. Alternatively, an immobilized antibody specific for the species to be anchored can be used to anchor the species to the solid surface.

[0182] In order to conduct the assay, the partner of the immobilized species is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted components are removed (*e.g.*, by washing) and any complexes formed will remain immobilized on the solid surface. Where the non-immobilized species is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized species is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds that inhibit complex formation or that disrupt preformed complexes can be detected.

[0183] Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from unreacted components, and complexes detected; *e.g.*, using an immobilized antibody specific for one of the binding components to anchor any complexes formed in solution, and a labeled antibody specific for the other partner to detect anchored complexes. Again, depending upon the order of addition of reactants to the liquid phase, test compounds that inhibit complex or that disrupt preformed complexes can be identified.

[0184] In an alternate embodiment, a homogeneous assay can be used. For example, a preformed complex of the target gene product and the interactive cellular or extracellular binding partner product is prepared in that either the target gene products or their binding partners are labeled, but the signal generated by the label is quenched due to complex formation (see, *e.g.*, U.S. Patent No. 4,109,496 that utilizes this approach for immunoassays). The addition of a test substance that competes with and displaces one of the species from the preformed complex will result in the generation of a signal above background. In this way, test substances that disrupt target gene product-binding partner interaction can be identified.

[0185] Also, binding partners of *CDK10, FPGT, PCLO* or *REPS2* molecules can be identified in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al., Cell 72:223-232* (1993); Madura *et al., J. Biol. Chem. 268:* 12046-12054 (1993); Bartel *et al., Biotechniques 14:* 920-924 (1993); Iwabuchi *et al., Oncogene 8:* 1693-1696 (1993); and Brent WO94/10300), to identify other polypeptides, which bind to or interact with *CDK10, FPGT, PCLO* or *REPS2* ("*CDK10, FPGT, PCLO* or *REPS2* -binding polypeptides" or "*CDK10, FPGT, PCLO* or *REPS2* -bp") and are involved in *CDK10, FPGT, PCLO* or *REPS2* activity. Such *CDK10, FPGT, PCLO* or *REPS2* -bps can be activators or inhibitors of signals by the *CDK10, FPGT, PCLO* or *REPS2* polypeptides or *CDK10, FPGT, PCLO* or *REPS2* targets as, for example, downstream elements of a *CDK10, FPGT, PCLO* or *REPS2* -mediated signaling pathway.

[0186] A two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a *CDK10, FPGT, PCLO* or *REPS2* polypeptide is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified polypeptide ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. (Alternatively the: *CDK10, FPGT, PCLO* or *REPS2* polypeptide can be the fused to the activator domain.) If the "bait" and the "prey" polypeptides are able to interact, *in vivo,* forming a *CDK10, FPGT, PCLO* or *REPS2* -dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the polypeptide which interacts with the *CDK10, FPGT, PCLO* or *REPS2* polypeptide.

[0187] Candidate therapeutics for treating melanoma are identified from a group of test molecules that interact with a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid or polypeptide. Test molecules often are ranked according to the degree with which they interact or modulate (*e.g.*, agonize or antagonize) DNA replication and/or processing, RNA transcription and/or processing, polypeptide production and/or processing, and/or function of *CDK10, FPGT, PCLO* or *REPS2* molecules, for example, and then top ranking modulators are selected. Also, pharmacogenomic information described herein can determine the rank of a modulator. Candidate therapeutics typically are formulated for administration to a subject.

Therapeutic Treatments

[0188] Formulations or pharmaceutical compositions typically include in combination with a pharmaceutically acceptable carrier a compound, an antisense nucleic acid, a ribozyme, an antibody, a

binding partner that interacts with a *CDK10, FPGT, PCLO* or *REPS2* polypeptide, a *CDK10, FPGT, PCLO* or *REPS2* nucleic acid, or a fragment thereof. The formulated molecule may be one that is identified by a screening method described above. Also, formulations may comprise a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or fragment thereof and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Supplementary active compounds can also be incorporated into the compositions.

[0189] A pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0190] Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules, *e.g.*, gelatin capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0191] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be

preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0192] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation often utilized are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0193] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0194] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams (*e.g.*, sunscreen) as generally known in the art. Molecules can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0195] In one embodiment, active molecules are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

Materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0196] It is advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0197] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Molecules which exhibit high therapeutic indices often are utilized. While molecules that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0198] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such molecules lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any molecules used in the method, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0199] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, sometimes about 0.01 to 25 mg/kg body weight, often about 0.1 to 20 mg/kg body weight, and more often about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The protein or polypeptide can be administered one time per week for between about 1 to 10 weeks, sometimes between 2 to 8 weeks, often between about 3 to 7 weeks, and more often for about 4, 5, or 6 weeks. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject,

including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[0200] With regard to polypeptide formulations, featured herein is a method for treating melanoma in a subject, which comprises contacting one or more cells in the subject with a first *CDK10, FPGT, PCLO* or *REPS2* polypeptide, where genomic DNA in the subject comprises a second *CDK10, FPGT, PCLO* or *REPS2* nucleic acid having one or more polymorphic variations associated with melanoma. The first *CDK10, FPGT, PCLO* or *REPS2* polypeptide comprises fewer polymorphic variations associated with melanoma than the second *CDK10, FPGT, PCLO* or *REPS2* polypeptide. The first and second *CDK10, FPGT, PCLO* or *REPS2* polypeptides are encoded by a nucleic acid which comprises a nucleotide sequence selected from the group consisting of the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence set forth in Figures 8A-8C, 9, 10A-10B and 11; and a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence set forth in Figures 8A-8C, 9, 10A-10B and 11. The second *CDK10, FPGT, PCLO* or *REPS2* polypeptide also may be encoded by a fragment of the foregoing nucleic acids comprising the one or more polymorphic variations. The subject is often a human.

[0201] For antibodies, a dosage of 0.1 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg) is often utilized. If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is often appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the brain). A method for lipidation of antibodies is described by Cruikshank *et al., J. Acquired Immune Deficiency Syndromes* and *Human Retrovirology 14:*193 (1997).

[0202] Antibody conjugates can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a polypeptide such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or

other growth factors. Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[0203] For compounds, exemplary doses include milligram or microgram amounts of the compound per kilogram of subject or sample weight, for example, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram. It is understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[0204] *CDK10, FPGT, PCLO* or *REPS2* nucleic acid molecules can be inserted into vectors and used in gene therapy methods for treating melanoma. Featured herein is a method for treating melanoma in a subject, which comprises contacting one or more cells in the subject with a first *CDK10, FPGT, PCLO* or *REPS2* nucleic acid. Genomic DNA in the subject comprises a second *CDK10, FPGT, PCLO* or *REPS2* nucleic acid comprising one or more polymorphic variations associated with melanoma, and the first *CDK10, FPGT, PCLO* or *REPS2* nucleic acid comprises fewer polymorphic variations associated with melanoma. The first and second *CDK10, FPGT, PCLO* or *REPS2* nucleic acids typically comprise a nucleotide sequence selected from the group consisting of the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence set forth in Figures 8A-8C, 9, 10A-10B and 11; and a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence set forth in Figures 8A-8C, 9, 10A-10B and 11. The second *CDK10, FPGT, PCLO* or *REPS2* nucleic acid may also be a fragment of the foregoing comprising one or more polymorphic variations. The subject is often a human.

[0205] Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see *e.g.*, Chen *et al.*, (1994) *Proc. Natl. Acad. Sci. USA 91*:3054-3057). Pharmaceutical preparations of gene therapy vectors can include a gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells (*e.g.*, retroviral vectors) the pharmaceutical preparation can

include one or more cells which produce the gene delivery system. Examples of gene delivery vectors are described herein.

[0206] Pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0207] Pharmaceutical compositions of active ingredients can be administered by any of the paths described herein for therapeutic and prophylactic methods for treating melanoma. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from pharmacogenomic analyses described herein. As used herein, the term "treatment" is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease, a symptom of disease or a predisposition toward a disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease, the symptoms of disease or the predisposition toward disease. A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides.

[0208] Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the *CDK10, FPGT, PCLO* or *REPS2* aberrance, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of *CDK10, FPGT, PCLO* or *REPS2* aberrance, for example, a *CDK10, FPGT, PCLO* or *REPS2* molecule, *CDK10, FPGT, PCLO* or *REPS2* agonist, or *CDK10, FPGT, PCLO* or *REPS2* antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

[0209] As discussed, successful treatment of *CDK10, FPGT, PCLO* or *REPS2* disorders can be brought about by techniques that serve to inhibit the expression or activity of target gene products. For example, compounds (*e.g.*, an agent identified using an assays described above) that exhibit negative modulatory activity can be used to prevent and/or treat melanoma. Such molecules can include, but are not limited to peptides, phosphopeptides, small organic or inorganic molecules, or antibodies (including, for example, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and FAb, $F(ab')_2$ and FAb expression library fragments, scFV molecules, and epitope-binding fragments thereof).

[0210] Further, antisense and ribozyme molecules that inhibit expression of the target gene can also be used to reduce the level of target gene expression, thus effectively reducing the level of target gene activity. Still further, triple helix molecules can be utilized in reducing the level of target gene activity. Antisense, ribozyme and triple helix molecules are discussed above.

[0211] It is possible that the use of antisense, ribozyme, and/or triple helix molecules to reduce or inhibit mutant gene expression can also reduce or inhibit the transcription (triple helix) and/or translation (antisense, ribozyme) of mRNA produced by normal target gene alleles, such that the concentration of

normal target gene product present can be lower than is necessary for a normal phenotype. In such cases, nucleic acid molecules that encode and express target gene polypeptides exhibiting normal target gene activity can be introduced into cells via gene therapy method. Alternatively, in instances in that the target gene encodes an extracellular polypeptide, it can be preferable to co-administer normal target gene polypeptide into the cell or tissue in order to maintain the requisite level of cellular or tissue target gene activity.

[0212] Another method by which nucleic acid molecules may be utilized in treating or preventing a disease characterized by *CDK10, FPGT, PCLO* or *REPS2* expression is through the use of aptamer molecules specific for *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Aptamers are nucleic acid molecules having a tertiary structure which permits them to specifically bind to polypeptide ligands (see, *e.g.*, Osborne, *et al., Curr. Opin. Chem. Biol.1(1):* 5-9 (1997); and Patel, D. J., *Curr. Opin. Chem. Biol. Jun;1(1):* 32-46 (1997)). Since nucleic acid molecules may in many cases be more conveniently introduced into target cells than therapeutic polypeptide molecules may be, aptamers offer a method by which *CDK10, FPGT, PCLO* or *REPS2* polypeptide activity may be specifically decreased without the introduction of drugs or other molecules which may have pluripotent effects.

[0213] Antibodies can be generated that are both specific for target gene product and that reduce target gene product activity. Such antibodies may, therefore, by administered in instances whereby negative modulatory techniques are appropriate for the treatment of *CDK10, FPGT, PCLO* or *REPS2* disorders. For a description of antibodies, see the Antibody section above.

[0214] In circumstances where injection of an animal or a human subject with a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or epitope for stimulating antibody production is harmful to the subject, it is possible to generate an immune response against *CDK10, FPGT, PCLO* or *REPS2* through the use of anti-idiotypic antibodies (see, for example, Herlyn, D., *Ann. Med.;31(1):* 66-78 (1999); and Bhattacharya-Chatterjee & Foon, *Cancer Treat. Res.; 94:* 51-68 (1998)). If an anti-idiotypic antibody is introduced into a mammal or human subject, it should stimulate the production of anti-anti-idiotypic antibodies, which should be specific to the *CDK10, FPGT, PCLO* or *REPS2* polypeptide. Vaccines directed to a disease characterized by *CDK10, FPGT, PCLO* or *REPS2* expression may also be generated in this fashion.

[0215] In instances where the target antigen is intracellular and whole antibodies are used, internalizing antibodies often are utilized. Lipofectin or liposomes can be used to deliver the antibody or a fragment of the Fab region that binds to the target antigen into cells. Where fragments of the antibody are used, the smallest inhibitory fragment that binds to the target antigen often are utilized. For example, peptides having an amino acid sequence corresponding to the Fv region of the antibody can be used. Alternatively, single chain neutralizing antibodies that bind to intracellular target antigens can also be administered. Such single chain antibodies can be administered, for example, by expressing nucleotide

sequences encoding single-chain antibodies within the target cell population (see *e.g.*, Marasco *et al., Proc. Natl. Acad. Sci. USA 90:* 7889-7893 (1993)).

[0216] *CDK10, FPGT, PCLO* or *REPS2* molecules and compounds that inhibit target gene expression, synthesis and/or activity can be administered to a patient at therapeutically effective doses to prevent, treat or ameliorate *CDK10, FPGT, PCLO* or *REPS2* disorders. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms of the disorders.

[0217] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds that exhibit large therapeutic indices often are utilized. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0218] Data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (*i.e.*, the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

[0219] Another example of effective dose determination for an individual is the ability to directly assay levels of "free" and "bound" compound in the serum of the test subject. Such assays may utilize antibody mimics and/or "biosensors" that have been created through molecular imprinting techniques. The compound which is able to modulate *CDK10, FPGT, PCLO* or *REPS2* activity is used as a template, or "imprinting molecule", to spatially organize polymerizable monomers prior to their polymerization with catalytic reagents. The subsequent removal of the imprinted molecule leaves a polymer matrix which contains a repeated "negative image" of the compound and is able to selectively rebind the molecule under biological assay conditions. A detailed review of this technique can be seen in Ansell *et al., Current Opinion in Biotechnology 7:* 89-94 (1996) and in Shea, *Trends in Polymer Science 2:* 166-173 (1994). Such "imprinted" affinity matrixes are amenable to ligand-binding assays, whereby the immobilized monoclonal antibody component is replaced by an appropriately imprinted matrix. An

example of the use of such matrixes in this way can be seen in Vlatakis, *et al., Nature 361:* 645-647 (1993). Through the use of isotope-labeling, the "free" concentration of compound which modulates the expression or activity of *CDK10, FPGT, PCLO* or *REPS2* can be readily monitored and used in calculations of IC_{50}. Such "imprinted" affinity matrixes can also be designed to include fluorescent groups whose photon-emitting properties measurably change upon local and selective binding of target compound. These changes can be readily assayed in real time using appropriate fiberoptic devices, in turn allowing the dose in a test subject to be quickly optimized based on its individual IC_{50}. A rudimentary example of such a "biosensor" is discussed in Kriz *et al., Analytical Chemistry 67:* 2142-2144 (1995).

[0220] Provided herein are methods of modulating *CDK10, FPGT, PCLO* or *REPS2* expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method involves contacting a cell with *CDK10, FPGT, PCLO* or *REPS2* or an agent that modulates one or more activities of *CDK10, FPGT, PCLO* or *REPS2* polypeptide activity associated with the cell. An agent that modulates *CDK10, FPGT, PCLO* or *REPS2* polypeptide activity can be an agent as described herein, such as a nucleic acid or a polypeptide, a naturally-occurring target molecule of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide (*e.g.*, a *CDK10, FPGT, PCLO* or *REPS2* substrate or receptor), a *CDK10, FPGT, PCLO* or *REPS2* antibody, a *CDK10, FPGT, PCLO* or *REPS2* agonist or antagonist, a peptidomimetic of a *CDK10, FPGT, PCLO* or *REPS2* agonist or antagonist, or other small molecule.

[0221] In one embodiment, the agent stimulates one or more *CDK10, FPGT, PCLO* or *REPS2* activities. Examples of such stimulatory agents include active *CDK10, FPGT, PCLO* or *REPS2* polypeptide and a nucleic acid molecule encoding *CDK10, FPGT, PCLO* or *REPS2* . In another embodiment, the agent inhibits one or more *CDK10, FPGT, PCLO* or *REPS2* activities. Examples of such inhibitory agents include antisense *CDK10, FPGT, PCLO* or *REPS2* nucleic acid molecules, anti-*CDK10, FPGT, PCLO* or *REPS2* antibodies, and *CDK10, FPGT, PCLO* or *REPS2* inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, provided are methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or nucleic acid molecule. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, upregulates or downregulates) *CDK10, FPGT, PCLO* or *REPS2* expression or activity. In another embodiment, the method involves administering a *CDK10, FPGT, PCLO* or *REPS2* polypeptide or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted *CDK10, FPGT, PCLO* or *REPS2* expression or activity.

[0222] Stimulation of *CDK10, FPGT, PCLO* or *REPS2* activity is desirable in situations in which *CDK10, FPGT, PCLO* or *REPS2* is abnormally downregulated and/or in which increased *CDK10, FPGT,*

PCLO or *REPS2* activity is likely to have a beneficial effect. For example, stimulation of *CDK10, FPGT, PCLO* or *REPS2* activity is desirable in situations in which a *CDK10, FPGT, PCLO* or *REPS2* is downregulated and/or in which increased *CDK10, FPGT, PCLO* or *REPS2* activity is likely to have a beneficial effect. Likewise, inhibition of *CDK10, FPGT, PCLO* or *REPS2* activity is desirable in situations in which *CDK10, FPGT, PCLO* or *REPS2* is abnormally upregulated and/or in which decreased *CDK10, FPGT, PCLO* or *REPS2* activity is likely to have a beneficial effect.

[0223] The examples set forth below are intended to illustrate but not limit the invention.

Examples

[0224] In the following studies a group of subjects was selected according to specific parameters pertaining to melanoma. Nucleic acid samples obtained from individuals in the study group were subjected to genetic analyses that identified associations between melanoma and certain polymorphic variants in human genomic DNA. This procedure was repeated in a second group of subjects that served as a replication cohort. Polymorphic variants proximal to the incident SNPs were identified and analyzed in cases and controls. In addition, methods are described for producing target polypeptides encoded by the target nucleic acids *in vitro* or *in vivo*, which can be utilized in methods that screen test molecules for those that interact with target polypeptides. Test molecules identified as being interactors with target polypeptides can be screened further as melanoma therapeutics. Also, methods are described for comparing the expression of target mRNA in cancer and non-cancer cells, producing siRNA molecules capable of inhibiting target expression, measuring the effect of siRNA molecules on cellular proliferation of the target, and screening for target inhibitors.

Example 1

Samples and Pooling Strategies

Sample Selection

[0225] Blood samples were collected from individuals diagnosed with melanoma, which were referred to as case samples. Also, blood samples were collected from individuals not diagnosed with melanoma or a history of melanoma; these samples served as gender and age-matched controls. A database was created that listed all phenotypic trait information gathered from individuals for each case and control sample. Genomic DNA was extracted from each of the blood samples for genetic analyses.

DNA Extraction from Blood Samples

[0226] Six to ten milliliters of whole blood was transferred to a 50 ml tube containing 27 ml of red cell lysis solution (RCL). The tube was inverted until the contents were mixed. Each tube was incubated

for 10 minutes at room temperature and inverted once during the incubation. The tubes were then centrifuged for 20 minutes at 3000 x g and the supernatant was carefully poured off. 100-200 μl of residual liquid was left in the tube and was pipetted repeatedly to resuspend the pellet in the residual supernatant. White cell lysis solution (WCL) was added to the tube and pipetted repeatedly until completely mixed. While no incubation was normally required, the solution was incubated at 37°C or room temperature if cell clumps were visible after mixing until the solution was homogeneous. Two ml of protein precipitation was added to the cell lysate. The mixtures were vortexed vigorously at high speed for 20 sec to mix the protein precipitation solution uniformly with the cell lysate, and then centrifuged for 10 minutes at 3000 x g. The supernatant containing the DNA was then poured into a clean 15 ml tube, which contained 7 ml of 100% isopropanol. The samples were mixed by inverting the tubes gently until white threads of DNA were visible. Samples were centrifuged for 3 minutes at 2000 x g and the DNA was visible as a small white pellet. The supernatant was decanted and 5 ml of 70% ethanol was added to each tube. Each tube was inverted several times to wash the DNA pellet, and then centrifuged for 1 minute at 2000 x g. The ethanol was decanted and each tube was drained on clean absorbent paper. The DNA was dried in the tube by inversion for 10 minutes, and then 1000 μl of 1X TE was added. The size of each sample was estimated, and less TE buffer was added during the following DNA hydration step if the sample was smaller. The DNA was allowed to rehydrate overnight at room temperature, and DNA samples were stored at 2-8°C.

[0227] DNA was quantified by placing samples on a hematology mixer for at least 1 hour. DNA was serially diluted (typically 1:80, 1:160, 1:320, and 1:640 dilutions) so that it would be within the measurable range of standards. 125 μl of diluted DNA was transferred to a clear U-bottom microtitre plate, and 125 μl of 1X TE buffer was transferred into each well using a multichannel pipette. The DNA and 1X TE were mixed by repeated pipetting at least 15 times, and then the plates were sealed. 50 μl of diluted DNA was added to wells A5-H12 of a black flat bottom microtitre plate. Standards were inverted six times to mix them, and then 50 μl of 1X TE buffer was pipetted into well A1, 1000 ng/ml of standard was pipetted into well A2, 500 ng/ml of standard was pipetted into well A3, and 250 ng/ml of standard was pipetted into well A4. PicoGreen (Molecular Probes, Eugene, Oregon) was thawed and freshly diluted 1:200 according to the number of plates that were being measured. PicoGreen was vortexed and then 50μl was pipetted into all wells of the black plate with the diluted DNA. DNA and PicoGreen were mixed by pipetting repeatedly at least 10 times with the multichannel pipette. The plate was placed into a Fluoroskan Ascent Machine (microplate fluorometer produced by Labsystems) and the samples were allowed to incubate for 3 minutes before the machine was run using filter pairs 485 nm excitation and 538 nm emission wavelengths. Samples having measured DNA concentrations of greater than 450 ng/μl

were re-measured for conformation. Samples having measured DNA concentrations of 20 ng/μl or less were re-measured for confirmation.

Pooling Strategies

[0228] Samples were placed into one of four groups, based on gender and disease status. The four groups were male case samples, male control samples, female case samples, and female control samples. A select set of samples from each group were utilized to generate pools, and one pool was created for each group. Each individual sample in a pool was represented by an equal amount of genomic DNA. For example, where 25 ng of genomic DNA was utilized in each PCR reaction and there were 200 individuals in each pool, each individual would provide 125 pg of genomic DNA. Inclusion or exclusion of samples for a pool was based upon the following criteria: the sample was derived from an individual characterized as Caucasian; the sample was derived from an individual of German paternal and maternal descent; the database included relevant phenotype information for the individual; case samples were derived from individuals diagnosed with melanoma; control samples were derived from individuals free of cancer; and sufficient genomic DNA was extracted from each blood sample for all allelotyping and genotyping reactions performed during the study. Phenotype information included sex of the individual, number of nevi (few, moderate, numerous), hair color (black, brown, blond, red), diagnosed with melanoma (tumor thickness, date of primary diagnosis, age of individual as of primary diagnosis, post-operative tumor classification, presence of nodes, occurrence of metastases, subtype, location), country or origin of mother and father, presence of certain conditions for each individual (coronary heart disease, cardiomyopathy, arteriosclerosis, abnormal blood clotting/thrombosis, emphysema, asthma, diabetes type 1, diabetes type 2, Alzheimer's disease, epilepsy, schizophrenia, manic depression/bipolar disorder, autoimmune disease, thyroid disorder, and hypertension), presence of cancer in the donor individual or blood relative (melanoma, basaliom/spinaliom/lentigo malignant/mycosis fungoides, breast cancer, colon cancer, rectum cancer, lung cancer, lung cancer, bronchus cancer, prostate cancer, stomach cancer, leukemia, lymphoma, or other cancer in donor, donor parent, donor aunt or uncle, donor offspring or donor grandparent. Samples that met these criteria were added to appropriate pools based on gender and disease status.

[0229] The selection process yielded the pools set forth in Table 1, which were used in the studies that follow:

Table 1

	Male control	Male case	Female control	Female case
Pool size (Number)	217	236	233	266
Pool Criteria (ex: case/control)	control	Case	control	case
Mean Age (ex: years)	48	51	47	49

Example 2

Association of NRP1 Polymorphic Variants with Melanoma

[0230] A whole-genome screen was performed to identify particular SNPs associated with occurrence of melanoma. As described in Example 1, two sets of samples were utilized: female individuals having melanoma (female cases) and samples from female individuals not having melanoma or any history of melanoma (female controls), and male individuals having melanoma (male cases) and samples from male individuals not having melanoma or any history of melanoma (male controls). The initial screen of each pool was performed in an allelotyping study, in which certain samples in each group were pooled. By pooling DNA from each group, an allele frequency for each SNP in each group was calculated. These allele frequencies were then compared to one another. Particular SNPs were considered as being associated with melanoma when allele frequency differences calculated between case and control pools were statistically significant. SNP disease association results obtained from the allelotyping study were then validated by genotyping each associated SNP across all samples from each pool. The results of the genotyping were then analyzed, allele frequencies for each group were calculated from the individual genotyping results, and a p-value was calculated to determine whether the case and control groups had statistically significantly differences in allele frequencies for a particular SNP. When the genotyping results agreed with the original allelotyping results, the SNP disease association was considered validated at the genetic level.

SNP Panel Used for Genetic Analyses

[0231] A whole-genome SNP screen began with an initial screen of approximately 25,000 SNPs over each set of disease and control samples using a pooling approach. The pools studied in the screen are described in Example 1. The SNPs analyzed in this study were part of a set of 25,488 SNPs

confirmed as being statistically polymorphic as each is characterized as having a minor allele frequency of greater than 10%. The SNPs in the set reside in genes or in close proximity to genes, and many reside in gene exons. Specifically, SNPs in the set are located in exons, introns, and within 5,000 base-pairs upstream of a transcription start site of a gene. In addition, SNPs were selected according to the following criteria: they are located in ESTs; they are located in Locuslink or Ensembl genes; and they are located in Genomatix promoter predictions. SNPs in the set were also selected on the basis of even spacing across the genome, as depicted in Table 2.

Table 2

General Statistics		Spacing Statistics	
Total # of SNPs	25,488	Median	37,058 bp
# of Exonic SNPs	>4,335 (17%)	Minimum*	1,000 bp
# SNPs with refSNP ID	20,776 (81%)	Maximum*	3,000,000 bp
Gene Coverage	>10,000	Mean	122,412 bp
Chromosome Coverage	All	Std Deviation	373,325 bp
		**Excludes outliers*	

Genotyping Results

[0232] The genetic studies summarized above and described in more detail below identified allelic variants associated with melanoma. The allelic variants identified from the SNP panel described in Table 2 are summarized below in Table 3.

Table 3

SNP Reference	Chromosome Position	Contig Identification	Contig Position	Sequence Identification	Sequence Position	Allelic Variability	Melanoma Associated Allele
rs8404	89465509	NT_010542	1319962	NM_003674	UTR	C/T	C
rs1044639	82049807	NT_007933	7685796	XM_168530	UTR	C/A	A
rs2034453	74096924	NT_004464	5157491	NM_003838	intragenic	A/G	A
				NM_015978	intronic		
rs1904528	16205791	NT_011757	3918204	NM_004726	UTR	C/T	C

[0233] Table 3 includes information pertaining to the incident polymorphic variant associated with melanoma identified herein. Public information pertaining to the polymorphism and the genomic

sequence that includes the polymorphism are indicated. The genomic sequence identified in Table 3 may be accessed at the http address www.ncbi.nih.gov/entrez/query.fcgi, for example, by using the publicly available SNP reference number (*e.g.*, rs8404). The chromosome position refers to the position of the SNP within NCBI's Genome Build 33, which may be accessed at the following http address: www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=. The "Contig Position" provided in Table 3 corresponds to a nucleotide position set forth in the contig sequence, and designates the polymorphic site corresponding to the SNP reference number. The sequence containing the polymorphisms also may be referenced by the "Sequence Identification" set forth in Table 3. The "Sequence Identification" corresponds to cDNA sequence that encodes associated target polypeptides (*e.g.*, CDK10) of the invention. The position of the SNP within the cDNA sequence is provided in the "Sequence Position" column of Table 3. In the case of rs2034453, the genetic evidence suggests an association with a region on chromosome 1 band p31.1 that includes two genes: fucose-1-phosphate guanylyltransferase (FPGT) (NM_003838) and cardiac ankyrin repeat kinase (CARK) (NM_015978). Also, the allelic variation at the polymorphic site and the allelic variant identified as associated with melanoma is specified in Table 3. All nucleotide sequences referenced and accessed by the parameters set forth in Table 3 are incorporated herein by reference.

Assay for Verifying, Allelotyping, and Genotyping SNPs

[0234] A MassARRAY™ system (Sequenom, Inc.) was utilized to perform SNP genotyping in a high-throughput fashion. This genotyping platform was complemented by a homogeneous, single-tube assay method (hME™ or homogeneous MassEXTEND™ (Sequenom, Inc.)) in which two genotyping primers anneal to and amplify a genomic target surrounding a polymorphic site of interest. A third primer (the MassEXTEND™ primer), which is complementary to the amplified target up to but not including the polymorphism, was then enzymatically extended one or a few bases through the polymorphic site and then terminated.

[0235] For each polymorphism, SpectroDESIGNER™ software (Sequenom, Inc.) was used to generate a set of PCR primers and a MassEXTEND™ primer which where used to genotype the polymorphism. Other primer design software could be used or one of ordinary skill in the art could manually design primers based on his or her knowledge of the relevant factors and considerations in designing such primers. Table 4 shows PCR primers and Table 5 shows extension primers used for analyzing the polymorphism set forth in Table 3. The initial PCR amplification reaction was performed in a 5 μl total volume containing 1X PCR buffer with 1.5 mM $MgCl_2$ (Qiagen), 200 μM each of dATP, dGTP, dCTP, dTTP (Gibco-BRL), 2.5 ng of genomic DNA, 0.1 units of HotStar DNA polymerase

(Qiagen), and 200 nM each of forward and reverse PCR primers specific for the polymorphic region of interest.

Table 4: PCR Primers

SNP Reference	Forward PCR primer	Reverse PCR primer
rs8404	ACGTTGGATGGCCTCCTGTTGG GTCCTC	ACGTTGGATGAAGGTATGGGGTGG GAGC
rs1044639	CGCAAACAAAAAGGACACAC	CTCCTTTGTTTCCACCATCC
rs2034453	TTGCTGGACAATAGAAAGAC	GTGACTGGAAACTGAGAATG
rs1904528	GAAGACTGAAAAAAATCCACG	GCTATCTCTTTCACATTGCTC

[0236] Samples were incubated at 95°C for 15 minutes, followed by 45 cycles of 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minute, finishing with a 3 minute final extension at 72°C. Following amplification, shrimp alkaline phosphatase (SAP) (0.3 units in a 2 μl volume) (Amersham Pharmacia) was added to each reaction (total reaction volume was 7 μl) to remove any residual dNTPs that were not consumed in the PCR step. Samples were incubated for 20 minutes at 37°C, followed by 5 minutes at 85°C to denature the SAP.

[0237] Once the SAP reaction was complete, a primer extension reaction was initiated by adding a polymorphism-specific MassEXTEND™ primer cocktail to each sample. Each MassEXTEND™ cocktail included a specific combination of dideoxynucleotides (ddNTPs) and deoxynucleotides (dNTPs) used to distinguish polymorphic alleles from one another. Methods for verifying, allelotyping and genotyping SNPs are disclosed, for example, in U.S. Pat. No. 6,258,538, the content of which is hereby incorporated by reference. In Table 5, ddNTPs are shown and the fourth nucleotide not shown is the dNTP.

Table 5: Extension Primers

SNP Reference	Extend Primers	Termination Mix
rs8404	CGAGACTACCAGGAGAGCCC	ACG
rs1044639	CATCCATCCAACCTGGCTC	CGT
rs2034453	AAACTGAGAATGTTGATGGACA	ACT
rs1904528	TCACATTGCTCTGCACTTTTG	ACG

[0238] The MassEXTEND™ reaction was performed in a total volume of 9 μl, with the addition of 1X ThermoSequenase buffer, 0.576 units of ThermoSequenase (Amersham Pharmacia), 600 nM MassEXTEND™ primer, 2 mM of ddATP and/or ddCTP and/or ddGTP and/or ddTTP, and 2 mM of

dATP or dCTP or dGTP or dTTP. The deoxy nucleotide (dNTP) used in the assay normally was complementary to the nucleotide at the polymorphic site in the amplicon. Samples were incubated at 94°C for 2 minutes, followed by 55 cycles of 5 seconds at 94°C, 5 seconds at 52°C, and 5 seconds at 72°C.

[0239] Following incubation, samples were desalted by adding 16 μl of water (total reaction volume was 25 μl), 3 mg of SpectroCLEAN™ sample cleaning beads (Sequenom, Inc.) and allowed to incubate for 3 minutes with rotation. Samples were then robotically dispensed using a piezoelectric dispensing device (SpectroJET™ (Sequenom, Inc.)) onto either 96-spot or 384-spot silicon chips containing a matrix that crystallized each sample (SpectroCHIP™ (Sequenom, Inc.)). Subsequently, MALDI-TOF mass spectrometry (Biflex and Autoflex MALDI-TOF mass spectrometers (Bruker Daltonics) can be used) and SpectroTYPER RT™ software (Sequenom, Inc.) were used to analyze and interpret the SNP genotype for each sample.

Genetic Analysis

[0240] The minor allelic frequency for the polymorphism set forth in Table 3 was verified as being 10% or greater using the extension assay described above in a group of samples isolated from 92 individuals originating from the state of Utah in the United States, Venezuela and France (Coriell cell repositories).

[0241] Genotyping results for the allelic variant set forth in Table 3 are shown for females in Table 6 and for males in Table 7. In Table 6, "F case" and "F control" refer to female case and female control groups, and in Table 7, "M case" and "M control" refer to male case and male control groups.

Table 6: Female Genotyping Results

SNP Reference	F case	F control	p-value	Odds Ratio
rs8404	C = 0.144 T = 0.856	C = 0.094 T = 0.906	**0.016**	0.62
rs1044639	A = 0.614 C = 0.386	A = 0.528 C = 0.472	**0.006**	1.42
rs2034453	G = 0.854 A = 0.146	G = 0.901 A = 0.099	**0.023**	0.64
rs1904528	T = 0.771 C = 0.229	T = 0.838 C = 0.162	**0.008**	0.65

Table 7: Male Genotyping Results

SNP Reference	M case	M control	p-value	Odd Ratio
rs8404	C = 0.136 T = 0.864	C = 0.098 T = 0.902	0.071	0.69
rs1044639	A = 0.611 C = 0.389	A = 0.551 C = 0.449	0.072	1.28
rs2034453	G = 0.896 A = 0.104	G = 0.890 A = 0.110	0.767	1.07
rs1904528	T = 0.790 C = 0.210	T = 0.822 C = 0.178	0.396	0.82

[0242] Odds ratio results are shown in Tables 6 and 7. An odds ratio is an unbiased estimate of relative risk which can be obtained from most case-control studies. Relative risk (RR) is an estimate of the likelihood of disease in the exposed group (susceptibility allele or genotype carriers) compared to the unexposed group (not carriers). It can be calculated by the following equation:

RR = I_A/I_a

I_A is the incidence of disease in the A carriers and I_a is the incidence of disease in the non-carriers.

RR > 1 indicates the A allele increases disease susceptibility.

RR < 1 indicates the a allele increases disease susceptibility.

For example, RR = 1.5 indicates that carriers of the A allele have 1.5 times the risk of disease than non-carriers, *i.e.*, 50% more likely to get the disease.

Case-control studies do not allow the direct estimation of I_A and I_a, therefore relative risk cannot be directly estimated. However, the odds ratio (OR) can be calculated using the following equation:

OR = (nDAnda)/(ndAnDa) = p**DA(1 – pdA)/**p**dA(1 – pDA)**, or

OR = ((case f) / (1- case f)) / ((control f) / (1-control f)), where f = susceptibility allele frequency.

[0243] An odds ratio can be interpreted in the same way a relative risk is interpreted and can be directly estimated using the data from case-control studies, *i.e.*, case and control allele frequencies. The higher the odds ratio value, the larger the effect that particular allele has on the development of melanoma, thus possessing that particular allele translates to having a higher risk of developing melanoma.

[0244] The single marker alleles set forth in Table 3 were considered validated, since the genotyping data for the females, males or both pools were significantly associated with melanoma, and because the genotyping results agreed with the original allelotyping results. Particularly significant associations with melanoma are indicated by a calculated p-value of less than 0.05 for genotype results, which are set forth in bold text.

Example 3

Samples and Pooling Strategies for the Replication Cohort

[0245] The single marker alleles set forth in Table 3 were genotyped again in a replication cohort to further validate their association with melanoma. Like the original study population described in Examples 1 and 2, the replication cohort consisted of individuals diagnosed with melanoma (cases) and individuals free of melanoma (controls). The case and control samples were selected and genotyped as described below.

Sample Selection

[0246] Blood samples were collected from individuals diagnosed with melanoma, which were referred to case samples. Also, blood samples were collected from individuals not diagnosed with me lanoma or a history of melanoma; these samples served as gender and age-matched controls.

DNA Extraction from Blood Samples

[0247] Blood samples for DNA preparation were taken in 5 EDTA tubes. If it was not possible to get a blood sample from a patient, a sample from the cheek mucosa was taken. Red blood cells were lysed to facilitate their separation from the white blood cells. The white cells were pelletted and lysed to release the DNA. Lysis was done in the presence of a DNA preservative using an anionic detergent to solubilize the cellular components. Contaminating RNA was removed by treatment with an RNA digesting enzyme. Cytoplasmic and nuclear proteins were removed by salt precipitation.

[0248] Genomic DNA was then isolated by precipitation with alcohol (2-propanol and then ethanol) and rehydrated in water. The DNA was transferred to 2-ml tubes and stored at 4°C for short-term storage and at –70°C for long-term storage.

Pooling Strategies

[0249] Samples were placed into one of four groups based on disease status. The four groups were female case samples, female control samples, male case samples, and male control samples. A select set of samples from each group were utilized to generate pools, and one pool was created for each group.

[0250] Replication samples were obtained from QIMR (Queensland Institute of Medical Research) through Nick Martin. All samples are of Australian descent. Sample sources were as follows: a.) Queensland Familial Melanoma Study- 702 cutaneous malignant melanoma cases plus 46 unaffected relatives; and b.) Twin mole study- 2367 controls, consisting of adolescent twins and siblings closest in age that had nevi counted and other skin and pigmentary phenotypes assessed. The subjects available for replication from Australia included 702 mostly unrelated melanoma cases from the Queensland Familial

Melanoma study and 2367 controls from the Twin Mole study with subjects organized into pedigrees with up to eight unaffected individuals.

[0251] To facilitate a direct comparison with the discovery study design and subsequent meta analyses, we selected a subset of the Australian sample to produce a research data set of unrelated cases and controls. For cases, this was done by selecting the proband from all families within the familial melanoma study. For controls, this was accomplished by selecting the pedigree founders from the twin study, usually the father and mother of the collected twins. The resulting data set consisted of 376 female and 300 male cases, and 640 female and 515 male controls.

Example 4

Association of Polymorphic Variants with Melanoma in the Replication Cohort

[0252] The associated SNPs from the initial scan were re-validated by genotyping the associated SNP across the replication cohort described in Example 3. The results of the genotyping were then analyzed, allele frequencies for each group were calculated from the individual genotyping results, and a p-value was calculated to determine whether the case and control groups had statistically significantly differences in allele frequencies for a particular SNP. The replication genotyping results were considered significant with a calculated p-value of less than 0.05 for genotype results, which are set forth in bold text. See Tables 8 and 9 herein.

Assay for Verifying, Allelotyping, and Genotyping SNPs

[0253] Genotyping of the replication cohort was performed using the same methods used for the original genotyping, as described herein. A MassARRAY™ system (Sequenom, Inc.) was utilized to perform SNP genotyping in a high-throughput fashion. This genotyping platform was complemented by a homogeneous, single-tube assay method (hME™ or homogeneous MassEXTEND™ (Sequenom, Inc.)) in which two genotyping primers anneal to and amplify a genomic target surrounding a polymorphic site of interest. A third primer (the MassEXTEND™ primer), which is complementary to the amplified target up to but not including the polymorphism, was then enzymatically extended one or a few bases through the polymorphic site and then terminated.

[0254] For each polymorphism, SpectroDESIGNER™ software (Sequenom, Inc.) was used to generate a set of PCR primers and a MassEXTEND™ primer which where used to genotype the polymorphism. Other primer design software could be used or one of ordinary skill in the art could manually design primers based on his or her knowledge of the relevant factors and considerations in designing such primers. Table 4 shows PCR primers and Table 5 shows extension probes used for analyzing (*e.g.*, genotyping) polymorphisms. The initial PCR amplification reaction was performed in a 5 μl total volume containing 1X PCR buffer with 1.5 mM $MgCl_2$ (Qiagen), 200 μM each of dATP,

dGTP, dCTP, dTTP (Gibco-BRL), 2.5 ng of genomic DNA, 0.1 units of HotStar DNA polymerase (Qiagen), and 200 nM each of forward and reverse PCR primers specific for the polymorphic region of interest.

[0255] Samples were incubated at 95°C for 15 minutes, followed by 45 cycles of 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minute, finishing with a 3 minute final extension at 72°C. Following amplification, shrimp alkaline phosphatase (SAP) (0.3 units in a 2 μl volume) (Amersham Pharmacia) was added to each reaction (total reaction volume was 7 μl) to remove any residual dNTPs that were not consumed in the PCR step. Samples were incubated for 20 minutes at 37°C, followed by 5 minutes at 85°C to denature the SAP.

[0256] Once the SAP reaction was complete, a primer extension reaction was initiated by adding a polymorphism-specific MassEXTEND™ primer cocktail to each sample. Each MassEXTEND™ cocktail included a specific combination of dideoxynucleotides (ddNTPs) and deoxynucleotides (dNTPs) used to distinguish polymorphic alleles from one another. Methods for verifying, allelotyping and genotyping SNPs are disclosed, for example, in U.S. Pat. No. 6,258,538, the content of which is hereby incorporated by reference. In Table 5, ddNTPs are shown and the fourth nucleotide not shown is the dNTP.

[0257] The MassEXTEND™ reaction was performed in a total volume of 9 μl, with the addition of 1X ThermoSequenase buffer, 0.576 units of ThermoSequenase (Amersham Pharmacia), 600 nM MassEXTEND™ primer, 2 mM of ddATP and/or ddCTP and/or ddGTP and/or ddTTP, and 2 mM of dATP or dCTP or dGTP or dTTP. The deoxy nucleotide (dNTP) used in the assay normally was complementary to the nucleotide at the polymorphic site in the amplicon. Samples were incubated at 94°C for 2 minutes, followed by 55 cycles of 5 seconds at 94°C, 5 seconds at 52°C, and 5 seconds at 72°C.

[0258] Following incubation, samples were desalted by adding 16 μl of water (total reaction volume was 25 μl), 3 mg of SpectroCLEAN™ sample cleaning beads (Sequenom, Inc.) and allowed to incubate for 3 minutes with rotation. Samples were then robotically dispensed using a piezoelectric dispensing device (SpectroJET™ (Sequenom, Inc.)) onto either 96-spot or 384-spot silicon chips containing a matrix that crystallized each sample (SpectroCHIP™ (Sequenom, Inc.)). Subsequently, MALDI-TOF mass spectrometry (Biflex and Autoflex MALDI-TOF mass spectrometers (Bruker Daltonics) can be used) and SpectroTYPER RT™ software (Sequenom, Inc.) were used to analyze and interpret the SNP genotype for each sample.

Genetic Analysis

[0259] The minor allelic frequencies for the polymorphisms set forth in Table 3 were verified as being 10% or greater using the extension assay described above in a group of samples isolated from 92 individuals originating from the state of Utah in the United States, Venezuela and France (Coriell cell repositories).

[0260] Replication genotyping results are shown for females and males in Table 8. P-values and odds ratios are provided in Table 9.

Table 8: Female and Male Replication Genotyping Results

Incident SNP	RS ID	Gene	Allele frequency-females			Allele frequency- males		
			Case	Control	Delta	Case	Control	Delta
FCH-0186	8404	CDK10	0.87	0.91	-0.043	0.88	0.91	-0.029
GP01_084009695	2034453	FPGT	0.85	87.00	-0.022	0.84	0.87	-0.026
GP01_084009695	2034453	LOC51086 (CARK)	0.85	87.00	-0.022	0.84	0.87	-0.026
GP07_082717580	1044639	PCLO	0.60	0.57	0.031	0.61	0.56	0.042
GP-X_017643141	1904528	REPS2	0.78	0.79	-0.005	0.77	0.82	-0.051

Table 9: Female and Male Replication Genotyping Analysis

Incident SNP	RS ID	Gene	Replication F		Replication M		Summary	
			p-value	OR	p-value	OR	p-value	OR
FCH-0186	8404	CDK10	**0.002**	0.65	0.054	0.72	**0.000004**	0.67
GP01_084009695	2034453	FPGT	0.170	0.83	0.150	0.81	**0.014000**	0.82
GP01_084009695	2034453	LOC51086 (CARK)	0.170	0.83	0.150	0.81	**0.014000**	0.82
GP07_082717580	1044639	PCLO	0.180	1.13	0.100	1.19	**0.000290**	1.23
GP-X_017643141	1904528	REPS2	0.800	0.97	0.076	0.73	**0.033000**	0.80

[0261] Meta analyses, combining the results of the German discovery sample and the Australian replication sample, were carried out using a random effects (DerSimonian-Laird) procedure. Statistically significant associations with melanoma are indicated by a calculated p-value of less than 0.05 for genotype results, which are set forth in bold text.

[0262] The absence of a statistically significant association in the replication cohort should not be interpreted as minimizing the value of the original finding. There are many reasons why a biologically derived association identified in a sample from one population would not replicate in a sample from another population. The most important reason is differences in population history. Due to bottlenecks

and founder effects, there may be common disease predisposing alleles present in one population that are relatively rare in another, leading to a lack of association in the candidate region. Also, because common diseases such as melanoma are the result of susceptibilities in many genes and many environmental risk factors, differences in population-specific genetic and environmental backgrounds could mask the effects of a biologically relevant allele.

Example 5

CDK10 Proximal SNPs

[0263] It has been discovered that a polymorphic variation (rs8404) in the untranslated region of a gene encoding cyclin-dependent kinase 10 (CDK10) is associated with the occurrence of melanoma. See Table 3. Subsequently, ninety-three allelic variants located within or nearby the target gene were identified and subsequently allelotyped in melanoma case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 10. The chromosome position provided in column four of Table 10 is based on Genome "Build 33" of NCBI's GenBank.

Table 10

dbSNP rs#	Chromosome	Position in Fig. 1	Chromosome Position	Allele Variants	Allele Present in Fig. 1	IUPAC Code
460879	16	139	89415739	T/C	C	Y
460984	16	424	89416024	T/C	C	Y
2437957	16	2898	89418498	C/T	G	R
3815949	16	3166	89418766	C/G	C	S
2437956	16	3501	89419101	G/A	T	Y
2437955	16	3525	89419125	G/T	C	M
2434872	16	4165	89419765	C/G	C	S
467357	16	4647	89420247	G/A	A	R
258337	16	7960	89423560	A/T	T	W
258336	16	8081	89423681	T/G	T	K
258335	16	8194	89423794	A/G	G	R
164752	16	9640	89425240	G/A	G	R
154663	16	13285	89428885	T/C	T	Y
164753	16	14845	89430445	T/C	C	Y
258332	16	14933	89430533	G/A	G	R
2010623	16	16275	89431875	C/T	A	R
187283	16	16586	89432186	G/A	A	R
258330	16	16824	89432424	T/G	T	K
258328	16	17564	89433164	C/T	C	Y
459920	16	18077	89433677	T/C	T	Y
166297	16	18435	89434035	G/A	A	R
258318	16	19300	89434900	T/C	T	Y
258317	16	19488	89435088	C/T	C	Y
171805	16	20864	89436464	G/A	A	R

dbSNP rs#	Chromosome	Position in Fig. 1	Chromosome Position	Allele Variants	Allele Present in Fig. 1	IUPAC Code
2081984	16	21176	89436776	C/T	C	Y
464586	16	21338	89436938	C/T	A	R
460319	16	21343	89436943	G/T	G	K
447735	16	21599	89437199	A/G	T	Y
2377058	16	22081	89437681	T/C	A	R
604868	16	23427	89439027	G/A	T	Y
2118193	16	27153	89442753	C/T	G	R
467035	16	27535	89443135	C/G	C	S
2115401	16	27859	89443459	C/T	T	Y
417323	16	33527	89449127	T/G	T	K
2377233	16	34152	89449752	C/G	G	S
3751700	16	39455	89455055	G/A	G	R
2277905	16	39762	89455362	A/G	A	R
397891	16	40292	89455892	C/G	G	S
3794638	16	40697	89456297	G/T	C	M
3794637	16	40831	89456431	G/A	C	Y
258324	16	41516	89457116	C/A	T	K
258323	16	41955	89457555	C/G	G	S
2075880	16	42477	89458077	A/G	A	R
258322	16	43164	89458764	C/T	A	R
258321	16	43734	89459334	C/T	A	R
164744	16	44029	89459629	A/C	T	K
164743	16	44692	89460292	A/G	T	Y
164742	16	44986	89460586	C/T	A	R
187282	16	46234	89461834	T/C	A	R
465507	16	47754	89463354	G/C	C	S
2162943	16	47914	89463514	G/A	C	Y
1946482	16	49672	89465272	T/C	T	Y
4247353	16	50476	89466076	T/C	T	Y
462769	16	50525	89466125	A/G	T	Y
3803690	16	50621	89466221	C/G	G	S
417414	16	53410	89469010	A/G	C	Y
154661	16	53833	89469433	G/C	G	S
4785704	16	59632	89475232	G/A	A	R
4785584	16	59646	89475246	C/T	T	Y
4785585	16	59667	89475267	C/T	C	Y
4785705	16	59676	89475276	T/C	C	Y
4785586	16	59678	89475278	G/A	G	R
4785587	16	59881	89475481	A/G	G	R
2016968	16	60168	89475768	C/G	C	S
3751693	16	61658	89477258	C/T	G	R
3809646	16	74117	89489717	A/G	C	Y
4785590	16	77429	89493029	G/C	G	S
2099105	16	80817	89496417	A/G	T	Y
4785708	16	83831	89499431	C/T	C	Y
4785710	16	84018	89499618	T/C	C	Y
4785591	16	84775	89500375	C/T	C	Y

dbSNP rs#	Chromosome	Position in Fig. 1	Chromosome Position	Allele Variants	Allele Present in Fig. 1	IUPAC Code
4785592	16	84777	89500377	C/G	G	S
4785593	16	84889	89500489	C/T	C	Y
4785711	16	85208	89500808	C/G	C	S
4785712	16	85216	89500816	G/C	C	S
4785713	16	85360	89500960	G/C	C	S
4785714	16	85666	89501266	C/A	C	M
4785594	16	85778	89501378	C/G	G	S
3803689	16	87320	89502920	A/G	C	Y
4785715	16	87397	89502997	G/A	A	R
3764258	16	88276	89503876	C/G	C	S
4785716	16	88389	89503989	T/C	T	Y
4785717	16	88395	89503995	G/A	A	R
2077001	16	89352	89504952	C/T	G	R
2377049	16	90230	89505830	A/C	T	K
2003522	16	90548	89506148	C/G	C	S
1230	16	92117	89507717	C/T	C	Y
1800359	16	92523	89508123	A/G	A	R
1061646	16	93239	89508839	T/C	G	R
1800358	16	96581	89512181	C/T	T	Y
2286392	16	96811	89512411	C/T	A	R
2074904	16	98808	89514408	T/C	A	R
2074903	16	98925	89514525	A/G	T	Y

Assay for Verifying and Allelotyping SNPs

[0264] The methods used to verify and allelotype the ninety-three proximal SNPs of Table 10 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 11 and Table 12, respectively.

Table 11

dbSNP rs#	Forward PCR primer	Reverse PCR primer
460879	ACGTTGGATGTCCAGCCTCTAACCCACAAC	ACGTTGGATGCGAAACGCTGTGTCACCAAC
460984	ACGTTGGATGATGCTCTGGACAACAGGTGG	ACGTTGGATGTGAGGGAACGAAAAGTGCAG
2437957	ACGTTGGATGATCCAGCTTCCCTCAACCTC	ACGTTGGATGCAGCTCAGAGTTGACGGAAG
3815949	ACGTTGGATGTTTTTCTGCAGAAGGGCCTG	ACGTTGGATGCACACACCACCAAGCTCTTC
2437956	ACGTTGGATGTCAACACTGGGCTCCTAGGG	ACGTTGGATGTCTCCTGACCTCGTGATCTG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
2437955	ACGTTGGATGTCAACACTGGGCTCCTAGGG	ACGTTGGATGTCTCCTGACCTCGTGATCTG
2434872	ACGTTGGATGTAGACACCAGCTCTGTAGGG	ACGTTGGATGATTACAGGCATGAGCCACTG
467357	GGCGCACGCCTCCACGTCATCTCTGTGCTCTGGACG	GGCGCACGCCTGTGTGGTGCAGCCCAGAAT
258337	ACGTTGGATGTAGAATCCAAAAGATGGTGG	ACGTTGGATGTGCTGGGATTACAGGTGAAC
258336	ACGTTGGATGCTTTGAGGAGAAAGAGTCTG	ACGTTGGATGTTAAAGCCAGGGTTTGAGGC
258335	ACGTTGGATGTCCTGACCTCAAGTGATCTG	ACGTTGGATGAAAGAGCTGATTTCCAGCGG
164752	ACGTTGGATGAAGTGCTGGAATTACAGCCG	ACGTTGGATGAAAATATGCTGGCCAGGCCG
154663	ACGTTGGATGATTGCTCGAACCTTGAACCG	ACGTTGGATGGACAGAGTCTCACTCTGTAG
164753	ACGTTGGATGAGTGAGAAGAACAGAAGGGC	ACGTTGGATGGCCAAGCCACATCAATATCC
258332	ACGTTGGATGTGTGTCCTCACCCAAATCTC	ACGTTGGATGCCTGCCCCCATAATTCAATC
2010623	ACGTTGGATGCCATGACGCCCAGCTAATTT	ACGTTGGATGAACCAGGAGTTTGAGGCCAG
187283	ACGTTGGATGCCGGGTTCAAGCAATTCTTC	ACGTTGGATGAATTACCCAGGCATGGTGGC
258330	ACGTTGGATGGCTTTTTTCACTCAGCATGG	ACGTTGGATGGGTAGAGTATACTTAATTGC
258328	ACGTTGGATGTCAGGTTTCACCATGTTGCC	ACGTTGGATGCAGAACTTTGGGAAGCCTAG
459920	GGCGCACGCCTCCACGAACAGCCATGTGTAACCCTC	GGCGCACGCCTAATCGCAGGAGAGACACAC
166297	ACGTTGGATGACTTCATTCCTTGAACCGGG	ACGTTGGATGACTGCATTCTCATGAGGAGC
258318	ACGTTGGATGTGCGTCTGGCCTAATATTTC	ACGTTGGATGCACTATTGAAATTTTCTAGTC
258317	ACGTTGGATGTGAACTCCTGACCTCAAGTG	ACGTTGGATGGCCAAGTGTAGTGATTCACG
171805	ACGTTGGATGACCATGGTCTGCTTGGCAAC	ACGTTGGATGGCCTTTTGTTATGCCCAGAC
2081984	ACGTTGGATGTTCCAAGTAGCTGGGACCAC	ACGTTGGATGTATTACACTGGAACAGCTCG
464586	ACGTTGGATGGACCTTCAAGATCCTGTCTC	ACGTTGGATGATAGCCTCATCTGTGTCAGC
460319	ACGTTGGATGGACCTTCAAGATCCTGTCTC	ACGTTGGATGATAGCCTCATCTGTGTCAGC
447735	GGCGCACGCCTCCACGATGGCTTGGCTTGTCTGTAC	GGCGCACGCCCACAGCAGCTTCTGCTATAG
2377058	ACGTTGGATGGGGTTAGAAGACTCAGTCAC	ACGTTGGATGTACCAAGTGTCCCACAAAGC
604868	GGCGCACGCCTCCACGCAACCCTGG	GGCGCACGCCCTGCCCCCGCCGTGA

dbSNP rs#	Forward PCR primer	Reverse PCR primer
	TGTACCCTCC	GAAA
2118193	ACGTTGGATGTTTTTGAGACGGAGTCTCGC	ACGTTGGATGAGGAGAATGGCTGAACCTGG
467035	ACGTTGGATGCGTGTCTGTTTCCACTCTTG	ACGTTGGATGCCCTGTGTAGAAAAGAAGGC
2115401	ACGTTGGATGTGGCATCTTTGGGCGTTTTG	ACGTTGGATGCAACCCGCTTCAGCCTTGAG
417323	ACGTTGGATGGAGGACTGAAGAAAGAATTTG	ACGTTGGATGGCGAGACTCTGTCTCAAATA
2377233	ACGTTGGATGTCTCTTTTTGGACTTCAGGG	ACGTTGGATGTCCCACAGTGCTAGGATTAC
3751700	ACGTTGGATGTCAGGTCTTCCATGAGTGAG	ACGTTGGATGTTCAAGCTTAGCTTCTGGGC
2277905	ACGTTGGATGTCCTCCAGTTGGGAGTCCTT	ACGTTGGATGCACCTGGAAGACTCTCTCAC
397891	GGCGCACGCCTCCACGCGGGAGCGTCTCTTGGTAAC	GGCGCACGCCCAGGCGCGAAAGCTCCTTC
3794638	ACGTTGGATGAGCCTGCTCTTCCCAAGTCC	ACGTTGGATGCGGTCCCTGGAGATCTGAG
3794637	ACGTTGGATGGAGCCTTCAAGCTCGAACTC	ACGTTGGATGAGCCGCGAGCCACTTGTTTG
258324	ACGTTGGATGAAGCAGAGGATGTGAGAAGG	ACGTTGGATGAAGCATCTGGCCTGTCACTC
258323	ACGTTGGATGCACGCCCAGCTAATTTTTTC	ACGTTGGATGAGTCAGGAGATCTAGAGCAC
2075880	ACGTTGGATGAAGTGCTGGGATTACAAGCG	ACGTTGGATGAAAGCATTGGCCCAGTATCG
258322	ACGTTGGATGTCTGAAACAGGGCAGAAACC	ACGTTGGATGGGATGCTTACGTTTACCCAG
258321	ACGTTGGATGTTGGCAACAGAGTGAGACCC	ACGTTGGATGAGCTTCCAGAATGACCTACG
164744	ACGTTGGATGTCAGTCCCCACTCTGTGCAA	ACGTTGGATGACAGAGCAAAGTTGGGCACC
164743	ACGTTGGATGAAAAGTGCTTATTGGGCCGG	ACGTTGGATGAACTGCCGACCTCAGGTGAT
164742	ACGTTGGATGAACGAGCGAAACTCCGTCTC	ACGTTGGATGTGATAGCAGGTGCTGCAGTG
187282	GGCGCACGCCTCCACGTGGGAACCCCTGAGCTTTTA	GGCGCACGCCGTTGGAAGCACAAATTCGGC
465507	GGCGCACGCCTCCACGAAGCACCCACCTCAATACGG	TCCGAGTTGGGACAGGTTTC
2162943	ACGTTGGATGTGAGCTCAGGAACCAGGTGAC	ACGTTGGATGCAGCATCGACATGTGGTGAG
1946482	ACGTTGGATGTCCTCGCTATGTTGGAAATG	ACGTTGGATGACCACAACTCAAAGACAGCG
4247353	ACGTTGGATGAGCTGCTGTGACACCCAAGG	ACGTTGGATGAAGCTCTGCTGGAGCCAATC
462769	ACGTTGGATGAAGCCAGGTCAGCCGTGCA	ACGTTGGATGTCCTCAAGGGCCTGTTGGTG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
3803690	ACGTTGGATGACACTCGTGTGGAGAATCCC	ACGTTGGATGTCCCTGCAGTACGGAGTACG
417414	ACGTTGGATGCCACACCCAGCTCATTTTTG	ACGTTGGATGGAGATTGACACCAGCCTAAC
154661	GGCGCACGCCTCCACGCCCTTGAGGCCTCCCAGGG	GGCGCACGCCGGCCAGGAAGCAGCAGAAC
4785704	ACGTTGGATGCACGCCCGGCTGATTTTTTG	ACGTTGGATGCACGAGGTCAGGAGATCAAG
4785584	ACGTTGGATGTAATCCCAGCACTTTGGGAG	ACGTTGGATGGGTTTCACCGTGTTAGCCAG
4785585	ACGTTGGATGCCTGTAATCCCAGCACTTTG	ACGTTGGATGAGGATGGTCTTGATCTCCTG
4785705	ACGTTGGATGAGGATGGTCTTGATCTCCTG	ACGTTGGATGCCTGTAATCCCAGCACTTTG
4785586	ACGTTGGATGATCTCCTGACCTCGTGATCC	ACGTTGGATGAAATCCTACAAATGGCCGGG
4785587	ACGTTGGATGAACAAATCCTGGCGTGGGAG	ACGTTGGATGGGATACAGCTGAGCCAGGAC
2016968	ACGTTGGATGGACACTTCTGTCTCCCTATG	ACGTTGGATGAAAAGCAGTAGCTGTGGACC
3751693	ACGTTGGATGATCAGGTACCTGCATGGATG	ACGTTGGATGGCAGACACTACCTTCTGGAG
3809646	ACGTTGGATGAAAAATGCACGAACGCACGG	ACGTTGGATGTAGAGGAGATGTAGCAGGAG
4785590	ACGTTGGATGACCTCTTGCTGGTGCTAGAC	ACGTTGGATGCTAGAGCAGTGGAGACATTC
2099105	ACGTTGGATGATCAGAGGCTGCATAGCACC	ACGTTGGATGGATGACTAGAAGGGAGACTG
4785708	ACGTTGGATGTGTTCATGCTGAAGCTGCTG	ACGTTGGATGGAAAAGAGAAACGGGAGCAG
4785710	ACGTTGGATGTTGTTCCCAGGAGTCATGGC	ACGTTGGATGAGGTGTCCTGGGATTCAGAC
4785591	ACGTTGGATGATTGGGTGGCCCCTTGTTTG	ACGTTGGATGGAGGAGGTGAGTGGTCATTG
4785592	ACGTTGGATGATTGGGTGGCCCCTTGTTTG	ACGTTGGATGGAGGAGGTGAGTGGTCATTG
4785593	ACGTTGGATGCGCACTGAGAAGAACTGTTG	ACGTTGGATGGGCTAGGTCATGAAAACCAG
4785711	ACGTTGGATGTAAAGAGTGCATTGAGGCCG	ACGTTGGATGAACTCCTGACCTCATGATCC
4785712	ACGTTGGATGCAAAGTGCTGGGATTACAGG	ACGTTGGATGAACAACATGAGACCCTGTCG
4785713	ACGTTGGATGAAGTGAGCCTCTCACCTCAG	ACGTTGGATGTAGTTTACACTGCCGAGTCC
4785714	ACGTTGGATGCTGTGAAGGACTGAAAGCTC	ACGTTGGATGTGAGAGCAGTGGTGAGAGAA
4785594	ACGTTGGATGGCACTTGTGGTTCCTTTCTG	ACGTTGGATGTATCGTGGTGAAGAAGTTCC
3803689	ACGTTGGATGGTGTTTCTGCAGCCTA	ACGTTGGATGTAGGACTGCTTCAGGT

dbSNP rs#	Forward PCR primer	Reverse PCR primer
	ACTC	CTCG
4785715	ACGTTGGATGTGAAGCAGTCCTAGCCAGTG	ACGTTGGATGAAGAAACTTCTAGACCCCCC
3764258	ACGTTGGATGTTCATGCCTTCTGCCTTGCC	ACGTTGGATGATCTCAGCCTTCCAAAGTGC
4785716	ACGTTGGATGATGAAGGCACACCAGCTCTG	ACGTTGGATGTAATGACACGACCTACACAC
4785717	ACGTTGGATGATGAAGGCACACCAGCTCTG	ACGTTGGATGCGGTCTTAATGACACGACCT
2077001	ACGTTGGATGAGGCTAAGGCAGTAGGATTG	ACGTTGGATGTTTGGTAAAGACGGCCTCAC
2377049	ACGTTGGATGCACAAAGTGCTCAATCCCAG	ACGTTGGATGACCATATTGATTGGGCTGGG
2003522	ACGTTGGATGCTGAGATTGGGCTGTTGCAC	ACGTTGGATGCTTGGCATTTTACTCTACGC
1230	GGCGCACGCCTCCACGTCTCCTCGACTGCTTTAGTG	GGCGCACGCCCCAGTGGTTTATTTTCCCGC
1800359	GGCGCACGCCTCCACGAAAGAGCTTCTCACACGTGG	GGCGCACGCCGGCAGCTGTCAATTCTCATG
1061646	GGCGCACGCCTCCACGATAGGCAGAGATGTCCAGAG	AAAAAGCGAAAGGCAGCAGC
1800358	GGCGCACGCCTCCACGTTCTCTCTGTCCCAGTTTCC	GGCGCACGCCAATCGCAAAGTGCAGTGCAG
2286392	ACGTTGGATGCAGGTCCACGTGAGAGTGTG	ACGTTGGATGCAGTCAGCAGCTCTCAGAAC
2074904	ACGTTGGATGTGTAGTGGCCTGTAGGAGCA	ACGTTGGATGAGATGAGGGTGGCTGAGATG
2074903	ACGTTGGATGCGTCAATTAAGGCTCAAAGC	ACGTTGGATGCCTTCTCCAAATTCCACGTC

Table 12

dbSNP rs#	Extend Probe	Term Mix
460879	ACCAACCCCACGCTCTG	ACT
460984	CTTGTGAAGCTGAGTGG	ACT
2437957	CGGAAGGTGGATCAGCG	ACG
3815949	TCCAGCTGCTTTCCCCC	ACT
2437956	TCGGCCTCCCAAAGAGC	ACG
2437955	ACAGGCGTGAGCCACCG	CGT
2434872	GCGGATCCTATCATTTTTA	ACT
467357	GTGCAGCCCAGAATGGTTTC	ACG
258337	AAAGAATCCCAAGGGAC	CGT
258336	CTGGGCCAATTTAAAAGT	ACT
258335	TTTCCAGCGGTACAGTC	ACT

164752	GCTCAGGCCTGTAACCC	ACG
154663	GTGCGATCTCGCTCACC	ACT
164753	TCCTAACAGCTGCCACA	ACT
258332	CCATAATTCAATCACCTCC	ACG
2010623	GCCAACGTGGCGAAACC	ACG
187283	GGCGCACACCTGTAGTC	ACG
258330	AAGAGAAATGGAACACTTC	ACT
258328	CAGGCAGATCACTTGAG	ACG
459920	CCTCCCTCTTCCTCATTCC	ACT
166297	CTCTTCTAAGCCCATTC	ACG
258318	GACTTATTTCATCTTCCTCA	ACT
258317	ATTCACGCCTGTAATCC	ACG
171805	AGGGCTCCTTGGTCTAG	ACG
2081984	GGCACCTGGGTGACTTG	ACG
464586	CTAAGCACTGAGCGATA	ACG
460319	CTGCACTAAGCACTGAG	CGT
447735	TTCTGCTATAGGTCTCTGACA	ACT
2377058	CCACAAAGCTGTAAAACA	ACT
604868	CGCCGTGAGAAACTGCAG	ACG
2118193	GCAGTGAGCTGGGATCG	ACG
467035	AAGAAGGCACCAGACTC	ACT
2115401	CCTTGAGCACTGGAGTC	ACG
417323	ACACTTTTTATATTTGACAAACTT	ACT
2377233	GCTAGGATTACAGGTGT	ACT
3751700	CAGCTATGTCAGCATTC	ACG
2277905	CTCTCACCTGGAGGACC	ACT
397891	AAGCTCCTTCCCGGGCTTC	ACT
3794638	GGCTCAGGGATGCCTCG	CGT
3794637	TGTGGGGAGAATTTACA	ACG
258324	TGATGGCCTAGTCTCAA	CGT
258323	TAGAGCACCCTGACTAA	ACT
2075880	CCACCTTTTCTCATCAGA	ACT
258322	ACCCAGAAATGGTACAA	ACG
258321	GTGGTGTTTTTGGTTTTTT	ACG
164744	CCCCTGCCCAGTTCAAA	ACT
164743	GTGCTGGGATTACAGGC	ACT
164742	CCCCACCTCAGGGAGAA	ACG
187282	CACAAATTCGGCTGAGGCCT	ACT
465507	GGACAGGTTTCCAGGCCA	ACT
2162943	CATGTGGTGAGGAGATA	ACG
1946482	CACCCACCACTCCTCCC	ACT
4247353	CTGACCTGGCTTCGGGG	ACT
462769	ACCCCAAGCTCTGCTGG	ACT
3803690	GAGTACGGGGCTCAGGA	ACT
417414	CAACATGGTGAAACCCC	ACT
154661	GTCCAAACCAGGGCTGTCC	ACT
4785704	ATCAAGACCATCCTGGC	ACG

4785584	GTTAGCCAGGATGGTCT	ACG
4785585	CTCCTGACCTCGTGATC	ACG
4785705	CAGCACTTTGGGAGGCC	ACT
4785586	CCCAGCACTTTGGGAGG	ACG
4785587	TGAGCCAGGACGTTCCC	ACT
2016968	CTCTGTGCTTGCACCCT	ACT
3751693	GTGTCCTTCTGTTCGTT	ACG
3809646	CCAAAATCCGAGTGACG	ACT
4785590	TGCTGAAAACCCTGCCC	ACT
2099105	CTCAAGTTCTCCCCACC	ACT
4785708	GAGCAGTGGAGGAGGCC	ACG
4785710	GGATTCAGACTCAACCC	ACT
4785591	AGTGGTCATTGTGGGAA	ACG
4785592	TGGTCATTGTGGGAACG	ACT
4785593	GGGACAGGGAGAGAAGG	ACG
4785711	GGGATTACAGGCGTGAG	ACT
4785712	AGAGTGCATTGAGGCCG	ACT
4785713	TCATGTTGGCAGTCCCA	ACT
4785714	GGTGAGAGAATCCGTAT	CGT
4785594	GAAGTTCCTTTCTGTTCTT	ACT
3803689	TCAAAGTGTCCTTGGGC	ACT
4785715	CAAGTGAAAGTCTGGCC	ACG
3764258	GATTACAGGTGTGAGCA	ACT
4785716	GACCTACACACATGTGAA	ACT
4785717	GACACGACCTACACACA	ACG
2077001	ACGGCCTCACTATGTTG	ACG
2377049	CTGGTCTTGAACTGACT	ACT
2003522	TCTTGCTCTGTTGCCCA	ACT
1230	CGCAAACGCTGAGTGACT	ACG
1800359	CAATTCTCATGTCCCCCAC	ACT
1061646	GGTCTGCAACACCAAGAA	ACT
1800358	CCAGTCCGGGTTGGGTGC	ACG
2286392	TCAGAACGCCAGGATGC	ACG
2074904	CCTCCGCTGCCCCAGCC	ACT
2074903	CCATGAGTGTGGGTAATAA	ACT

Genetic Analysis1

[0265] Allelotyping results are shown for female (F) and male (M) cases and controls in Table 13 and Table 14, respectively. Allele frequency is noted in the fourth and fifth columns for melanoma pools and control pools, respectively.

Table 13: Females

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
1230	89507717	C/T	C = 0.646 T = 0.354	C = 0.667 T = 0.333	0.5648	1.10	T
154661	89469433	G/C	G = 0.043 C = 0.957	G = 0.081 C = 0.919	0.1895	1.99	C
154663	89428885	T/C	T = 0.196 C = 0.804	T = 0.209 C = 0.791	0.7105	1.08	C
164742	89460586	C/T	C = 0.653 T = 0.347	C = 0.701 T = 0.299	0.1632	1.25	T
164743	89460292	A/G	A = 0.161 G = 0.839	A = 0.244 G = 0.756	0.0477	1.68	G
164744	89459629	A/C	A = 0.654 C = 0.346	A = C =			
164752	89425240	G/A	G = 0.129 A = 0.871	G = 0.057 A = 0.943	**0.0102**	0.41	G
164753	89430445	T/C	T = 0.864 C = 0.136	T = 0.832 C = 0.168	0.2679	0.78	T
166297	89434035	G/A	G = 0.921 A = 0.079	G = 0.909 A = 0.091	0.6280	0.86	G
171805	89436464	G/A	G = 0.979 A = 0.021	G = 0.954 A = 0.046	0.2392	0.45	G
187282	89461834	T/C	T = 0.060 C = 0.940	T = 0.034 C = 0.966	0.2801	0.56	T
187283	89432186	G/A	G = 0.955 A = 0.045	G = 0.973 A = 0.027	0.4705	1.69	A
258317	89435088	C/T	C = T =	C = T =			
258318	89434900	T/C	T = 0.204 C = 0.796	T = 0.250 C = 0.750	0.1543	1.30	C
258321	89459334	C/T	C = 0.603 T = 0.397	C = T =			

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
258322	89458764	C/T	C = 0.909 T = 0.091	C = 0.952 T = 0.048	0.1337	2.00	T
258323	89457555	C/G	C = 0.823 G = 0.177	C = 0.779 G = 0.221	0.2597	0.76	C
258324	89457116	C/A	C = 0.898 A = 0.102	C = 0.891 A = 0.109	0.8124	0.94	C
258328	89433164	C/T	C = 0.870 T = 0.130	C = 0.906 T = 0.094	0.3402	1.43	T
258330	89432424	T/G	T = 0.583 G = 0.417	T = 0.626 G = 0.374	0.2752	1.20	G
258332	89430533	G/A	G = 0.950 A = 0.050	G = 0.941 A = 0.059	0.6814	0.84	G
258335	89423794	A/G	A = 0.770 G = 0.230	A = 0.753 G = 0.247	0.6280	0.91	A
258336	89423681	T/G	T = 0.619 G = 0.381	T = 0.556 G = 0.444	0.1140	0.77	T
258337	89423560	A/T	A = 0.572 T = 0.428	A = 0.643 T = 0.357	0.0628	1.35	T
397891	89455892	C/G	C = 0.695 G = 0.305	C = G =			
417323	89449127	T/G	T = 0.635 G = 0.365	T = 0.641 G = 0.359	0.8812	1.03	G
417414	89469010	A/G	A = G =	A = 0.232 G = 0.768			
447735	89437199	A/G	A = 0.700 G = 0.300	A = 0.660 G = 0.340	0.2640	0.83	A
459920	89433677	T/C	T = 0.723 C = 0.277	T = 0.687 C = 0.313	0.2956	0.84	T
460319	89436943	G/T	G = 0.166 T = 0.834	G = 0.213 T = 0.787	0.1390	1.36	T
460879	89415739	T/C	T = 0.492 C =	T = 0.595 C = 0.405	**0.0376**	1.52	C

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
			0.508				
460984	89416024	T/C	T = 0.781 C = 0.219	T = 0.846 C = 0.154	0.0661	1.55	C
462769	89466125	A/G	A = 0.666 G = 0.334	A = 0.688 G = 0.312	0.5827	1.10	G
464586	89436938	C/T	C = 0.355 T = 0.645	C = 0.158 T = 0.842	**0.0000**	0.34	C
465507	89463354	G/C	G = 0.022 C = 0.978	G = C =			
467035	89443135	C/G	C = 0.647 G = 0.353	C = 0.632 G = 0.368	0.6744	0.94	C
467357	89420247	G/A	G = 0.650 A = 0.350	G = 0.660 A = 0.340	0.7932	1.04	A
604868	89439027	G/A	G = 0.119 A = 0.881	G = 0.116 A = 0.884	0.9238	0.98	G
1061646	89508839	T/C	T = 0.388 C = 0.612	T = 0.355 C = 0.645	0.3444	0.87	T
1800358	89512181	C/T	C = 0.199 T = 0.801	C = 0.200 T = 0.800	0.9836	1.00	T
1800359	89508123	A/G	A = 0.706 G = 0.294	A = 0.776 G = 0.224	**0.0260**	1.45	G
1946482	89465272	T/C	T = 0.901 C = 0.099	T = 0.892 C = 0.108	0.7410	0.91	T
2003522	89506148	C/G	C = 0.388 G = 0.612	C = 0.345 G = 0.655	0.2567	0.83	C
2010623	89431875	C/T	C = 0.961 T = 0.039	C = 0.978 T = 0.022	0.4734	1.81	T
2016968	89475768	C/G	C = 0.655 G = 0.345	C = 0.639 G = 0.361	0.6664	0.93	C

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
2074903	89514525	A/G	A = 0.922 G = 0.078	A = 0.907 G = 0.093	0.5732	0.83	A
2074904	89514408	T/C	T = 0.915 C = 0.085	T = 0.919 C = 0.081	0.8477	1.06	C
2075880	89458077	A/G	A = 0.624 G = 0.376	A = 0.696 G = 0.304	**0.0403**	1.38	G
2077001	89504952	C/T	C = 0.412 T = 0.588	C = 0.460 T = 0.540	0.1898	1.22	T
2081984	89436776	C/T	C = 0.875 T = 0.125	C = 0.870 T = 0.130	0.8591	0.96	C
2099105	89496417	A/G	A = 0.439 G = 0.561	A = 0.386 G = 0.614	0.1427	0.80	A
2115401	89443459	C/T	C = 0.661 T = 0.339	C = 0.661 T = 0.339	0.9999	1.00	C
2118193	89442753	C/T	C = 0.814 T = 0.186	C = T =			
2162943	89463514	G/A	G = 0.796 A = 0.204	G = 0.834 A = 0.166	0.2175	1.28	A
2277905	89455362	A/G	A = 0.919 G = 0.081	A = 0.887 G = 0.113	0.2257	0.69	A
2286392	89512411	C/T	C = 0.266 T = 0.734	C = 0.271 T = 0.729	0.8865	1.02	T
2377049	89505830	A/C	A = 0.772 C = 0.228	A = 0.793 C = 0.207	0.5734	1.13	C
2377058	89437681	T/C	T = 0.780 C = 0.220	T = 0.796 C = 0.204	0.6094	1.10	C
2377233	89449752	C/G	C = 0.891 G = 0.109	C = 0.846 G = 0.154	0.1471	0.67	C
2434872	89419765	C/G	C = 0.531 G = 0.469	C = 0.547 G = 0.453	0.6409	1.07	G

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
2437955	89419125	G/T	G = 0.846 T = 0.154	G = 0.753 T = 0.247	**0.0227**	0.55	G
2437956	89419101	G/A	G = 0.754 A = 0.246	G = 0.756 A = 0.244	0.9642	1.01	A
2437957	89418498	C/T	C = 0.502 T = 0.498	C = 0.509 T = 0.491	0.8509	1.03	T
3751693	89477258	C/T	C = 0.377 T = 0.623	C = 0.367 T = 0.633	0.8164	0.96	C
3751700	89455055	G/A	G = 0.977 A = 0.023	G = A =			
3764258	89503876	C/G	C = 0.904 G = 0.096	C = 0.910 G = 0.090	0.7881	1.08	G
3794637	89456431	G/A	G = 0.837 A = 0.163	G = A =			
3794638	89456297	G/T	G = 0.924 T = 0.076	G = 0.902 T = 0.098	0.5231	0.75	G
3803689	89502920	A/G	A = 0.681 G = 0.319	A = 0.624 G = 0.376	0.0904	0.77	A
3803690	89466221	C/G	C = 0.669 G = 0.331	C = 0.702 G = 0.298	0.3623	1.17	G
3809646	89489717	A/G	A = 0.780 G = 0.220	A = 0.746 G = 0.254	0.3238	0.83	A
3815949	89418766	C/G	C = G =	C = 0.043 G = 0.957			
4247353	89466076	T/C	T = 0.377 C = 0.623	T = 0.419 C = 0.581	0.3605	1.19	C
4785584	89475246	C/T	C = 0.875 T = 0.125	C = 0.860 T = 0.140	0.5770	0.88	C
4785585	89475267	C/T	C = 0.797 T = 0.203	C = 0.801 T = 0.199	0.8823	1.03	T
4785586	8947527	G/A	G =	G = 0.822			

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
	8		A =	A = 0.178			
4785587	89475481	A/G	A = 0.759 G = 0.241	A = 0.714 G = 0.286	0.1701	0.80	A
4785590	89493029	G/C	G = 0.657 C = 0.343	G = 0.622 C = 0.378	0.3664	0.86	G
4785591	89500375	C/T	C = 0.717 T = 0.283	C = 0.756 T = 0.244	0.2397	1.23	T
4785592	89500377	C/G	C = 0.031 G = 0.969	C = G =			
4785593	89500489	C/T	C = 0.396 T = 0.604	C = 0.356 T = 0.644	0.2519	0.84	C
4785594	89501378	C/G	C = 0.708 G = 0.292	C = 0.753 G = 0.247	0.2422	1.26	G
4785704	89475232	G/A	G = 0.058 A = 0.942	G = 0.056 A = 0.944	0.8993	0.95	G
4785705	89475276	T/C	T = 0.513 C = 0.487	T = 0.482 C = 0.518	0.3839	0.88	T
4785708	89499431	C/T	C = 0.691 T = 0.309	C = 0.641 T = 0.359	0.1476	0.80	C
4785710	89499618	T/C	T = 0.554 C = 0.446	T = 0.599 C = 0.401	0.2751	1.20	C
4785711	89500808	C/G	C = 0.977 G = 0.023	C = G =			
4785712	89500816	G/C	G = 0.240 C = 0.760	G = 0.224 C = 0.776	0.6271	0.92	G
4785713	89500960	G/C	G = 0.582 C = 0.418	G = 0.528 C = 0.472	0.1411	0.80	G
4785714	8950126	C/A	C =	C = 0.631	**0.017**	0.67	C

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
	6		0.718 A = 0.282	A = 0.369	**9**		
4785715	89502997	G/A	G = 0.631 A = 0.369	G = 0.642 A = 0.358	0.7601	1.05	A
4785716	89503989	T/C	T = 0.860 C = 0.140	T = 0.958 C = 0.042	**0.0001**	3.74	C
4785717	89503995	G/A	G = 0.600 A = 0.400	G = 0.571 A = 0.429	0.4073	0.89	G

Table 14: Males

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
1230	89507717	C/T	C = 0.663 T = 0.337	C = 0.672 T = 0.328	0.798	1.04	T
154661	89469433	G/C	G = 0.024 C = 0.976	G = C =			
154663	89428885	T/C	T = 0.173 C = 0.827	T = 0.207 C = 0.793	0.316	1.25	C
164742	89460586	C/T	C = 0.678 T = 0.322	C = 0.760 T = 0.240	**0.024**	1.50	T
164743	89460292	A/G	A = 0.052 G = 0.948	A = G =			
164744	89459629	A/C	A = 0.715 C = 0.285	A = 0.574 C = 0.426	**0.001**	0.54	A
164752	89425240	G/A	G = 0.102 A = 0.898	G = 0.054 A = 0.946	0.069	0.51	G
164753	89430445	T/C	T = 0.903 C = 0.097	T = 0.808 C = 0.192	**0.001**	0.45	T
166297	89434035	G/A	G = 0.945	G = 0.916 A = 0.084	0.243	0.64	G

dbSNP rs#	Chromosome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			A = 0.055				
171805	89436464	G/A	G = A =	G = 0.964 A = 0.036			
187282	89461834	T/C	T = 0.066 C = 0.934	T = 0.047 C = 0.953	0.626	0.69	T
187283	89432186	G/A	G = 0.967 A = 0.033	G = 0.971 A = 0.029	0.904	1.13	A
258317	89435088	C/T	C = 0.975 T = 0.025	C = 0.979 T = 0.021	0.865	1.17	T
258318	89434900	T/C	T = 0.150 C = 0.850	T = 0.223 C = 0.777	**0.041**	1.63	C
258321	89459334	C/T	C = 0.607 T = 0.393	C = 0.735 T = 0.265	**0.005**	1.80	T
258322	89458764	C/T	C = 0.909 T = 0.091	C = 0.956 T = 0.044	**0.040**	2.17	T
258323	89457555	C/G	C = 0.817 G = 0.183	C = 0.785 G = 0.215	0.344	0.82	C
258324	89457116	C/A	C = 0.916 A = 0.084	C = 0.894 A = 0.106	0.406	0.77	C
258328	89433164	C/T	C = 0.855 T = 0.145	C = 0.782 T = 0.218	0.062	0.61	C
258330	89432424	T/G	T = 0.633 G = 0.367	T = 0.607 G = 0.393	0.482	0.89	T
258332	89430533	G/A	G = 0.952 A = 0.048	G = 0.933 A = 0.067	0.383	0.70	G
258335	89423794	A/G	A = 0.778 G = 0.222	A = 0.792 G = 0.208	0.726	1.09	G
258336	89423681	T/G	T = 0.588 G = 0.412	T = 0.522 G = 0.478	0.091	0.76	T
258337	89423560	A/T	A = 0.577 T = 0.423	A = 0.654 T = 0.346	**0.041**	1.38	T
397891	89455892	C/G	C = 0.608	C = G =			

dbSNP rs#	Chromosome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			G = 0.392				
417323	89449127	T/G	T = 0.625 G = 0.375	T = 0.664 G = 0.336	0.461	1.18	G
417414	89469010	A/G	A = 0.075 G = 0.925	A = 0.222 G = 0.778	**0.000**	3.51	G
447735	89437199	A/G	A = 0.687 G = 0.313	A = 0.654 G = 0.346	0.359	0.86	A
459920	89433677	T/C	T = 0.719 C = 0.281	T = 0.687 C = 0.313	0.358	0.86	T
460319	89436943	G/T	G = 0.156 T = 0.844	G = 0.230 T = 0.770	**0.020**	1.62	T
460879	89415739	T/C	T = 0.532 C = 0.468	T = C =			
460984	89416024	T/C	T = 0.794 C = 0.206	T = C =			
462769	89466125	A/G	A = 0.664 G = 0.336	A = 0.720 G = 0.280	0.131	1.30	G
464586	89436938	C/T	C = 0.305 T = 0.695	C = 0.133 T = 0.867	**0.000**	0.35	C
465507	89463354	G/C	G = 0.033 C = 0.967	G = C =			
467035	89443135	C/G	C = 0.662 G = 0.338	C = 0.621 G = 0.379	0.287	0.83	C
467357	89420247	G/A	G = 0.654 A = 0.346	G = 0.650 A = 0.350	0.913	0.98	G
604868	89439027	G/A	G = 0.103 A = 0.897	G = 0.109 A = 0.891	0.818	1.06	A
1061646	89508839	T/C	T = 0.376 C = 0.624	T = 0.322 C = 0.678	0.241	0.79	T
1800358	8951218	C/T	C =	C = 0.177	0.357	0.83	C

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
	1		0.205 T = 0.795	T = 0.823			
1800359	8950812 3	A/G	A = 0.756 G = 0.244	A = 0.806 G = 0.194	0.120	1.34	G
1946482	8946527 2	T/C	T = 0.896 C = 0.104	T = 0.878 C = 0.122	0.556	0.84	T
2003522	8950614 8	C/G	C = 0.355 G = 0.645	C = 0.316 G = 0.684	0.339	0.84	C
2010623	8943187 5	C/T	C = 0.971 T = 0.029	C = 0.952 T = 0.048	0.535	0.59	C
2016968	8947576 8	C/G	C = 0.668 G = 0.332	C = 0.635 G = 0.365	0.424	0.87	C
2074903	8951452 5	A/G	A = 0.915 G = 0.085	A = 0.914 G = 0.086	0.964	0.99	A
2074904	8951440 8	T/C	T = 0.932 C = 0.068	T = 0.920 C = 0.080	0.606	0.84	T
2075880	8945807 7	A/G	A = 0.597 G = 0.403	A = 0.707 G = 0.293	**0.004**	1.63	G
2077001	8950495 2	C/T	C = 0.461 T = 0.539	C = 0.475 T = 0.525	0.721	1.06	T
2081984	8943677 6	C/T	C = 0.860 T = 0.140	C = 0.846 T = 0.154	0.614	0.89	C
2099105	8949641 7	A/G	A = 0.421 G = 0.579	A = 0.366 G = 0.634	0.139	0.79	A
2115401	8944345 9	C/T	C = 0.673 T = 0.327	C = 0.652 T = 0.348	0.592	0.91	C
2118193	8944275 3	C/T	C = T =	C = T =			
2162943	8946351 4	G/A	G = 0.823 A = 0.177	G = 0.798 A = 0.202	0.498	0.85	G
2277905	8945536 2	A/G	A = 0.956 G =	A = 0.937 G = 0.063	0.468	0.68	A

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			0.044				
2286392	89512411	C/T	C = 0.269 T = 0.731	C = 0.287 T = 0.713	0.616	1.09	T
2377049	89505830	A/C	A = 0.777 C = 0.223	A = 0.800 C = 0.200	0.498	1.15	C
2377058	89437681	T/C	T = 0.840 C = 0.160	T = 0.840 C = 0.160	0.987	1.00	T
2377233	89449752	C/G	C = 0.899 G = 0.101	C = 0.833 G = 0.167	0.056	0.56	C
2434872	89419765	C/G	C = 0.544 G = 0.456	C = 0.586 G = 0.414	0.373	1.18	G
2437955	89419125	G/T	G = 0.887 T = 0.113	G = 0.826 T = 0.174	0.057	0.60	G
2437956	89419101	G/A	G = 0.781 A = 0.219	G = 0.724 A = 0.276	0.109	0.74	G
2437957	89418498	C/T	C = 0.542 T = 0.458	C = 0.512 T = 0.488	0.449	0.89	C
3751693	89477258	C/T	C = 0.390 T = 0.610	C = 0.382 T = 0.618	0.853	0.97	C
3751700	89455055	G/A	G = A =	G = 0.941 A = 0.059			
3764258	89503876	C/G	C = 0.918 G = 0.082	C = 0.913 G = 0.087	0.843	0.94	C
3794637	89456431	G/A	G = 0.874 A = 0.126	G = 0.833 A = 0.167	0.227	0.72	G
3794638	89456297	G/T	G = T =	G = 0.944 T = 0.056			
3803689	89502920	A/G	A = 0.638 G = 0.362	A = 0.614 G = 0.386	0.549	0.91	A
3803690	89466221	C/G	C = 0.687 G =	C = 0.691 G = 0.309	0.936	1.02	G

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			0.313				
3809646	89489717	A/G	A = 0.786 G = 0.214	A = 0.739 G = 0.261	0.227	0.77	A
3815949	89418766	C/G	C = G =	C = G =			
4247353	89466076	T/C	T = C =	T = 0.423 C = 0.577			
4785584	89475246	C/T	C = 0.894 T = 0.106	C = 0.869 T = 0.131	0.336	0.78	C
4785585	89475267	C/T	C = 0.810 T = 0.190	C = 0.811 T = 0.189	0.977	1.01	T
4785586	89475278	G/A	G = 0.804 A = 0.196	G = 0.852 A = 0.148	0.190	1.41	A
4785587	89475481	A/G	A = 0.743 G = 0.257	A = 0.690 G = 0.310	0.126	0.77	A
4785590	89493029	G/C	G = 0.643 C = 0.357	G = 0.606 C = 0.394	0.315	0.85	G
4785591	89500375	C/T	C = 0.767 T = 0.233	C = 0.769 T = 0.231	0.959	1.01	T
4785592	89500377	C/G	C = G =	C = G =			
4785593	89500489	C/T	C = 0.381 T = 0.619	C = 0.341 T = 0.659	0.256	0.84	C
4785594	89501378	C/G	C = 0.729 G = 0.271	C = 0.753 G = 0.247	0.521	1.13	G
4785704	89475232	G/A	G = 0.049 A = 0.951	G = 0.045 A = 0.955	0.855	0.92	G
4785705	89475276	T/C	T = 0.500 C = 0.500	T = 0.481 C = 0.519	0.621	0.93	T
4785708	89499431	C/T	C = 0.675 T = 0.325	C = 0.601 T = 0.399	**0.037**	0.73	C
4785710	89499618	T/C	T = 0.572 C =	T = 0.621 C = 0.379	0.202	1.22	C

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			0.428				
4785711	89500808	C/G	C = G =	C = G =			
4785712	89500816	G/C	G = 0.233 C = 0.767	G = 0.186 C = 0.814	0.164	0.76	G
4785713	89500960	G/C	G = 0.548 C = 0.452	G = 0.484 C = 0.516	0.080	0.77	G
4785714	89501266	C/A	C = 0.659 A = 0.341	C = 0.599 A = 0.401	0.093	0.77	C
4785715	89502997	G/A	G = 0.642 A = 0.358	G = 0.658 A = 0.342	0.649	1.07	A
4785716	89503989	T/C	T = 0.903 C = 0.097	T = C =			
4785717	89503995	G/A	G = 0.600 A = 0.400	G = 0.539 A = 0.461	0.095	0.78	G

[0266] Allelotyping results were considered significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The assay failed for those SNPs in which the allele frequency is blank. The combined allelotyping p-values for males and females were plotted in Figure 12 and separately for females and males in Figures 13 and 14, respectively. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figures 12, 13 and 14 can be determined by consulting Table 13 or 14. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0267] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The light gray line (or generally bottom-most curve) is a nonlinear smoother through the data points on the graph using a local polynomial

regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line (or generally top-most curve, *e.g.*, see peak in left-most graph just to the left of position 92150000) provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0268] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is place at the 3' end of each gene to show the direction of transcription.

Example 6

PCLO Proximal SNPs

[0269] It has been discovered that a polymorphic variation (rs1044639) in the untranslated region of a gene encoding presynaptic cytomatrix protein (PCLO) is associated with the occurrence of melanoma. See Table 3. Subsequently, sixty allelic variants located within or nearby the target gene were identified and subsequently allelotyped in melanoma case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 15. The chromosome position provided in column four of Table 15 is based on Genome "Build 33" of NCBI's GenBank.

Table 15

dbSNP rs#	Chromosome	Position in Fig. 2	Chromosome Position	Allele Variants	Allele Present in Fig. 2	IUPAC Code
2158220	7	118	82009218	T/C	T	Y
1024465	7	1263	82010363	G/A	A	R
4732483	7	5696	82014796	T/C	C	Y
4732485	7	8775	82017875	C/T	T	Y
1859176	7	17207	82026307	C/T	C	Y
1859177	7	17344	82026444	C/T	C	Y
2074401	7	18735	82027835	A/G	A	R
4299948	7	19057	82028157	T/G	G	K
4348435	7	20800	82029900	G/A	A	R
4348436	7	20821	82029921	G/C	C	S
4413718	7	20964	82030064	G/C	G	S
985199	7	21045	82030145	G/A	G	R
2522830	7	32252	82041352	G/A	G	R
2214414	7	33261	82042361	T/C	C	Y
2051791	7	33887	82042987	C/T	T	Y

dbSNP rs#	Chromosome	Position in Fig. 2	Chromosome Position	Allele Variants	Allele Present in Fig. 2	IUPAC Code
2214415	7	34631	82043731	G/A	A	R
2189247	7	36394	82045494	C/A	C	M
2522831	7	37249	82046349	T/C	T	Y
2715147	7	37554	82046654	T/C	C	Y
2715148	7	39184	82048284	A/C	A	M
2522832	7	39513	82048613	A/G	A	R
1044639	7	40707	82049807	G/T	T	K
2715149	7	41961	82051061	A/T	A	W
2522833	7	42857	82051957	C/A	A	M
2247523	7	43553	82052653	C/G	C	S
2371214	7	43821	82052921	T/C	T	Y
2189248	7	44454	82053554	T/C	T	Y
2715150	7	45044	82054144	A/G	A	R
2715151	7	45812	82054912	C/G	C	S
2371215	7	46643	82055743	T/A	T	W
2715152	7	46815	82055915	G/A	G	R
2715153	7	47007	82056107	T/C	C	Y
972346	7	49684	82058784	C/T	C	Y
2715154	7	50015	82059115	G/T	G	K
2522834	7	50095	82059195	T/C	C	Y
2023847	7	50442	82059542	G/T	T	K
2715155	7	51203	82060303	A/G	A	R
2715156	7	51983	82061083	A/G	G	R
2301722	7	54383	82063483	A/C	A	M
2257207	7	57333	82066433	A/T	A	W
2715157	7	57523	82066623	A/G	A	R
2715158	7	58755	82067855	G/C	G	S
2715159	7	60557	82069657	A/G	A	R
2522835	7	60645	82069745	A/T	T	W
2522836	7	62202	82071302	C/A	C	M
2522837	7	64531	82073631	A/G	A	R
2522838	7	64706	82073806	A/T	T	W
2522839	7	66797	82075897	G/A	A	R
2522840	7	67564	82076664	G/T	T	K
2522842	7	68811	82077911	G/T	G	K
2522843	7	68871	82077971	C/A	C	M
2522844	7	69241	82078341	T/C	C	Y
2522845	7	71058	82080158	T/G	T	K
2715161	7	71430	82080530	C/T	C	Y
4377905	7	83460	82092560	A/G	A	R
4579453	7	83870	82092970	T/C	T	Y
4260846	7	83985	82093085	C/A	C	M
1986481	7	85832	82094932	A/T	A	W
4628206	7	86492	82095592	A/T	T	W
2888017	7	89352	82098452	A/G	G	R

Assay for Verifying and Allelotyping SNPs

[0270] The methods used to verify and allelotype the sixty proximal SNPs of Table 15 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 16 and Table 17, respectively.

Table 16

dbSNP rs#	Forward PCR primer	Reverse PCR primer
2158220	ACGTTGGATGCCACAGCCCTTATTACAGTC	ACGTTGGATGGGGCAGGAGAGAGATTCTAT
1024465	GGCGCACGCCTCCACGCAAGCAAAACTCTTCTAAAG	GGCGCACGCCAGAGATTGTGTTAAGGCATC
4732483	ACGTTGGATGCCCACCAAGACTGTAAAAGC	ACGTTGGATGCAGGAAACAACAGATGCTGG
4732485	ACGTTGGATGAGGGAGTAGTGCAAGATAGG	ACGTTGGATGAAGTTCTTCCTGACAGCTTC
1859176	ACGTTGGATGGGACAAGTTGTTTTTCACTG	ACGTTGGATGGCTTATAGTGATTCATGCCC
1859177	ACGTTGGATGGATTAGTTATTGAGCAGAGGG	ACGTTGGATGCTACCAAAAGGGCACTTGAC
2074401	ACGTTGGATGGGTTTAGGTTTCAATTCTGG	ACGTTGGATGCCAGCATTTGTCAGATGAGG
4299948	ACGTTGGATGGAGGGAGACTCCATCTCAAA	ACGTTGGATGGAGAGAGGTTGGAATGACAC
4348435	ACGTTGGATGAAGGGTTAACAGAGTGCCTG	ACGTTGGATGCTAAGGCTACTACGAGCATG
4348436	ACGTTGGATGAAGGGTTAACAGAGTGCCTG	ACGTTGGATGTTTTGGTTGAATTCTAAGGC
4413718	ACGTTGGATGGAGGACTGTAAGCTTAGAATG	ACGTTGGATGTGTAGCTTTTTCTCTAGCCG
985199	ACGTTGGATGGAGAAAAAGCTACATGGCAC	ACGTTGGATGTTCCATCTTTTTAGAACGCC
2522830	ACGTTGGATGTGTATGTAAAAATGATGACC	ACGTTGGATGAATGCCAAAAGGATATTTGC
2214414	ACGTTGGATGAAAACTCCACTGTACACTCG	ACGTTGGATGTTTCAGGGATCTGCAAGGTC
2051791	ACGTTGGATGCAACTACCTAATTCAAATGTC	ACGTTGGATGGTCATTGGCAATGAGGATGC
2214415	ACGTTGGATGTCTTCCCCCAGATCATGTTG	ACGTTGGATGTTCCACTTTTCATCCACATG
2189247	ACGTTGGATGGAAGCATTCCTAAAACCTTG	ACGTTGGATGTCAAACAAAAATAGCTCAGG
2522831	ACGTTGGATGTGCTCACGCATAAAACAGGG	ACGTTGGATGGTACAGAGTGTTTTGTCATCC
2715147	ACGTTGGATGCTAGTTTTTCTCTCTGCACTT	ACGTTGGATGGATCCATGTATATTTCCAGGC
2715148	GGCGCACGCCTCCACGCAAGAGAGA	TACCAGTTGGAATGTGGATC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
	ACTTTCACCATG	
2522832	GGCGCACGCCTCCACGAGCACACAGCAAGAACATCC	GGCGCACGCCAATGCCATGCCCACAAAAGC
1044639	ACGTTGGATGCGCAAACAAAAAGGACACAC	ACGTTGGATGCTCCTTTGTTTCCACCATCC
2715149	ACGTTGGATGGTTCAGTATATCTAGGTAAGG	ACGTTGGATGAAACTGAGCTACTGCCTCTG
2522833	GGCGCACGCCTCCACGTTCCTTGGTTTATATCCTTG	TACCACCTTGGAGTGTTATC
2247523	ACGTTGGATGGGTAGTCATATCCCTATTTC	ACGTTGGATGGGGACAAAATGGAAAAGAATG
2371214	ACGTTGGATGGAAGGACTTCAGTAAGTCAC	ACGTTGGATGTTGATCCTAGGCAGGAGTAC
2189248	ACGTTGGATGAGATTAAAAATCACAAGATC	ACGTTGGATGTACACTTACTATGTACTTGT
2715150	ACGTTGGATGACACTGGAGGTGACAGTTTG	ACGTTGGATGACCATAGCAGCAAATAAGGG
2715151	ACGTTGGATGGGCATTGTGGTGCTAATCTC	ACGTTGGATGTAATTTTTGCCTACAGTTAC
2371215	ACGTTGGATGTAGAACACCTACAAGCATTTC	ACGTTGGATGTAAGTTGAATGCACAGTGAC
2715152	ACGTTGGATGGCCCCATAAACAATAATTTGG	ACGTTGGATGCATCTTTTTCTCAGTACACTC
2715153	ACGTTGGATGATAAATTTTTGGTTTATGTC	ACGTTGGATGAATGCAGATGTCCCAAGTTC
972346	ACGTTGGATGCCTATGTTTGGATCCTGGTC	ACGTTGGATGGGTGAGAAAACTTGAAGCTC
2715154	ACGTTGGATGCATCGTGAACAAGTTAGGCC	ACGTTGGATGGCGTAATTGTTCCACAACAC
2522834	ACGTTGGATGTGGCCAGATACATTTAGAAA	ACGTTGGATGTGGAGAATCAAACTCATTAC
2023847	ACGTTGGATGCAAAATCTGTGGAGTTGAAGG	ACGTTGGATGCAGCCTGACTTTATGCTCAC
2715155	ACGTTGGATGGTTTAGTAAAGGAAAACCAG	ACGTTGGATGGAAGGCTTCTTTGGTGTATC
2715156	ACGTTGGATGATAAGAGTCCTGTTAGCTAG	ACGTTGGATGATTGATCAGAGGGTGGGAAG
2301722	ACGTTGGATGTTCCAAGGCCTTTGCTTGTC	ACGTTGGATGAGGCAGCTAATAAGCTACCC
2257207	ACGTTGGATGGCTGTCAGCACTGAAATGTA	ACGTTGGATGGTACCGAAAGGTATCTATAGG
2715157	ACGTTGGATGGAAGAAAAAAATGCTTAACTC	ACGTTGGATGGCACAATTGTGGCTGAATAC
2715158	ACGTTGGATGAGGTCATCAGGGTAGTACTG	ACGTTGGATGAAGCAGAAGTGGAGTGTGAG
2715159	ACGTTGGATGAGTAGCATAATTCCTCTGGC	ACGTTGGATGCCACAAAAGACCCTAATAGC
2522835	ACGTTGGATGAGCCAGAGGAATTATGCTAC	ACGTTGGATGCCATTCCATATGTCTGTCTG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
2522836	ACGTTGGATGTCACTTGAATATGGGAGGCG	ACGTTGGATGACAGAGTCTCACTCTGTCCC
2522837	ACGTTGGATGCATGATGAGATAGATTTAAC	ACGTTGGATGAAACATAGGAAAAAGTGATG
2522838	ACGTTGGATGCTAAAAAGAATCAAGTACGC	ACGTTGGATGCCTGTGAAAGTAATGCTTGG
2522839	ACGTTGGATGCCACAATTATGTTGTTGAACC	ACGTTGGATGTACACCACTGCACTCCAGTC
2522840	ACGTTGGATGGGAGGAAGAGTACATTAATA	ACGTTGGATGTGTGCTCCTGCAGAAATGTG
2522842	ACGTTGGATGCCATGCCTGGCCTTTAATAG	ACGTTGGATGAATCCTATCATCGATGCTAC
2522843	ACGTTGGATGTACTAAGTTCTTGAATTACC	ACGTTGGATGTCGATGATAGGATTTGTTGC
2522844	ACGTTGGATGTGGTAGGCACTACACAATTC	ACGTTGGATGCCAATTGTTTTCTAGTAGACT
2522845	ACGTTGGATGAAACCAGTAGTGGATCAGCC	ACGTTGGATGATGTACACCAGTGGTTTGCC
2715161	ACGTTGGATGAACAGGGCTGGAATTGGAGG	ACGTTGGATGTAGCTCCTACATATGGAGTG
4377905	ACGTTGGATGTATGGCTGTATCAATATCAC	ACGTTGGATGAATGCAAACTGTCTAAGCAC
4579453	ACGTTGGATGGACTGTAATCCCAGCTACTC	ACGTTGGATGTCTCAGCTCACTGCACTGTC
4260846	ACGTTGGATGGGAAATATACCATATAAATG	ACGTTGGATGAGAGCAAGATGCCGTCTCAG
1986481	ACGTTGGATGAGTACCCAGGTGTTCTTAGC	ACGTTGGATGAAGCATGACATTATGTTTCC
4628206	ACGTTGGATGCTTCACAGAAGAGAGTTTCC	ACGTTGGATGGCGTTAGGTACACATGACAC
2888017	ACGTTGGATGCATCTCCTTGCCAGCATCTC	ACGTTGGATGCACTAGTCATCAGGGAAATC

Table 17

dbSNP rs#	Extend Probe	Term Mix
2158220	CTGAGGCCTGCCCCTGA	ACT
1024465	TTAAGGCATCTCTGTATATACTAA	ACG
4732483	CAGATGCTGGAGAGGAT	ACT
4732485	GACAGCTTCAGATATTTCA	ACG
1859176	CATGCCCAATTCATATAGATA	ACG
1859177	TCTGTCTTGTTCCCATC	ACG
2074401	CAGATGAGGTTTCTGAAG	ACT

4299948	AAGGACTATAGGGCTACTA	ACT
4348435	CATGCCTACCTGTTAATATG	ACG
4348436	GAATTCTAAGGCTACTACGA	ACT
4413718	AAGAAGTGGTCTACTGTC	ACT
985199	GAACGCCTTATCTAAGCA	ACG
2522830	AGGATATTTGCAAACGTG	ACG
2214414	TGCAAGGTCAAAATATTCTT	ACT
2051791	GATGCTTTAAAACAAAAACTACA	ACG
2214415	CCATAATATTTCACCCATTCT	ACG
2189247	AAAATAGCTCAGGTTTTTCA	CGT
2522831	ACATTAAGTGGATGAGGT	ACT
2715147	TATTTCCAGGCACTTCA	ACT
2715148	GAATGTGGATCAGTGTTT	ACT
2522832	AGACAATCTCTAAAAATTAA	ACT
1044639	CATCCATCCAACCTGGCTC	CGT
2715149	CCTCTGTGGGATAAAACA	CGT
2522833	GAGTGTTATCGAGGTGAG	CGT
2247523	TGAGTAAGTTGCAATTACAAA	ACT
2371214	CAGGAGTACTCTAGATTAGT	ACT
2189248	CAAATAATCATGAAATTGGTAGC	ACT
2715150	AAATAAGGGAAAGGAAGTC	ACT
2715151	TTGCCTACAGTTACTTATCT	ACT
2371215	GTAGTTTTCTTTGCCCT	CGT
2715152	CAATGTTTTAGTTTTGCTTTTC	ACG
2715153	TTTGGTTCATCAATTGTAAAATA	ACT
972346	GAAGCTCAGAAAAATTAAGG	ACG
2715154	TTCCACAACACTCACTT	CGT
2522834	CATTTTAACTTTTGTCCAATCA	ACT
2023847	TAAGAATCCCCCTGTTT	CGT
2715155	GGTGTATCTACTTTCATAAAATT	ACT
2715156	AGGGTGGGAAGAAAAAA	ACT
2301722	GGTCTTTCTTTTAATCACAC	ACT
2257207	CGAAAGGTATCTATAGGTTTAAT A	CGT
2715157	AACAAATATTTGAGAAAACTGC	ACT
2715158	TGTGCAGAAGGTTGACA	ACT
2715159	CCTAATAGCCAAAGCAATTTT	ACT
2522835	CATATGTCTGTCTGCTTTTA	CGT
2522836	CAGTGGTGTGATCTCTG	CGT
2522837	CAATGGATTTAACAAATTTGTAG	ACT
2522838	ATGCTTGGAGCCATTTC	CGT
2522839	GACAGAGTGGGACCTGT	ACG
2522840	TGCAGAAATGTGACAATG	CGT
2522842	GATGCTACATATTCAGCAAAA	CGT
2522843	CAAAGTCTTTTGCTTAATAGG	CGT
2522844	ACACCATAAAATGTTAGACATAA	ACT
2522845	CTGCTGGCTTCCTACTT	ACT

2715161	CTACATATGGAGTGAGAACA	ACG
4377905	AACTGTCTAAGCACTCTAAA	ACT
4579453	TCTGCCTCCCTGGTTCA	ACT
4260846	ACAAACAAACAAACAAAAAAC	CGT
1986481	TTTTGCCAACTATTATCCC	CGT
4628206	CATGACACAGACCACAT	CGT
2888017	GAAATCCAAATTAAAACCACA	ACT

Genetic Analysis

[0271] Allelotyping results are shown for female (F) and male (M) cases and controls in Table 18 and Table 19, respectively. Allele frequency is noted in the fourth and fifth columns for melanoma pools and control pools, respectively.

Table 18: Females

dbSNP rs#	Chromosome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
972346	82058784	C/T	C = 0.950 T = 0.050	C = 0.957 T = 0.043	0.710	1.18	T
985199	82030145	G/A	G = 0.244 A = 0.756	G = 0.245 A = 0.755	0.985	1.00	A
1024465	82010363	G/A	G = 0.846 A = 0.154	G = 0.845 A = 0.155	0.984	1.00	G
1044639	82049807	G/T	G = 0.414 T = 0.586	G = 0.486 T = 0.514	**0.039**	1.34	T
1859176	82026307	C/T	C = 0.647 T = 0.353	C = 0.761 T = 0.239	**0.001**	1.74	T
1859177	82026444	C/T	C = 0.979 T = 0.021	C = T =			
1986481	82094932	A/T	A = 0.438 T = 0.562	A = 0.375 T = 0.625	0.080	0.77	A
2023847	82059542	G/T	G = 0.465 T = 0.535	G = 0.358 T = 0.642	**0.003**	0.64	G
2051791	82042987	C/T	C = 0.450 T = 0.550	C = 0.541 T = 0.459	**0.013**	1.44	T
2074401	8202783	A/G	A = 0.620	A = 0.557	0.118	0.77	A

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
	5		G = 0.380	G = 0.443			
2158220	82009218	T/C	T = 0.733 C = 0.267	T = C =			
2189247	82045494	C/A	C = 0.690 A = 0.310	C = 0.608 A = 0.392	**0.039**	0.70	C
2189248	82053554	T/C	T = 0.276 C = 0.724	T = 0.274 C = 0.726	0.945	0.99	T
2214414	82042361	T/C	T = 0.582 C = 0.418	T = 0.652 C = 0.348	0.064	1.34	C
2214415	82043731	G/A	G = 0.577 A = 0.423	G = 0.612 A = 0.388	0.412	1.16	A
2247523	82052653	C/G	C = 0.634 G = 0.366	C = 0.575 G = 0.425	0.101	0.78	C
2257207	82066433	A/T	A = 0.612 T = 0.388	A = 0.557 T = 0.443	0.150	0.80	A
2301722	82063483	A/C	A = 0.968 C = 0.032	A = 0.962 C = 0.038	0.733	0.82	A
2371214	82052921	T/C	T = 0.637 C = 0.363	T = 0.570 C = 0.430	0.061	0.75	T
2371215	82055743	T/A	T = 0.627 A = 0.373	T = 0.536 A = 0.464	**0.016**	0.69	T
2522830	82041352	G/A	G = 0.631 A = 0.369	G = 0.569 A = 0.431	0.102	0.77	G
2522831	82046349	T/C	T = C =	T = 0.672 C = 0.328			
2522832	82048613	A/G	A = G =	A = 0.621 G = 0.379			
2522833	82051957	C/A	C = 0.384 A = 0.616	C = 0.524 A = 0.476	**0.000**	1.76	A
2522834	82059195	T/C	T = 0.424 C = 0.576	T = 0.424 C = 0.576	0.994	1.00	C
2522835	82069745	A/T	A = 0.542 T = 0.458	A = 0.685 T = 0.315	**0.000**	1.84	T
2522836	8207130	C/A	C =	C = 0.520	0.737	0.95	C

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
	2		0.533 A = 0.467	A = 0.480			
2522837	82073631	A/G	A = 0.649 G = 0.351	A = 0.564 G = 0.436	**0.030**	0.70	A
2522838	82073806	A/T	A = 0.459 T = 0.541	A = 0.512 T = 0.488	0.158	1.24	T
2522839	82075897	G/A	G = 0.650 A = 0.350	G = 0.677 A = 0.323	0.552	1.13	A
2522840	82076664	G/T	G = 0.512 T = 0.488	G = 0.556 T = 0.444	0.312	1.19	T
2522842	82077911	G/T	G = 0.648 T = 0.352	G = 0.585 T = 0.415	0.083	0.76	G
2522843	82077971	C/A	C = 0.568 A = 0.432	C = 0.570 A = 0.430	0.963	1.01	A
2522844	82078341	T/C	T = 0.460 C = 0.540	T = 0.518 C = 0.482	0.137	1.26	C
2522845	82080158	T/G	T = 0.658 G = 0.342	T = 0.593 G = 0.407	0.066	0.76	T
2715147	82046654	T/C	T = 0.598 C = 0.402	T = 0.656 C = 0.344	0.115	1.28	C
2715148	82048284	A/C	A = 0.559 C = 0.441	A = 0.463 C = 0.537	**0.009**	0.68	A
2715149	82051061	A/T	A = 0.928 T = 0.072	A = 0.963 T = 0.037	0.262	2.01	T
2715150	82054144	A/G	A = 0.787 G = 0.213	A = 0.750 G = 0.250	0.246	0.81	A
2715151	82054912	C/G	C = 0.632 G = 0.368	C = 0.546 G = 0.454	**0.017**	0.70	C
2715152	82055915	G/A	G = 0.681 A = 0.319	G = 0.650 A = 0.350	0.368	0.87	G
2715153	82056107	T/C	T = 0.549 C = 0.451	T = 0.604 C = 0.396	0.191	1.26	C
2715154	8205911	G/T	G =	G = 0.558	**0.011**	0.67	G

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
	5		0.653 T = 0.347	T = 0.442			
2715155	82060303	A/G	A = 0.674 G = 0.326	A = 0.593 G = 0.407	**0.041**	0.70	A
2715156	82061083	A/G	A = 0.496 G = 0.504	A = 0.557 G = 0.443	0.106	1.27	G
2715157	82066623	A/G	A = 0.614 G = 0.386	A = 0.530 G = 0.470	**0.016**	0.71	A
2715158	82067855	G/C	G = 0.743 C = 0.257	G = 0.681 C = 0.319	0.069	0.74	G
2715159	82069657	A/G	A = 0.726 G = 0.274	A = 0.619 G = 0.381	**0.002**	0.61	A
2715161	82080530	C/T	C = 0.616 T = 0.384	C = 0.558 T = 0.442	0.108	0.79	C
2888017	82098452	A/G	A = 0.868 G = 0.132	A = 0.866 G = 0.134	0.931	0.98	A
4260846	82093085	C/A	C = 0.729 A = 0.271	C = 0.709 A = 0.291	0.540	0.90	C
4299948	82028157	T/G	T = G =	T = 0.246 G = 0.754			
4348435	82029900	G/A	G = 0.736 A = 0.264	G = 0.742 A = 0.258	0.838	1.03	A
4348436	82029921	G/C	G = 0.814 C = 0.186	G = 0.821 C = 0.179	0.801	1.05	C
4377905	82092560	A/G	A = 0.956 G = 0.044	A = 0.961 G = 0.039	0.795	1.14	G
4413718	82030064	G/C	G = 0.960 C = 0.040	G = 0.972 C = 0.028	0.568	1.44	C
4579453	82092970	T/C	T = 0.957 C = 0.043	T = 0.912 C = 0.088	**0.048**	0.46	T
4628206	8209559	A/T	A = 0.854	A = 0.847	0.790	0.94	A

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
	2		T = 0.146	T = 0.153			
4732483	82014796	T/C	T = 0.112 C = 0.888	T = 0.108 C = 0.892	0.866	0.96	T
4732485	82017875	C/T	C = 0.050 T = 0.950	C = 0.047 T = 0.953	0.894	0.94	C

Table 19: Males

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
972346	82058784	C/T	C = 0.960 T = 0.040	C = 0.972 T = 0.028	0.567	1.43	T
985199	82030145	G/A	G = 0.224 A = 0.776	G = 0.222 A = 0.778	0.950	0.99	G
1024465	82010363	G/A	G = 0.865 A = 0.135	G = 0.878 A = 0.122	0.664	1.13	A
1044639	82049807	G/T	G = 0.429 T = 0.571	G = 0.489 T = 0.511	0.111	1.27	T
1859176	82026307	C/T	C = 0.657 T = 0.343	C = T =			
1859177	82026444	C/T	C = T =	C = T =			
1986481	82094932	A/T	A = 0.485 T = 0.515	A = 0.417 T = 0.583	0.067	0.76	A
2023847	82059542	G/T	G = 0.467 T = 0.533	G = 0.400 T = 0.600	0.072	0.76	G
2051791	82042987	C/T	C = 0.469 T = 0.531	C = 0.562 T = 0.438	**0.033**	1.45	T
2074401	82027835	A/G	A = 0.633 G = 0.367	A = 0.574 G = 0.426	0.123	0.78	A
2158220	82009218	T/C	T = 0.740 C = 0.260	T = 0.682 C = 0.318	0.105	0.75	T

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
2189247	82045494	C/A	C = 0.654 A = 0.346	C = 0.626 A = 0.374	0.438	0.89	C
2189248	82053554	T/C	T = 0.246 C = 0.754	T = 0.238 C = 0.762	0.831	0.96	T
2214414	82042361	T/C	T = 0.557 C = 0.443	T = 0.632 C = 0.368	0.068	1.37	C
2214415	82043731	G/A	G = 0.623 A = 0.377	G = 0.622 A = 0.378	0.979	0.99	G
2247523	82052653	C/G	C = 0.646 G = 0.354	C = 0.582 G = 0.418	0.081	0.76	C
2257207	82066433	A/T	A = 0.623 T = 0.377	A = 0.582 T = 0.418	0.278	0.84	A
2301722	82063483	A/C	A = 0.966 C = 0.034	A = 0.980 C = 0.020	0.483	1.71	C
2371214	82052921	T/C	T = 0.620 C = 0.380	T = 0.593 C = 0.407	0.501	0.89	T
2371215	82055743	T/A	T = 0.620 A = 0.380	T = 0.544 A = 0.456	**0.038**	0.73	T
2522830	82041352	G/A	G = 0.660 A = 0.340	G = 0.574 A = 0.426	**0.025**	0.70	G
2522831	82046349	T/C	T = 0.714 C = 0.286	T = 0.700 C = 0.300	0.728	0.93	T
2522832	82048613	A/G	A = 0.663 G = 0.337	A = 0.629 G = 0.371	0.367	0.86	A
2522833	82051957	C/A	C = 0.397 A = 0.603	C = 0.504 A = 0.496	**0.006**	1.54	A
2522834	82059195	T/C	T = 0.387 C = 0.613	T = 0.428 C = 0.572	0.260	1.19	C
2522835	82069745	A/T	A = 0.535 T = 0.465	A = 0.652 T = 0.348	**0.001**	1.63	T
2522836	82071302	C/A	C = 0.570 A = 0.430	C = 0.544 A = 0.456	0.535	0.90	C
2522837	8207363	A/G	A = 0.640	A = 0.607	0.383	0.87	A

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
	1		G = 0.360	G = 0.393			
2522838	82073806	A/T	A = 0.452 T = 0.548	A = 0.518 T = 0.482	0.097	1.30	T
2522839	82075897	G/A	G = A =	G = 0.664 A = 0.336			
2522840	82076664	G/T	G = 0.488 T = 0.512	G = 0.551 T = 0.449	0.120	1.29	T
2522842	82077911	G/T	G = 0.647 T = 0.353	G = 0.604 T = 0.396	0.222	0.83	G
2522843	82077971	C/A	C = 0.576 A = 0.424	C = 0.543 A = 0.457	0.387	0.87	C
2522844	82078341	T/C	T = 0.459 C = 0.541	T = 0.501 C = 0.499	0.257	1.19	C
2522845	82080158	T/G	T = 0.678 G = 0.322	T = 0.604 G = 0.396	0.062	0.73	T
2715147	82046654	T/C	T = 0.573 C = 0.427	T = 0.612 C = 0.388	0.366	1.17	C
2715148	82048284	A/C	A = 0.557 C = 0.443	A = 0.502 C = 0.498	0.166	0.80	A
2715149	82051061	A/T	A = 0.907 T = 0.093	A = 0.941 T = 0.059	0.177	1.62	T
2715150	82054144	A/G	A = 0.802 G = 0.198	A = 0.779 G = 0.221	0.490	0.87	A
2715151	82054912	C/G	C = 0.631 G = 0.369	C = 0.597 G = 0.403	0.438	0.86	C
2715152	82055915	G/A	G = 0.718 A = 0.282	G = 0.688 A = 0.312	0.480	0.87	G
2715153	82056107	T/C	T = 0.491 C = 0.509	T = 0.595 C = 0.405	**0.023**	1.52	C
2715154	82059115	G/T	G = 0.632 T = 0.368	G = 0.574 T = 0.426	0.108	0.78	G
2715155	82060303	A/G	A = 0.663 G =	A = G =			

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			0.337				
2715156	82061083	A/G	A = 0.412 G = 0.588	A = 0.533 G = 0.467	**0.009**	1.63	G
2715157	82066623	A/G	A = 0.618 G = 0.382	A = G =			
2715158	82067855	G/C	G = 0.749 C = 0.251	G = 0.683 C = 0.317	0.112	0.72	G
2715159	82069657	A/G	A = 0.733 G = 0.267	A = 0.635 G = 0.365	**0.005**	0.63	A
2715161	82080530	C/T	C = 0.667 T = 0.333	C = 0.592 T = 0.408	0.066	0.73	C
2888017	82098452	A/G	A = 0.902 G = 0.098	A = 0.895 G = 0.105	0.788	0.92	A
4260846	82093085	C/A	C = 0.726 A = 0.274	C = 0.708 A = 0.292	0.618	0.91	C
4299948	82028157	T/G	T = 0.089 G = 0.911	T = 0.337 G = 0.663	**0.000**	5.20	G
4348435	82029900	G/A	G = 0.760 A = 0.240	G = 0.773 A = 0.227	0.701	1.07	A
4348436	82029921	G/C	G = 0.832 C = 0.168	G = 0.865 C = 0.135	0.257	1.29	C
4377905	82092560	A/G	A = 0.956 G = 0.044	A = 0.979 G = 0.021	0.243	2.19	G
4413718	82030064	G/C	G = 0.961 C = 0.039	G = 0.980 C = 0.020	0.339	1.96	C
4579453	82092970	T/C	T = 0.960 C = 0.040	T = 0.900 C = 0.100	**0.021**	0.37	T
4628206	82095592	A/T	A = 0.864 T = 0.136	A = 0.859 T = 0.141	0.851	0.96	A
4732483	82014796	T/C	T = 0.115 C =	T = 0.111 C = 0.889	0.903	0.97	T

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
			0.885				
4732485	82017875	C/T	C = 0.038 T = 0.962	C = 0.029 T = 0.971	0.690	0.76	C

[0272] Allelotyping results were considered significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The assay failed for those SNPs in which the allele frequency is blank. The combined allelotyping p-values for males and females were plotted in Figure 15 and separately for females and males in Figures 16 and 17, respectively. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figures 15, 16 and 17 can be determined by consulting Table 18 or 19. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0273] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The light gray line (or generally bottom-most curve) is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line (or generally top-most curve, *e.g.*, see peak in left-most graph just to the left of position 92150000) provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0274] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is place at the 3' end of each gene to show the direction of transcription.

Example 7

FPGT/CARK Proximal SNPs

[0275] It has been discovered that a polymorphic variation (rs2034453) in an intron of a gene encoding cardiac ankyrin repeat kinase (CARK) and near a gene encoding fucose-1-phosphate guanylyltransferase (FPGT) is associated with the occurrence of melanoma. See Table 3. Subsequently, seventy-one allelic variants located within or nearby the target genes were identified and subsequently allelotyped in melanoma case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 20. The chromosome position provided in column four of Table 20 is based on Genome "Build 33" of NCBI's GenBank.

Table 20

dbSNP rs#	Chromosome	Position in Fig. 3	Chromosome Position	Allele Variants	Allele Present in Fig. 3	IUPAC Code
1412825	1	157	74048557	G/C	C	S
4422957	1	492	74048892	C/T	T	Y
944795	1	1291	74049691	C/G	G	S
792310	1	1836	74050236	G/A	G	R
526736	1	2085	74050485	A/T	A	W
522042	1	2617	74051017	G/A	C	Y
577367	1	4029	74052429	C/T	A	R
575754	1	4171	74052571	T/C	G	R
573721	1	4444	74052844	G/T	C	M
487917	1	5239	74053639	C/T	G	R
792307	1	5343	74053743	G/A	C	Y
476350	1	5650	74054050	T/C	C	Y
571848	1	7862	74056262	A/G	A	R
491623	1	8817	74057217	A/G	G	R
956	1	8983	74057383	T/A	T	W
520806	1	9684	74058084	C/T	C	Y
522759	1	9925	74058325	T/C	T	Y
545664	1	10120	74058520	G/A	A	R
545721	1	10142	74058542	C/T	T	Y
536355	1	10519	74058919	G/A	A	R
553044	1	10916	74059316	G/T	T	K
581353	1	11729	74060129	A/G	A	R
560808	1	14576	74062976	C/A	C	M
485929	1	14628	74063028	A/G	A	R
477134	1	15257	74063657	T/G	T	K
505634	1	15994	74064394	G/A	A	R
542136	1	16203	74064603	G/A	A	R
545680	1	16583	74064983	T/C	T	Y
575961	1	17553	74065953	C/T	T	Y
792321	1	18311	74066711	A/G	A	R

dbSNP rs#	Chromosome	Position in Fig. 3	Chromosome Position	Allele Variants	Allele Present in Fig. 3	IUPAC Code
524306	1	18596	74066996	T/A	A	W
495027	1	18602	74067002	A/C	C	M
525358	1	19647	74068047	A/G	A	R
471496	1	20249	74068649	G/A	G	R
504866	1	21583	74069983	C/T	T	Y
532396	1	23235	74071635	T/C	C	Y
533371	1	23355	74071755	G/A	A	R
567060	1	24707	74073107	A/G	A	R
3753183	1	35442	74083842	G/T	T	K
492302	1	35674	74084074	G/C	C	S
518769	1	36255	74084655	A/G	G	R
474215	1	36594	74084994	T/C	C	Y
500203	1	37994	74086394	T/A	A	W
532221	1	38293	74086693	T/A	T	W
792323	1	43937	74092337	C/T	C	Y
3765651	1	45705	74094105	A/C	C	M
481387	1	46793	74095193	C/T	C	Y
483259	1	46972	74095372	T/C	C	Y
2034453	1	48524	74096924	A/G	A	R
792324	1	49414	74097814	T/C	T	Y
792327	1	55056	74103456	G/A	A	R
792328	1	55487	74103887	C/A	C	M
570631	1	56198	74104598	T/A	T	W
4593767	1	59436	74107836	G/A	G	R
576802	1	60639	74109039	T/A	A	W
518574	1	67381	74115781	A/G	A	R
524252	1	68940	74117340	C/T	C	Y
2039407	1	70713	74119113	A/T	A	W
503770	1	71789	74120189	T/C	T	Y
503904	1	71848	74120248	A/G	A	R
2027013	1	72488	74120888	T/G	G	K
514012	1	73424	74121824	A/G	A	R
1412827	1	73940	74122340	A/G	A	R
473834	1	79377	74127777	G/A	A	R
480267	1	80067	74128467	A/G	G	R
792329	1	82225	74130625	C/T	C	Y
572180	1	85542	74133942	G/T	G	K
1333029	1	85665	74134065	G/A	G	R
485414	1	85785	74134185	A/G	A	R
1412823	1	86109	74134509	A/T	T	W
548881	1	94888	74143288	C/T	C	Y

Assay for Verifying and Allelotyping SNPs

[0276] The methods used to verify and allelotype the seventy-one proximal SNPs of Table 20 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 21 and Table 22, respectively.

Table 21

dbSNP rs#	Forward PCR primer	Reverse PCR primer
1412825	GGCGCACGCCTCCACGTCCTGAGACCGTTGCTAGAG	GGCGCACGCCTTGGCTGGCGCCCGGAAAA
4422957	ACGTTGGATGATTAGCTAGCTACTCCTGGG	ACGTTGGATGGTTTGCTGGACTGTCACTTC
944795	ACGTTGGATGCCAGCTTTGCAAATCAATTC	ACGTTGGATGGAAGGGATCTTTGGGTTGTG
792310	ACGTTGGATGAAAGGAGTTACCCCTTGGAG	ACGTTGGATGACTGACCATAAAGCGCGTAC
526736	ACGTTGGATGACTGATAAGGTCCAAAGGAG	ACGTTGGATGCCTTGAAAAACTTCCAGAATG
522042	ACGTTGGATGAGGAGAATGGCCTGAACCTG	ACGTTGGATGGAAGGAGTCTTGCTCTGTTG
577367	GGCGCACGCCTCCACGTACTAGACTTTTGCCAGTAC	GGCGCACGCCTTTTTAAGCATTGTGGCCTC
575754	ACGTTGGATGCAAAGGTTTTCATGTAACCA	ACGTTGGATGGAAAAGTAGGAAGGACATGG
573721	ACGTTGGATGCCTGGTATCTAATTTAATTTT	ACGTTGGATGCTGGTTTGAAGCCTAAAAATG
487917	ACGTTGGATGTACCAGCATCACCACTTGAG	ACGTTGGATGTCACCTAGTGATGTTGGAGC
792307	ACGTTGGATGCTAATGCTAAAATACTTGCTTC	ACGTTGGATGGGGACAACCTATGTATATGC
476350	ACGTTGGATGGGTTTCACCGTGTTAGCCAG	ACGTTGGATGATACCAACACTTTGGGAGGC
571848	ACGTTGGATGCTCAAAAAGGCAAAGTGTAC	ACGTTGGATGCAGGGAACAAATTTTTCTAG
491623	ACGTTGGATGCATAACTTGAGATTCTAGCC	ACGTTGGATGAGAAGCAGGCAGGAAAATGG
956	GGCGCACGCCTCCACGCTCCTTGGGAAAAACTTTGG	GGCGCACGCCAGTCTGTGCTACTTTATGTC
520806	ACGTTGGATGTTCAGACAGGTCACTTCTGG	ACGTTGGATGGTCAGAAAGAGATTTCTCACA
522759	ACGTTGGATGGCTCAATACTGTATTTTAACC	ACGTTGGATGCAAAGCAACCAGAATCCATG
545664	GGCGCACGCCTCCACGGACCAAGTTCACATGTGAGC	GGCGCACGCCCCCAGAAAACAGAATGTGCC
545721	GGCGCACGCCTCCACGCCCAGAAAACAGAATGTGCC	GGCGCACGCCGACCAAGTTCACATGTGAGC
536355	GGCGCACGCCTCCACGGACCTACAT	ATAGCAGGCTTTTACACACC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
	GGATAAGTTTG	
553044	ACGTTGGATGCTGCCTTCTGTCACATATAG	ACGTTGGATGCAAGTCCAGACGGCATCATG
581353	ACGTTGGATGCAATCAGTTACTTGCATGCAC	ACGTTGGATGATCACCTACCTGCACATCAG
560808	ACGTTGGATGAGGCTTTCTGCAACTTTGCG	ACGTTGGATGCAATGCCTTATTGTGTGCAG
485929	ACGTTGGATGTTCAATGCCTCATACACCCC	ACGTTGGATGACGCAAAGTTGCAGAAAGCC
477134	ACGTTGGATGCTGTGCTCTGATATGTATCC	ACGTTGGATGCTGAATCATTGGAGCTAGGG
505634	ACGTTGGATGTTCTCCTCATCTTCCTCACC	ACGTTGGATGAGGAGTGAATGTGGATAGAG
542136	ACGTTGGATGAAGCCAGCAGGATTATGAAG	ACGTTGGATGCTCTGTTATTGGAAAAAATTC
545680	ACGTTGGATGCCCCCACAAATTCTGTAACG	ACGTTGGATGAATGAAAGTACACTCTACAG
575961	ACGTTGGATGGCACTGGACACCTGTTATTC	ACGTTGGATGGCACAAAATATACCATCGTC
792321	GGCGCACGCCTCCACGCTTCTCTGGTCTCCTGATAG	GGCGCACGCCGTTTCCCATGGCCTAAGATG
524306	GGCGCACGCCTCCACGAAGCCTCCCAAAAATATGCC	GGCGCACGCCTTGGTTTGGGATAAAGGAGG
495027	GGCGCACGCCTCCACGTTGGTTTGGGATAAAGGAGG	GGCGCACGCCCCTAATAATCTAAAGCCTCCC
525358	GGCGCACGCCTCCACGCACACTACACTTTGACTGGG	GGCGCACGCCATCTCTTAGTTTGGTACGCG
471496	ACGTTGGATGGTTTATTTACTTTGAACCTG	ACGTTGGATGTCATTTCCAAGAAATATGTG
504866	ACGTTGGATGTAAAAATCTTAGACAGTGGG	ACGTTGGATGTCTAAATTGTGTCCAGACTC
532396	GGCGCACGCCTCCACGCAAGACTTGTAATCAAATCC	GGCGCACGCCTTCTAACTGTGGTGTTTCTG
533371	GGCGCACGCCTCCACGTTACTGGTACGGGAAGAATG	GGCGCACGCCGGAAATTGTACATGCAAAGG
567060	ACGTTGGATGAACAAGAGCGAAACCCTGTC	ACGTTGGATGATAAACCAAGAGGCATGGTG
3753183	ACGTTGGATGTGTGGGAGAATTCAACTGAG	ACGTTGGATGAGCTTTGGCTTTCAAAGGTG
492302	ACGTTGGATGTTCCTCCATATGTGGAAAAC	ACGTTGGATGTCTTATTTCTAATATCTCGG
518769	ACGTTGGATGCAAACAACTCTCTTTTTGAA	ACGTTGGATGGGAAGCCTTACCTCTGAAAC
474215	ACGTTGGATGATGGAAGGTGCATGAAAGAG	ACGTTGGATGCAGTTCTGACCATGTGACTC
500203	GGCGCACGCCTCCACGGCAAAATGTAGACACAGATC	GGCGCACGCCTCGAATGGGTTCTTCATTAC
532221	ACGTTGGATGTATGTCTGAGGTTCTACGGG	ACGTTGGATGCTTTGTATAAGTGTCTTCAG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
792323	ACGTTGGATGAATGGCGTGAATCCAGGAGG	ACGTTGGATGTTTTTCAGACGGAGTCTCGC
3765651	ACGTTGGATGTGGATCACAAAACTGCACAC	ACGTTGGATGCCCAAAGGTTACTTTCTTTC
481387	GGCGCACGCCTCCACGCCATTCAATAAGTCTGGCAC	GGCGCACGCCAACCTGAAGTGAGCCTTAAG
483259	GGCGCACGCCTCCACGTTTGAGTCTCTCCACTGTTG	GGCGCACGCCCAGAACTGCACATGAGATTC
2034453	ACGTTGGATGTTGCTGGACAATAGAAAGAC	ACGTTGGATGGTGACTGGAAACTGAGAATG
792324	ACGTTGGATGTGTGATCTTGCTGGCTTCAG	ACGTTGGATGTGCTTCTCACTCTTTGGGTC
792327	ACGTTGGATGTGGTCCGTTTTACAGAGAGC	ACGTTGGATGTGTGTCTAGCTCAGGGATTG
792328	ACGTTGGATGTCAGCAGGCCATAGCTGCCTC	ACGTTGGATGATGCAAGAGCCCATGGCAGG
570631	ACGTTGGATGAAGACTGAAGTGGCAACAGG	ACGTTGGATGTTGCATTTTGTCCCATTTCC
4593767	ACGTTGGATGGTCCAATCTGCTGTTTTCAAC	ACGTTGGATGATTGATATATGAAGAAACAG
576802	GGCGCACGCCTCCACGGGCAATGGATGACAATAGTA	GGCGCACGCCTCTACTTTTGCATTGCTTCC
518574	ACGTTGGATGAGGTGGTGGTAAAAGAAGGG	ACGTTGGATGGAGCTCCAGAGGAAAAATTG
524252	GGCGCACGCCTCCACGTGGAAGAATGAGGCTTAGAC	GGCGCACGCCTGGGAGATCTATTCTACCTC
2039407	GGCGCACGCCTCCACGTAAGGTGGTTACAATTACTC	GGCGCACGCCAATGACTATGTGCACTGGAG
503770	GGCGCACGCCTCCACGTTGAGATGCCATTGATAGGC	GGCGCACGCCAATGCATCTTTGGTCCTGAC
503904	GGCGCACGCCTCCACGCTAAGCTGCTTTCCCATTCC	GGCGCACGCCGAAGTCAGGACCAAAGATGC
2027013	ACGTTGGATGCTTCCCGTTTTTCTACCTGC	ACGTTGGATGGAGCCAATGAAAGAAGAAAGG
514012	GGCGCACGCCTCCACGCTCAGATGGTGGAAAGTAGG	GGCGCACGCCTCTTGTTCAAGCGGTAGAGG
1412827	GGCGCACGCCTCCACGCCTCTGTATATCTAGCTACC	GGCGCACGCCGCTTTGGATAGTCAATTCAG
473834	GGCGCACGCCTCCACGCTACCTTCACATCTGTAGTC	GGCGCACGCCTCTTGTGGGTATAAGCTGTG
480267	GGCGCACGCCTCCACGTTGGAGAGGAAACTAAAGCG	GGCGCACGCCCATCCAAATGTTTCAGTAGAG
792329	ACGTTGGATGCACCACGCCCAGCTAATTTT	ACGTTGGATGGTCAGGAGATCAAGACCATC
572180	ACGTTGGATGCAGGTCTTTGGCATAGACTC	ACGTTGGATGAGCTTTTCTTGCTTATGCTC
1333029	ACGTTGGATGGCCCTGGAAAATGATGGAAG	ACGTTGGATGGGGATTTCTCATATCAGGTTG
485414	ACGTTGGATGGTGTATATACATTATCT	ACGTTGGATGGCACTGAATTTGCTTC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
	ACAT	CAAC
1412823	GGCGCACGCCTCCACGAAACCTCTGAGCTCACTATG	GGCGCACGCCGTATTCCTAATTAAGGGGAAG
548881	ACGTTGGATGCACCCTGGGAAACTATAAAC	ACGTTGGATGGTAGTTCTATAAGGTTTTGCC
1412825	GGCGCACGCCTCCACGTCCTGAGACCGTTGCTAGAG	GGCGCACGCCTTGGCTGGCGCCCGGAAAA
4422957	ACGTTGGATGATTAGCTAGCTACTCCTGGG	ACGTTGGATGGTTTGCTGGACTGTCACTTC
944795	ACGTTGGATGCCAGCTTTGCAAATCAATTC	ACGTTGGATGGAAGGGATCTTTGGGTTGTG
792310	ACGTTGGATGAAAGGAGTTACCCCTTGGAG	ACGTTGGATGACTGACCATAAAGCGCGTAC
526736	ACGTTGGATGACTGATAAGGTCCAAAGGAG	ACGTTGGATGCCTTGAAAAACTTCCAGAATG
522042	ACGTTGGATGAGGAGAATGGCCTGAACCTG	ACGTTGGATGGAAGGAGTCTTGCTCTGTTG
577367	GGCGCACGCCTCCACGTACTAGACTTTTGCCAGTAC	GGCGCACGCCTTTTTAAGCATTGTGGCCTC
575754	ACGTTGGATGCAAAGGTTTTCATGTAACCA	ACGTTGGATGGAAAAGTAGGAAGGACATGG
573721	ACGTTGGATGCCTGGTATCTAATTTAATTTT	ACGTTGGATGCTGGTTTGAAGCCTAAAAATG
487917	ACGTTGGATGTACCAGCATCACCACTTGAG	ACGTTGGATGTCACCTAGTGATGTTGGAGC
792307	ACGTTGGATGCTAATGCTAAAATACTTGCTTC	ACGTTGGATGGGGACAACCTATGTATATGC
476350	ACGTTGGATGGGTTTCACCGTGTTAGCCAG	ACGTTGGATGATACCAACACTTTGGGAGGC
571848	ACGTTGGATGCTCAAAAAGGCAAAGTGTAC	ACGTTGGATGCAGGGAACAAATTTTTCTAG
491623	ACGTTGGATGCATAACTTGAGATTCTAGCC	ACGTTGGATGAGAAGCAGGCAGGAAAATGG
956	GGCGCACGCCTCCACGCTCCTTGGGAAAAACTTTGG	GGCGCACGCCAGTCTGTGCTACTTTATGTC
520806	ACGTTGGATGTTCAGACAGGTCACTTCTGG	ACGTTGGATGGTCAGAAAGAGATTTCTCACA
522759	ACGTTGGATGGCTCAATACTGTATTTTAACC	ACGTTGGATGCAAAGCAACCAGAATCCATG
545664	GGCGCACGCCTCCACGGACCAAGTTCACATGTGAGC	GGCGCACGCCCCCAGAAAACAGAATGTGCC
545721	GGCGCACGCCTCCACGCCCAGAAAACAGAATGTGCC	GGCGCACGCCGACCAAGTTCACATGTGAGC
536355	GGCGCACGCCTCCACGGACCTACATGGATAAGTTTG	ATAGCAGGCTTTTACACACC
553044	ACGTTGGATGCTGCCTTCTGTCACATATAG	ACGTTGGATGCAAGTCCAGACGGCATCATG
581353	ACGTTGGATGCAATCAGTTACTTGCATGCAC	ACGTTGGATGATCACCTACCTGCACATCAG

Table 22

dbSNP rs#	Extend Probe	Term Mix
1412825	GCGCCCGGAAAACCATGAT	ACT
4422957	CCGTTTACTTCTCATCTG	ACG
944795	CCTAACACCAAGTGTCC	ACT
792310	TTGGCTCCAGCAGGATC	ACG
526736	TTCCAGAATGTTACTTAAAAGA	CGT
522042	TAGCTCACTCCAAGCTC	ACG
577367	GCATTGTGGCCTCTGGCTA	ACG
575754	GGACATGGTCTCAGAAT	ACT
573721	GAAGCCTAAAAATGTGTAAAA	CGT
487917	CCATTGTAAAGTCCTAGCA	ACG
792307	TGCTGTCCATCATTGAG	ACG
476350	GGCAGGCAGATCACGAG	ACT
571848	AAAAGCAGTTTGATGTAGAG	ACT
491623	ACAGGTGATAAACAGTTTC	ACT
956	GTCAATATAAAAATTGGTAAAC	CGT
520806	AAGAGATTTCTCACAAATTGA	ACG
522759	CAGAATCCATGCATTGT	ACT
545664	GCTATTAGCCAGGCAGCAA	ACG
545721	GCTGCCTGGCTAATAGCTA	ACG
536355	CTGAGTATATGATGTAAG	ACG
553044	GTATGTAAACAGCAACTCTG	CGT
581353	GTCTAAAGATGTTCATCCC	ACT
560808	GTGTGCAGTAATAACAATGAT	CGT
485929	AGAAAGCCTGCAAAGGA	ACT
477134	TGGAGCTAGGGAGGAAG	ACT
505634	ATGTGGATAGAGAAATTCAAA	ACG
542136	TTTTCTTCCTTGTAGCATC	ACG
545680	CACTCTACAGTGTGGGA	ACT
575961	CATCGTCATAGTAGAGATTC	ACG
792321	AAGATGAATGGACTCTCCTGT	ACT
524306	GGACATATTTACTTCTAGCTGAT	CGT
495027	CCTCCCAAAAATATGCCTTTG	ACT
525358	CGAGAGTGCTCGGTGCATA	ACT
471496	GAAATATGTGTTTTAACGAGAA	ACG
504866	GTGTCCAGACTCTTGATT	ACG
532396	CTGTGGTGTTTCTGATGCCT	ACT
533371	TGCAAAGGTGTTAGAAGCACCT C	ACG
567060	AGGCATGGTGCTTAGAT	ACT
3753183	CGATGAGTTTGAAAATCCA	CGT

492302	TCTCGGATCTTCCATCC	ACT
518769	CTGAGCAAAAATATATGGTGA	ACT
474215	GTGACTCTAATATCCAAGCTA	ACT
500203	AAACATCTGCATTTTAAAC	CGT
532221	TGTCTTCAGTATTCACCTTA	CGT
792323	AGGCTGGAGTGCAGTGG	ACG
3765651	TTCCTAGCCTTTACCTTT	ACT
481387	AGGCGTATAGTAGGTGTTTAG	ACG
483259	CTCTTATTTAAACTTGATCTCTC	ACT
2034453	AAACTGAGAATGTTGATGGACA	ACT
792324	GTCCGCACTGCCTTTAT	ACT
792327	ATGCACCAATCAGCACC	ACG
792328	GGGAAGCTCAGGCATGG	CGT
570631	TCCCATTTCCATTATTTTTTTT	CGT
4593767	GAAGAAACAGAAAAATGTGC	ACG
576802	TTGCATTGCTTCCAAAATGATC	CGT
518574	AGAGGAAAAATTGCCTATG	ACT
524252	TTCTCAAGGATATAGCTGGAG	ACG
2039407	GTGCACTGGAGCAGTTCTG	CGT
503770	CTGCTAAGTCTGAGTCCCAT	ACT
503904	AAGATGCATTTATCAGATTGTAT A	ACT
2027013	AAGAAGAAAGGTTGAAGAC	ACT
514012	GTAGAGGATTGATTAGAACTGA	ACT
1412827	TTCTAACAGTGTATTTAATCATCA	ACT
473834	CAGAAGAGTCTCTGGGGAG	ACG
480267	ATTTTGTTTACCAAGAAGCCTC	ACT
792329	GACCATCCTGGCTAACA	ACG
572180	CTTATGCTCTTCTACCTCA	CGT
1333029	GTTGATTTGGTTAGCAATAAT	ACG
485414	AACATCCTAGGTCCTCT	ACT
1412823	CCTAATTAAGGGGAAGAAGAAG	CGT
548881	GGTTTTGCCTAATATATTTTGAT G	ACG
1412825	GCGCCCGGAAAACCATGAT	ACT
4422957	CCGTTTACTTCTCATCTG	ACG
944795	CCTAACACCAAGTGTCC	ACT
792310	TTGGCTCCAGCAGGATC	ACG
526736	TTCCAGAATGTTACTTAAAAGA	CGT
522042	TAGCTCACTCCAAGCTC	ACG
577367	GCATTGTGGCCTCTGGCTA	ACG
575754	GGACATGGTCTCAGAAT	ACT
573721	GAAGCCTAAAAATGTGTAAAA	CGT
487917	CCATTGTAAAGTCCTAGCA	ACG
792307	TGCTGTCCATCATTGAG	ACG
476350	GGCAGGCAGATCACGAG	ACT
571848	AAAAGCAGTTTGATGTAGAG	ACT

491623	ACAGGTGATAAACAGTTTC	ACT
956	GTCAATATAAAAATTGGTAAAC	CGT
520806	AAGAGATTTCTCACAAATTGA	ACG
522759	CAGAATCCATGCATTGT	ACT
545664	GCTATTAGCCAGGCAGCAA	ACG
545721	GCTGCCTGGCTAATAGCTA	ACG
536355	CTGAGTATATGATGTAAG	ACG
553044	GTATGTAAACAGCAACTCTG	CGT
581353	GTCTAAAGATGTTCATCCC	ACT

Genetic Analysis

[0277] Allelotyping results are shown for female (F) and male (M) cases and controls in Table 23 and Table 24, respectively. Allele frequency is noted in the fourth and fifth columns for melanoma pools and control pools, respectively.

Table 23: Females

dbSNP rs#	Chromosome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
956	74057383	T/A	T = 0.613 A = 0.387	T = 0.642 A = 0.358	0.428	1.13	A
471496	74068649	G/A	G = 0.116 A = 0.884	G = 0.123 A = 0.877	0.777	1.08	A
473834	74127777	G/A	G = 0.143 A = 0.857	G = 0.192 A = 0.808	0.082	1.43	A
474215	74084994	T/C	T = 0.557 C = 0.443	T = 0.452 C = 0.548	**0.004**	0.66	T
476350	74054050	T/C	T = 0.031 C = 0.969	T = 0.035 C = 0.965	0.887	1.14	C
477134	74063657	T/G	T = 0.560 G = 0.440	T = 0.625 G = 0.375	0.079	1.31	G
480267	74128467	A/G	A = 0.318 G = 0.682	A = 0.356 G = 0.644	0.306	1.19	G
481387	74095193	C/T	C = 0.517 T = 0.483	C = 0.447 T = 0.553	0.066	0.76	C
483259	74095372	T/C	T = 0.581 C =	T = 0.666 C = 0.334	**0.024**	1.44	C

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
			0.419				
485414	74134185	A/G	A = 0.911 G = 0.089	A = 0.907 G = 0.093	0.856	0.95	A
485929	74063028	A/G	A = 0.716 G = 0.284	A = 0.718 G = 0.282	0.949	1.01	G
487917	74053639	C/T	C = 0.568 T = 0.432	C = 0.643 T = 0.357	0.032	1.37	T
491623	74057217	A/G	A = 0.622 G = 0.378	A = 0.529 G = 0.471	**0.014**	0.68	A
492302	74084074	G/C	G = C =	G = 0.389 C = 0.611			
495027	74067002	A/C	A = 0.586 C = 0.414	A = 0.500 C = 0.500	**0.020**	0.71	A
500203	74086394	T/A	T = 0.508 A = 0.492	T = 0.425 A = 0.575	**0.025**	0.72	T
503770	74120189	T/C	T = 0.853 C = 0.147	T = 0.816 C = 0.184	0.188	0.76	T
503904	74120248	A/G	A = 0.838 G = 0.162	A = 0.810 G = 0.190	0.338	0.82	A
504866	74069983	C/T	C = 0.577 T = 0.423	C = 0.466 T = 0.534	**0.005**	0.64	C
505634	74064394	G/A	G = 0.923 A = 0.077	G = 0.946 A = 0.054	0.337	1.46	A
514012	74121824	A/G	A = 0.860 G = 0.140	A = 0.811 G = 0.189	0.095	0.70	A
518574	74115781	A/G	A = 0.974 G = 0.026	A = 0.970 G = 0.030	0.823	0.85	A
518769	74084655	A/G	A = 0.875 G = 0.125	A = 0.875 G = 0.125	0.997	1.00	G
520806	74058084	C/T	C = 0.586 T = 0.414	C = 0.644 T = 0.356	0.103	1.28	T
522042	74051017	G/A	G = 0.699 A = 0.301	G = A =			

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
522759	74058325	T/C	T = 0.691 C = 0.309	T = 0.743 C = 0.257	0.118	1.29	C
524252	74117340	C/T	C = 0.829 T = 0.171	C = 0.827 T = 0.173	0.945	0.99	C
524306	74066996	T/A	T = 0.560 A = 0.440	T = 0.468 A = 0.532	**0.010**	0.69	T
525358	74068047	A/G	A = 0.150 G = 0.850	A = 0.141 G = 0.859	0.763	0.93	A
526736	74050485	A/T	A = 0.638 T = 0.362	A = 0.653 T = 0.347	0.710	1.07	T
532221	74086693	T/A	T = 0.726 A = 0.274	T = 0.784 A = 0.216	0.066	1.37	A
532396	74071635	T/C	T = 0.952 C = 0.048	T = 0.956 C = 0.044	0.830	1.11	C
533371	74071755	G/A	G = 0.528 A = 0.472	G = 0.484 A = 0.516	0.214	0.84	G
536355	74058919	G/A	G = 0.535 A = 0.465	G = 0.465 A = 0.535	0.068	0.76	G
542136	74064603	G/A	G = 0.626 A = 0.374	G = 0.525 A = 0.475	0.011	0.66	G
545664	74058520	G/A	G = 0.563 A = 0.437	G = 0.504 A = 0.496	0.095	0.79	G
545680	74064983	T/C	T = 0.686 C = 0.314	T = 0.719 C = 0.281	0.324	1.17	C
545721	74058542	C/T	C = 0.511 T = 0.489	C = 0.459 T = 0.541	0.203	0.81	C
548881	74143288	C/T	C = 0.899 T = 0.101	C = 0.863 T = 0.137	0.224	0.71	C
553044	74059316	G/T	G = 0.504 T = 0.496	G = 0.488 T = 0.512	0.668	0.94	G
560808	74062976	C/A	C = 0.567 A = 0.433	C = 0.640 A = 0.360	0.046	1.36	A
567060	74073107	A/G	A = 0.670 G =	A = 0.707 G = 0.293	0.287	1.19	G

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
			0.330				
570631	74104598	T/A	T = 0.376 A = 0.624	T = 0.350 A = 0.650	0.575	0.90	T
571848	74056262	A/G	A = 0.555 G = 0.445	A = 0.608 G = 0.392	0.139	1.24	G
572180	74133942	G/T	G = 0.869 T = 0.131	G = 0.838 T = 0.162	0.259	0.78	G
573721	74052844	G/T	G = 0.145 T = 0.855	G = 0.152 T = 0.848	0.862	1.05	T
575754	74052571	T/C	T = 0.923 C = 0.077	T = 0.938 C = 0.062	0.510	1.25	C
575961	74065953	C/T	C = T =	C = 0.948 T = 0.052			
576802	74109039	T/A	T = 0.860 A = 0.140	T = 0.847 A = 0.153	0.626	0.90	T
577367	74052429	C/T	C = 0.540 T = 0.460	C = 0.461 T = 0.539	**0.037**	0.73	C
581353	74060129	A/G	A = 0.604 G = 0.396	A = 0.643 G = 0.357	0.320	1.18	G
792307	74053743	G/A	G = 0.530 A = 0.470	G = 0.617 A = 0.383	**0.020**	1.43	A
792310	74050236	G/A	G = 0.508 A = 0.492	G = 0.567 A = 0.433	0.107	1.26	A
792321	74066711	A/G	A = 0.645 G = 0.355	A = 0.676 G = 0.324	0.421	1.15	G
792323	74092337	C/T	C = 0.815 T = 0.185	C = 0.817 T = 0.183	0.933	1.02	T
792324	74097814	T/C	T = 0.068 C = 0.932	T = 0.052 C = 0.948	0.533	0.76	T
792327	74103456	G/A	G = 0.957 A = 0.043	G = 0.960 A = 0.040	0.893	1.07	A
792328	74103887	C/A	C = A =	C = 0.337 A = 0.663			
792329	74130625	C/T	C = 0.732	C = 0.744 T = 0.256	0.688	1.07	T

dbSNP rs#	Chromsome Position	Alleles	Female Case AF	Female Control AF	F p-Value	Odds Ratio	Melanoma Associated Allele
			T = 0.268				
944795	74049691	C/G	C = 0.592 G = 0.408	C = 0.535 G = 0.465	0.112	0.79	C
1333029	74134065	G/A	G = 0.945 A = 0.055	G = 0.973 A = 0.027	0.172	2.06	A
1412823	74134509	A/T	A = 0.774 T = 0.226	A = 0.780 T = 0.220	0.878	1.03	T
1412825	74048557	G/C	G = 0.540 C = 0.460	G = 0.500 C = 0.500	0.301	0.85	G
1412827	74122340	A/G	A = 0.386 G = 0.614	A = 0.327 G = 0.673	0.113	0.77	A
2027013	74120888	T/G	T = 0.148 G = 0.852	T = 0.075 G = 0.925	**0.005**	0.47	T
2034453	74096924	A/G	A = 0.209 G = 0.791	A = 0.143 G = 0.857	**0.030**	0.63	A
2039407	74119113	A/T	A = 0.930 T = 0.070	A = 0.963 T = 0.037	0.116	1.94	T
3753183	74083842	G/T	G = 0.090 T = 0.910	G = 0.054 T = 0.946	0.106	0.57	G
3765651	74094105	A/C	A = 0.666 C = 0.334	A = 0.711 C = 0.289	0.205	1.23	C
4422957	74048892	C/T	C = 0.485 T = 0.515	C = 0.428 T = 0.572	0.113	0.80	C
4593767	74107836	G/A	G = 0.231 A = 0.769	G = 0.270 A = 0.730	0.221	1.23	A

Table 24: Males

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
956	7405738	T/A	T = 0.625	T = 0.627	0.951	1.01	A

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
	3		A = 0.375	A = 0.373			
471496	74068649	G/A	G = 0.097 A = 0.903	G = 0.097 A = 0.903	0.976	0.99	G
473834	74127777	G/A	G = 0.179 A = 0.821	G = 0.185 A = 0.815	0.826	1.04	A
474215	74084994	T/C	T = 0.486 C = 0.514	T = 0.434 C = 0.566	0.162	0.81	T
476350	74054050	T/C	T = 0.053 C = 0.947	T = 0.047 C = 0.953	0.799	0.88	T
477134	74063657	T/G	T = 0.587 G = 0.413	T = 0.613 G = 0.387	0.490	1.11	G
480267	74128467	A/G	A = 0.333 G = 0.667	A = 0.365 G = 0.635	0.467	1.15	G
481387	74095193	C/T	C = 0.480 T = 0.520	C = 0.463 T = 0.537	0.645	0.93	C
483259	74095372	T/C	T = 0.637 C = 0.363	T = 0.661 C = 0.339	0.506	1.11	C
485414	74134185	A/G	A = 0.897 G = 0.103	A = 0.923 G = 0.077	0.318	1.37	G
485929	74063028	A/G	A = 0.693 G = 0.307	A = 0.715 G = 0.285	0.515	1.11	G
487917	74053639	C/T	C = 0.629 T = 0.371	C = 0.685 T = 0.315	0.180	1.28	T
491623	74057217	A/G	A = 0.577 G = 0.423	A = 0.565 G = 0.435	0.778	0.95	A
492302	74084074	G/C	G = C =	G = C =			
495027	74067002	A/C	A = 0.563 C = 0.437	A = 0.501 C = 0.499	0.104	0.78	A
500203	74086394	T/A	T = 0.453 A = 0.547	T = 0.423 A = 0.577	0.416	0.89	T
503770	74120189	T/C	T = 0.824 C = 0.176	T = 0.826 C = 0.174	0.942	1.02	C

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
503904	74120248	A/G	A = 0.814 G = 0.186	A = 0.809 G = 0.191	0.891	0.97	A
504866	74069983	C/T	C = 0.605 T = 0.395	C = 0.507 T = 0.493	**0.040**	0.67	C
505634	74064394	G/A	G = 0.939 A = 0.061	G = 0.948 A = 0.052	0.714	1.18	A
514012	74121824	A/G	A = 0.821 G = 0.179	A = 0.801 G = 0.199	0.516	0.88	A
518574	74115781	A/G	A = 0.966 G = 0.034	A = 0.969 G = 0.031	0.883	1.09	G
518769	74084655	A/G	A = 0.874 G = 0.126	A = 0.871 G = 0.129	0.921	0.97	A
520806	74058084	C/T	C = 0.631 T = 0.369	C = 0.664 T = 0.336	0.358	1.16	T
522042	74051017	G/A	G = A =	G = A =			
522759	74058325	T/C	T = 0.724 C = 0.276	T = 0.752 C = 0.248	0.406	1.15	C
524252	74117340	C/T	C = 0.839 T = 0.161	C = 0.840 T = 0.160	0.963	1.01	T
524306	74066996	T/A	T = 0.518 A = 0.482	T = 0.478 A = 0.522	0.298	0.85	T
525358	74068047	A/G	A = 0.127 G = 0.873	A = 0.133 G = 0.867	0.847	1.05	G
526736	74050485	A/T	A = 0.588 T = 0.412	A = T =			
532221	74086693	T/A	T = 0.723 A = 0.277	T = 0.822 A = 0.178	**0.002**	1.77	A
532396	74071635	T/C	T = 0.961 C = 0.039	T = 0.971 C = 0.029	0.676	1.36	C
533371	74071755	G/A	G = 0.510 A = 0.490	G = 0.511 A = 0.489	0.995	1.00	A
536355	74058919	G/A	G = A =	G = 0.502 A = 0.498			
542136	7406460	G/A	G =	G = 0.552			

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
	3		A =	A = 0.448			
545664	74058520	G/A	G = 0.534 A = 0.466	G = 0.525 A = 0.475	0.810	0.96	G
545680	74064983	T/C	T = 0.708 C = 0.292	T = 0.715 C = 0.285	0.837	1.04	C
545721	74058542	C/T	C = 0.535 T = 0.465	C = 0.480 T = 0.520	0.215	0.80	C
548881	74143288	C/T	C = 0.921 T = 0.079	C = 0.899 T = 0.101	0.434	0.76	C
553044	74059316	G/T	G = 0.471 T = 0.529	G = 0.490 T = 0.510	0.624	1.08	T
560808	74062976	C/A	C = 0.593 A = 0.407	C = 0.614 A = 0.386	0.562	1.09	A
567060	74073107	A/G	A = 0.699 G = 0.301	A = 0.698 G = 0.302	0.968	0.99	A
570631	74104598	T/A	T = 0.385 A = 0.615	T = 0.373 A = 0.627	0.786	0.95	T
571848	74056262	A/G	A = 0.601 G = 0.399	A = 0.603 G = 0.397	0.950	1.01	G
572180	74133942	G/T	G = 0.845 T = 0.155	G = 0.851 T = 0.149	0.834	1.05	T
573721	74052844	G/T	G = 0.095 T = 0.905	G = 0.137 T = 0.863	0.247	1.52	T
575754	74052571	T/C	T = 0.929 C = 0.071	T = 0.947 C = 0.053	0.429	1.36	C
575961	74065953	C/T	C = T =	C = 0.963 T = 0.037			
576802	74109039	T/A	T = 0.834 A = 0.166	T = 0.865 A = 0.135	0.266	1.28	A
577367	74052429	C/T	C = 0.540 T = 0.460	C = T =			
581353	74060129	A/G	A = 0.633 G = 0.367	A = 0.647 G = 0.353	0.681	1.07	G
792307	7405374	G/A	G =	G = 0.654	0.128	1.30	A

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
	3		0.592 A = 0.408	A = 0.346			
792310	74050236	G/A	G = 0.548 A = 0.452	G = 0.565 A = 0.435	0.653	1.07	A
792321	74066711	A/G	A = 0.667 G = 0.333	A = 0.673 G = 0.327	0.877	1.03	G
792323	74092337	C/T	C = 0.820 T = 0.180	C = 0.825 T = 0.175	0.892	1.03	T
792324	74097814	T/C	T = 0.070 C = 0.930	T = 0.061 C = 0.939	0.701	0.86	T
792327	74103456	G/A	G = 0.963 A = 0.037	G = 0.978 A = 0.022	0.477	1.72	A
792328	74103887	C/A	C = A =	C = A =			
792329	74130625	C/T	C = 0.754 T = 0.246	C = 0.756 T = 0.244	0.951	1.01	T
944795	74049691	C/G	C = 0.554 G = 0.446	C = 0.540 G = 0.460	0.722	0.95	C
1333029	74134065	G/A	G = 0.962 A = 0.038	G = A =			
1412823	74134509	A/T	A = 0.762 T = 0.238	A = 0.761 T = 0.239	0.993	1.00	A
1412825	74048557	G/C	G = 0.521 C = 0.479	G = 0.518 C = 0.482	0.953	0.99	G
1412827	74122340	A/G	A = 0.365 G = 0.635	A = 0.388 G = 0.612	0.572	1.10	G
2027013	74120888	T/G	T = 0.093 G = 0.907	T = G =			
2034453	74096924	A/G	A = 0.173 G = 0.827	A = 0.151 G = 0.849	0.506	0.85	A
2039407	74119113	A/T	A = 0.946 T = 0.054	A = 0.944 T = 0.056	0.931	0.96	A
3753183	7408384	G/T	G =	G = 0.041	0.075	0.49	G

dbSNP rs#	Chromsome Position	Alleles	Male Case AF	Male Control AF	M p-Value	Odds Ratio	Melanoma Associated Allele
	2		0.081 T = 0.919	T = 0.959			
3765651	74094105	A/C	A = 0.704 C = 0.296	A = 0.704 C = 0.296	0.998	1.00	A
4422957	74048892	C/T	C = 0.462 T = 0.538	C = 0.450 T = 0.550	0.757	0.96	C
4593767	74107836	G/A	G = 0.300 A = 0.700	G = 0.260 A = 0.740	0.269	0.82	G

[0278] Allelotyping results were considered significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The assay failed for those SNPs in which the allele frequency is blank. The combined allelotyping p-values for males and females were plotted in Figure 18 and separately for females and males in Figures 19 and 20, respectively. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figures 18, 19 and 20 can be determined by consulting Table 23 or 24. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0279] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The light gray line (or generally bottom-most curve) is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line (or generally top-most curve, *e.g.*, see peak in left-most graph just to the left of position 92150000) provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0280] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is place at the 3' end of each gene to show the direction of transcription.

Example 8

Inhibition of CDK10 Gene Expression by Transfection of Specific siRNAs

[0281] RNAi-based gene inhibition was selected as an effective way to inhibit expression of CDK10 in cultured cells. Algorithms useful for designing siRNA molecules specific for the CDK10 targets are disclosed at the http address www.dhramacon.com. siRNAs were selected from this list for use in RNAi experiments following a filtering protocol that involved the removal of any siRNA with complementarity to common motifs or domains present in any target as well as siRNAs complementary to sequences containing SNPs. From this filtered set of siRNAs, four were selected that showed no off-target homology following BLAST analysis against various Genbank nucleotide databases. Table 25 summarizes the features of the duplexes that were ordered from Dharmacon Research, Inc., and subsequently used as a cocktail in the assays described herein to inhibit expression of CDK10. A non-homologous siRNA reagent was used as a negative control.

Table 25: CDK10 siRNAs used for cell transfection

siRNA	siRNA Target	Sequence Specificity	SEQ ID NO:
CDK10_59	CDK10	GATCCGTCTGAAGTGTATT	
CDK10_149	CDK10	GAAGCTGAACCGCATTGGA	
CDK10_175	CDK10	CCTACGGCATTGTGTATCG	
CDK10_532	CDK10	ACTTGCTCATGACCGACAA	

[0282] Two melanoma cell lines (M14 and A375) were selected for RNAi experiments. On day 1, cells were transfected with siRNA cocktails (18.75 nM) using LIPOFECTAMINE 2000 (LF2000™) Reagent. On days 1, 3 & 6, cellular proliferation was measured using the WST-1 assay (Roche, catalog #1 644 807). Briefly, the WST-1 assay is a colorimetric assay used to determine cellular proliferation by measuring the cleavage of WST-1 by mitochondrial dehydrogenases in living cells. By measuring absorbance, a highly accurate measure of cellular proliferation is obtained. On day 1, WST-1 reagent was added to each well and allowed to incubate for 3-4 h. Subsequently, absorbance was measured at 450 nm and 620 nm using a Tecan Ultra plate reader. This process was repeated on day's 3 and 6. The extent of proliferation on days 3 and 6 were calculated relative to day 1, based on absorbance readings for each sample on each day. From the triplicate repeats of each time point, means and standard deviations were calculated and the effect of siRNA inhibition of each target on cellular proliferation was assessed

and compared to cells transfected with a positive control siRNA (siRAD21_1175) and a negative control siRNA (siLuciferase GL2). All experiments were performed in duplicate.

Example 9

Cell Proliferation

[0283] The siRNAs from Example 8 were transfected in cell lines grown in 6-well plates. Cells were trypsinized on the following day and distributed into 96-well plates. Wst-1 reagent was added on the indicated days and the absorbance at 650 nm and 450 nm was measured. The difference in absorbance between these 2 wavelengths is an indication of the metabolic activity in each well that was measured. Metabolic activity is directly proportional to the number of cells in each well.

[0284] Suppression of target mRNA levels correlated with decreased cell proliferation as seen in A375 melanoma cells. See Figure 21.

Example 10

Screening Assay to Detect Modulators of CDK10

[0285] The following is an exemplary assay for finding modulators of CDK10. CDK10 may be screened using, for example, the non-radioactive IMAP system available from Molecular Devices, Sunnyvale CA94089, according to the manufacturers instructions. The ability of a given compound to modulate activity of the kinase is determined by comparison of fluorescence polarization values in the IMAP assay in the presence of the compound with values obtained in solvent controls. Preferably, the test compound should produce a result that differs by at least 3 standard deviations from a set of at least 30 replicate control samples. More specifically, IMAP is a technology that uses the specific binding of metal (M III) coordination complexes to phosphate groups at high salt concentration and a fluorescence polarization readout. In a microwell assay format, fluorescently labeled peptides are phosphorylated in a kinase reaction. After the reaction, proprietary IMAP nanoparticles derivatized with metal (M^{III}) coordination complexes are added to the assay to bind the phosphorylated peptides. The binding causes a change in the motion of the peptide, and results in an increase in the observed fluorescence polarization. This assay, unlike antibody-based homogeneous kinase assays, is applicable to a wide variety of tyrosine and serine/threonine kinases. IMAP technology is largely independent of the sequence of the substrate peptides. In addition, the technology is useful in assays of phosphodiesterases and phosphatases. In a typical reaction on a 384-well plate the following would be combined: 10 ul of the kinase in question, 5 ul of test compound, 5 ul of substrate, such as Myelin Basic Protein Fragment 4-14 (MDL Number MFCD00133371; CAS Number 126768-94-3) or a similarly-sized peptide, at a concentration of 30-1000 nM; and ATP at a concentration of 1-30 ul. The substrate may be labeled with a fluorophore such as fluorescein-5-isothiocyanate (FITC Isomer I). These reagents would be allowed to react at room

temperature for one hour. Then 60 ul of IMAP binding reagent is added and the fluorescence polarization is read.

Example 11

Screening Assay to Detect Modulators of CARK

[0286] The following is an exemplary assay for finding modulators of CARK. CARK may be screened using, for example, the non-radioactive IMAP system available from Molecular Devices, Sunnyvale CA94089, according to the manufacturers instructions. The ability of a given compound to modulate activity of the kinase is determined by comparison of fluorescence polarization values in the IMAP assay in the presence of the compound with values obtained in solvent controls. Preferably, the test compound should produce a result that differs by at least 3 standard deviations from a set of at least 30 replicate control samples. More specifically, IMAP is a technology that uses the specific binding of metal (M III) coordination complexes to phosphate groups at high salt concentration and a fluorescence polarization readout. In a microwell assay format, fluorescently labeled peptides are phosphorylated in a kinase reaction. After the reaction, proprietary IMAP nanoparticles derivatized with metal (M^{III}) coordination complexes are added to the assay to bind the phosphorylated peptides. The binding causes a change in the motion of the peptide, and results in an increase in the observed fluorescence polarization. This assay, unlike antibody-based homogeneous kinase assays, is applicable to a wide variety of tyrosine and serine/threonine kinases. IMAP technology is largely independent of the sequence of the substrate peptides. In addition, the technology is useful in assays of phosphodiesterases and phosphatases. In a typical reaction on a 384-well plate the following would be combined: 10 ul of the kinase in question, 5 ul of test compound, 5 ul of substrate, such as Myelin Basic Protein Fragment 4-14 (MDL Number MFCD00133371; CAS Number 126768-94-3) or a similarly-sized peptide, at a concentration of 30-1000 nM; and ATP at a concentration of 1-30 ul. The substrate may be labeled with a fluorophore such as fluorescein-5-isothiocyanate (FITC Isomer I). These reagents would be allowed to react at room temperature for one hour. Then 60 ul of IMAP binding reagent is added and the fluorescence polarization is read.

Example 12

Screening Assay to Detect Modulators of FPGT

[0287] The following is an exemplary assay for finding modulators of FPGT. Incubate enzyme plus test sample plus substrates (fucose-1-phosphate and alpha-33P GTP (Amersham)) under conditions described (Pastuszak,I., Ketchum,C., Hermanson,G., Sjoberg,E.J., Drake,R. and Elbein,A.D. GDP-L-fucose pyrophosphorylase. Purification, cDNA cloning, and properties of the enzyme J. Biol. Chem. 273 (46), 30165-30174 (1998)). Add to the reaction mixture streptavidin coated scintillation proximity beads

(Amersham) precoated with biotinylated lotus lectin (Vector Labs, Burlingame CA94010). Measure bead-associated radioactivity by scintillation counting. The ability of a given compound to modulate activity of the enzyme is determined by comparison of bead-bound radioactivity in the presence of the compound with values obtained in solvent controls. Preferably, the test compound should produce a result that differs by at least 3 standard deviations from a set of at least 30 replicate control samples.

Example 13

In Vitro Production of target polypeptides

[0288] Target polypeptides encoded by the polynucleotides provided in Figured 1-7 may be produced by the methods described herein.

[0289] cDNA is cloned into a pIVEX 2.3-MCS vector (Roche Biochem) using a directional cloning method. A cDNA insert is prepared using PCR with forward and reverse primers having 5' restriction site tags (in frame) and 5-6 additional nucleotides in addition to 3' gene-specific portions, the latter of which is typically about twenty to about twenty-five base pairs in length. A Sal I restriction site is introduced by the forward primer and a Sma I restriction site is introduced by the reverse primer. The ends of PCR products are cut with the corresponding restriction enzymes (*i.e.*, Sal I and Sma I) and the products are gel-purified. The pIVEX 2.3-MCS vector is linearized using the same restriction enzymes, and the fragment with the correct sized fragment is isolated by gel-purification. Purified PCR product is ligated into the linearized pIVEX 2.3-MCS vector and *E. coli* cells transformed for plasmid amplification. The newly constructed expression vector is verified by restriction mapping and used for protein production.

[0290] *E. coli* lysate is reconstituted with 0.25 ml of Reconstitution Buffer, the Reaction Mix is reconstituted with 0.8 ml of Reconstitution Buffer; the Feeding Mix is reconstituted with 10.5 ml of Reconstitution Buffer; and the Energy Mix is reconstituted with 0.6 ml of Reconstitution Buffer. 0.5 ml of the Energy Mix was added to the Feeding Mix to obtain the Feeding Solution. 0.75 ml of Reaction Mix, 50 μl of Energy Mix, and 10 μg of the template DNA is added to the *E. coli* lysate.

[0291] Using the reaction device (Roche Biochem), 1 ml of the Reaction Solution is loaded into the reaction compartment. The reaction device is turned upside-down and 10 ml of the Feeding Solution is loaded into the feeding compartment. All lids are closed and the reaction device is loaded into the RTS500 instrument. The instrument is run at 30°C for 24 hours with a stir bar speed of 150 rpm. The pIVEX 2.3 MCS vector includes a nucleotide sequence that encodes six consecutive histidine amino acids on the C-terminal end of the target polypeptide for the purpose of protein purification. target polypeptide is purified by contacting the contents of reaction device with resin modified with Ni^{2+} ions. target polypeptide is eluted from the resin with a solution containing free Ni^{2+} ions.

Example 14

Cellular Production of target polypeptides

[0292] Nucleic acids are cloned into DNA plasmids having phage recombination cites and target polypeptides are expressed therefrom in a variety of host cells. Alpha phage genomic DNA contains short sequences known as attP sites, and *E. coli* genomic DNA contains unique, short sequences known as attB sites. These regions share homology, allowing for integration of phage DNA into *E. coli* via directional, site-specific recombination using the phage protein Int and the *E. coli* protein IHF. Integration produces two new att sites, L and R, which flank the inserted prophage DNA. Phage excision from *E. coli* genomic DNA can also be accomplished using these two proteins with the addition of a second phage protein, Xis. DNA vectors have been produced where the integration/excision process is modified to allow for the directional integration or excision of a target DNA fragment into a backbone vector in a rapid *in vitro* reaction (Gateway™ Technology (Invitrogen, Inc.)).

[0293] A first step is to transfer the nucleic acid insert into a shuttle vector that contains attL sites surrounding the negative selection gene, ccdB (*e.g.* pENTER vector, Invitrogen, Inc.). This transfer process is accomplished by digesting the nucleic acid from a DNA vector used for sequencing, and to ligate it into the multicloning site of the shuttle vector, which will place it between the two attL sites while removing the negative selection gene ccdB. A second method is to amplify the nucleic acid by the polymerase chain reaction (PCR) with primers containing attB sites. The amplified fragment then is integrated into the shuttle vector using Int and IHF. A third method is to utilize a topoisomerase-mediated process, in which the nucleic acid is amplified via PCR using gene-specific primers with the 5' upstream primer containing an additional CACC sequence (*e.g.*, TOPO® expression kit (Invitrogen, Inc.)). In conjunction with Topoisomerase I, the PCR amplified fragment can be cloned into the shuttle vector via the attL sites in the correct orientation.

[0294] Once the nucleic acid is transferred into the shuttle vector, it can be cloned into an expression vector having attR sites. Several vectors containing attR sites for expression of target polypeptide as a native polypeptide, N-fusion polypeptide, and C-fusion polypeptides are commercially available (*e.g.*, pDEST (Invitrogen, Inc.)), and any vector can be converted into an expression vector for receiving a nucleic acid from the shuttle vector by introducing an insert having an attR site flanked by an antibiotic resistant gene for selection using the standard methods described above. Transfer of the nucleic acid from the shuttle vector is accomplished by directional recombination using Int, IHF, and Xis (LR clonase). Then the desired sequence can be transferred to an expression vector by carrying out a one hour incubation at room temperature with Int, IHF, and Xis, a ten minute incubation at 37°C with proteinase K, transforming bacteria and allowing expression for one hour, and then plating on selective media. Generally, 90% cloning efficiency is achieved by this method. Examples of expression vectors

are pDEST 14 bacterial expression vector with att7 promoter, pDEST 15 bacterial expression vector with a T7 promoter and a N-terminal GST tag, pDEST 17 bacterial vector with a T7 promoter and a N-terminal polyhistidine affinity tag, and pDEST 12.2 mammalian expression vector with a CMV promoter and neo resistance gene. These expression vectors or others like them are transformed or transfected into cells for expression of the target polypeptide or polypeptide variants. These expression vectors are often transfected, for example, into murine-transformed cell lines (e.g., adipocyte cell line 3T3-L1, (ATCC), human embryonic kidney cell line 293, and rat cardiomyocyte cell line H9C2).

[0295] Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with reference to one or more specific embodiments, those of skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, yet these modifications and improvements are within the scope and spirit of the invention, as set forth in the claims which follow. Also, citation of the above publications or documents is not intended as an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents. U.S. patents and other publications and documents referenced are incorporated herein by reference.

What is claimed is:

1. A method for identifying a subject at risk of melanoma, which comprises detecting the presence or absence of one or more polymorphic variations associated with melanoma in a nucleic acid sample from a subject, wherein the polymorphic variation is detected in a nucleotide sequence selected from the group consisting of

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c);

whereby the presence of the polymorphic variation is indicative of the subject being at risk of melanoma.

2. The method of claim 1, which further comprises obtaining the nucleic acid sample from the subject.

3. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

4. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

5. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

6. The method of claim 1, wherein a polymorphic variation is detected at position 38753 in SEQ ID NO: 4.

7. The method of claim 3, wherein one or more polymorphic variations are detected at one or more positions in linkage disequilibrium with one or more nucleotides at positions in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

8. The method of claim 4, wherein the one or more polymorphic variations are detected at one or more positions in linkage disequilibrium with one or more nucleotides at positions in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

9. The method of claim 5, wherein one or more polymorphic variations are detected at one or more positions in linkage disequilibrium with one or more nucleotides at positions in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

10. The method of claim 6, wherein one or more polymorphic variations are detected at one or more positions in linkage disequilibrium with a nucleotide at position 38753 in SEQ ID NO: 4.

11. The method of claim 1, wherein detecting the presence or absence of the one or more polymorphic variations comprises:

hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to a nucleotide sequence in the nucleic acid and hybridizes to a region adjacent to the polymorphic variation;

extending the oligonucleotide in the presence of one or more nucleotides, yielding extension products; and

detecting the presence or absence of a polymorphic variation in the extension products.

12. The method of claim 1, wherein the subject is a human.

13. A method for identifying a polymorphic variation associated with melanoma proximal to an incident polymorphic variation associated with melanoma, which comprises:

identifying a polymorphic variation proximal to the incident polymorphic variation associated with melanoma, wherein the polymorphic variation is detected in a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c) comprising the polymorphic variation;

determining the presence or absence of an association of the proximal polymorphic variant with melanoma.

14. The method of claim 13, wherein the incident polymorphic variation is at a position in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

15. The method of claim 13, wherein the incident polymorphic variation is at a position in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

16. The method of claim 13, wherein the incident polymorphic variation is at a position in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

17. The method of claim 13, wherein the incident polymorphic variation is at position 38753 in SEQ ID NO: 4.

18. The method of claim 13, wherein the proximal polymorphic variation is within a region between about 5 kb 5' of the incident polymorphic variation and about 5 kb 3' of the incident polymorphic variation.

19. The method of claim 13, which further comprises determining whether the proximal polymorphic variation is in linkage disequilibrium with the incident polymorphic variation.

20. The method of claim 13, which further comprises identifying a second polymorphic variation proximal to the identified proximal polymorphic variation associated with melanoma and determining if the second proximal polymorphic variation is associated with melanoma.

21. The method of claim 20, wherein the second proximal polymorphic variant is within a region between about 5 kb 5' of the incident polymorphic variation and about 5 kb 3' of the proximal polymorphic variation associated with melanoma.

22. An isolated nucleic acid comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c); and

(e) a nucleotide sequence complementary to the nucleotide sequences of (a), (b), (c), or (d);

wherein the nucleotide sequence comprises one or more nucleotides selected from the group consisting of a cytosine at position 139 in SEQ ID NO: 1, a guanine at position 3525 in SEQ ID NO: 1, a thymine at position 7960 in SEQ ID NO: 1, a guanine at position 9640 in SEQ ID NO: 1, a thymine at position 14845 in SEQ ID NO: 1, a cytosine at position 19300 in SEQ ID NO: 1, a cytosine at position 21338 in SEQ ID NO: 1, a thymine at position 21343 in SEQ ID NO: 1, a guanine at position 42477 in SEQ ID NO: 1, a thymine at position 43164 in SEQ ID NO: 1, a thymine at position 43734 in SEQ ID NO: 1, an adenine at position 44029 in SEQ ID NO: 1, a thymine at position 44986 in SEQ ID NO: 1, a guanine at position 53410 in SEQ ID NO: 1, a cytosine at position 83831 in SEQ ID NO: 1, a cytosine at position 85666 in SEQ ID NO: 1, a cytosine at position 88389 in SEQ ID NO: 1, a guanine at position 92523 in SEQ ID NO: 1, a thymine at position 17207 in SEQ ID NO: 2, a guanine at position 19057 in SEQ ID NO: 2, a guanine at position 32252 in SEQ ID NO: 2, a thymine at position 33887 in SEQ ID NO: 2, a cytosine at position 36394 in SEQ ID NO: 2, an adenine at position 39184 in SEQ ID NO: 2, a thymine at position 40707 in SEQ ID NO: 2, an adenine at position 42857 in SEQ ID NO: 2, a cytosine at position 45812 in SEQ ID NO: 2, a thymine at position 46643 in SEQ ID NO: 2, a cytosine at position 47007 in SEQ ID NO: 2, a guanine at position 50015 in SEQ ID NO: 2, a guanine at position 50442 in SEQ ID NO: 2, an adenine at position 51203 in SEQ ID NO: 2, a guanine at position 51983 in SEQ ID NO: 2, an adenine at position 57523 in SEQ ID NO: 2, an adenine at position 60557 in SEQ ID NO: 2, a thymine at position 60645 in SEQ ID NO: 2, an adenine at position 64531 in SEQ ID NO: 2, a thymine at position 83870 in SEQ ID NO: 2, a cytosine at position 4029 in SEQ ID NO: 3, an adenine at position 5343 in SEQ ID NO: 3, an adenine at position 8817 in SEQ ID NO: 3, a thymine at position 18596 in SEQ ID NO: 3, an adenine at position 18602 in SEQ ID NO: 3, a cytosine at position 21583 in SEQ ID

NO: 3, a thymine at position 36594 in SEQ ID NO: 3, a thymine at position 37994 in SEQ ID NO: 3, an adenine at position 38293 in SEQ ID NO: 3, a cytosine at position 46972 in SEQ ID NO: 3, an adenine at position 48524 in SEQ ID NO: 3, a thymine at position 72488 in SEQ ID NO: 3 and a cytosine at position 38753 in SEQ ID NO: 4.

23. An oligonucleotide comprising a nucleotide sequence complementary to a portion of the nucleotide sequence of (a), (b), (c), or (d) in claim 22, wherein the 3' end of the oligonucleotide is adjacent to a polymorphic variation associated with melanoma.

24. A microarray comprising an isolated nucleic acid of claim 22 linked to a solid support.

25. An isolated polypeptide encoded by the isolated nucleic acid sequence of claim 22.

26. A method for identifying a candidate molecule that modulates cell proliferation, which comprises:

(a) introducing a test molecule to a system which comprises a nucleic acid comprising a nucleotide sequence selected from the group consisting of:

(i) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(ii) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(iii) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(iv) a fragment of a nucleotide sequence of (i), (ii), or (iii); or

introducing a test molecule to a system which comprises a protein encoded by a nucleotide sequence of (i), (ii), (iii), or (iv); and

(b) determining the presence or absence of an interaction between the test molecule and the nucleic acid or protein,

whereby the presence of an interaction between the test molecule and the nucleic acid or protein identifies the test molecule as a candidate molecule that modulates cell proliferation.

27. The method of claim 26, wherein the system is an animal.

28. The method of claim 26, wherein the system is a cell.

29. The method of claim 26, wherein the nucleotide sequence comprises one or more polymorphic variations associated with melanoma.

30. The method of claim 29, wherein the nucleotide sequence comprises a polymorphic variation associated with melanoma at one or more positions in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

31. The method of claim 29, wherein the nucleotide sequence comprises a polymorphic variation associated with melanoma at one or more positions in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

32. The method of claim 29, wherein the nucleotide sequence comprises a polymorphic variation associated with melanoma at one or more positions in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

33. The method of claim 29, wherein the nucleotide sequence comprises a polymorphic variation associated with melanoma at position 38753 in SEQ ID NO: 4.

34. A method for treating melanoma in a subject, which comprises administering a candidate molecule identified by the method of claim 26 to a subject in need thereof, whereby the candidate molecule treats melanoma in the subject.

35. A method for identifying a candidate therapeutic for treating melanoma, which comprises:

(a) introducing a test molecule to a system which comprises a nucleic acid comprising a nucleotide sequence selected from the group consisting of:

(i) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(ii) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(iii) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(iv) a fragment of a nucleotide sequence of (i), (ii), or (iii); or

introducing a test molecule to a system which comprises a protein encoded by a nucleotide sequence of (i), (ii), (iii), or (iv); and

(b) determining the presence or absence of an interaction between the test molecule and the nucleic acid or protein,

whereby the presence of an interaction between the test molecule and the nucleic acid or protein identifies the test molecule as a candidate therapeutic for treating melanoma.

36. A method for treating melanoma in a subject, which comprises contacting one or more cells of a subject in need thereof with a nucleic acid, wherein the nucleic acid comprises a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c); and

(e) a nucleotide sequence complementary to the nucleotide sequences of (a), (b), (c), or (d);

whereby contacting the one or more cells of the subject with the nucleic acid treats melanoma in the subject.

37. The method of claim 36, wherein the nucleic acid is duplex RNA.

38. The method of claim 37, wherein the duplex RNA comprises a strand comprising the nucleotide sequence GATCCGTCTGAAGTGTATT (SEQ ID NO:), GAAGCTGAACCGCATTGGA (SEQ ID NO:), CCTACGGCATTGTGTATCG (SEQ ID NO:) or ACTTGCTCATGACCGACAA (SEQ ID NO:).

39. A method for treating melanoma in a subject, which comprises contacting one or more cells of a subject in need thereof with a protein, wherein the protein is encoded by a nucleotide sequence which comprises a polynucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c);

whereby contacting the one or more cells of the subject with the protein treats melanoma in the subject.

40. A method for treating melanoma in a subject, which comprises:

detecting the presence or absence of one or more polymorphic variations associated with melanoma in a nucleic acid sample from a subject, wherein the polymorphic variation is detected in a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c) comprising the polymorphic variation; and

administering a melanoma treatment to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

41. The method of claim 40, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

42. The method of claim 40, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

43. The method of claim 40, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

44. The method of claim 40, wherein a polymorphic variation is detected at position 38753 in SEQ ID NO: 4.

45. The method of claim 40, which further comprises extracting and analyzing a tissue biopsy sample from the subject.

46. The method of claim 40, wherein the treatment is one or more selected from the group consisting of administering cisplatin, administering carmustine, administering vinblastine, administering vincristine, administering bleomycin, administering a combination of the foregoing, and surgery.

47. A method for preventing melanoma in a subject, which comprises:

detecting the presence or absence of one or more polymorphic variations associated with melanoma in a nucleic acid sample from a subject, wherein the polymorphic variation is detected in a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c) comprising the polymorphic variation; and

administering a melanoma preventative to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

48. The method of claim 47, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

49. The method of claim 47, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

50. The method of claim 47, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

51. The method of claim 47, wherein a polymorphic variation is detected at position 38753 in SEQ ID NO: 4.

52. The method of claim 47, wherein the preventative reduces ultraviolet (UV) light exposure to the subject.

53. A method of targeting information for preventing or treating melanoma to a subject in need thereof, which comprises:

detecting the presence or absence of one or more polymorphic variations associated with melanoma in a nucleic acid sample from a subject, wherein the polymorphic variation is detected in a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(b) a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4;

(c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4; and

(d) a fragment of a nucleotide sequence of (a), (b), or (c) comprising the polymorphic variation comprising the polymorphic variation; and

directing information for preventing or treating melanoma to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

54. The method of claim 53, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 1 selected from the group consisting of 139, 3525, 7960, 9640, 14845, 19300, 21338, 21343, 42477, 43164, 43734, 44029, 44986, 53410, 83831, 85666, 88389 and 92523.

55. The method of claim 53, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 2 selected from the group consisting of 17207, 19057, 32252, 33887, 36394, 39184, 40707, 42857, 45812, 46643, 47007, 50015, 50442, 51203, 51983, 57523, 60557, 60645, 64531 and 83870.

56. The method of claim 53, wherein the one or more polymorphic variations are detected at one or more positions in SEQ ID NO: 3 selected from the group consisting of 4029, 5343, 8817, 18596, 18602, 21583, 36594, 37994, 38293, 46972, 48524 and 72488.

57. The method of claim 53, wherein a polymorphic variation is detected at position 38753 in SEQ ID NO: 4.

58. The method of claim 53, wherein the information comprises a description of methods for reducing ultraviolet (UV) light exposure to the subject.

59. The method of claim 53, wherein the information comprises a description of chemotherapeutic treatments and surgical treatments of melanoma.

60. A composition comprising a melanoma cell and an antibody that specifically binds to a protein, polypeptide or peptide encoded by a nucleotide sequence 90% or more identical to the nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4.

61. A composition comprising a melanoma cell and a RNA, DNA, PNA or ribozyme molecule comprising a nucleotide sequence identical to or 90% or more identical to a portion of a nucleotide sequence of SEQ ID NO: 1, 2, 3 or 4.

62. The composition of claim 61, wherein the RNA molecule is a short inhibitory RNA molecule.

DEMANDE OU BREVET VOLUMINEUX

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FIGURE 1-A

>16:89415601-89514700

```
1       ggggcagcag cagggcggct cgcttggggg cggctgcagc tggggcctct gagtcgagat
61      cagggctccc tggtcggagc ctcagcccaa gctctcctcc agcctctaac ccacaaccct
121     ctctcccttc ccacagcaYc agagcgtggg gttggtgaca cagcgtttcg gggaccgacc
181     ctacctccgt gacagctggt cctcctggct gcgcacagag ctctcgccca cggcagaggc
241     gccctcgggc agctggctga gctggtccag cacctccagg ccattctcct cggcgatctg
301     catgatgagg ctgtccacct gctcctgcgg cgtggtcagg gtggtggccg agctcatgga
361     gtcctccatc acctgggggc aggggcatgc tctggacaac aggtggggcc aggcccatgg
421     ggcYccactc agcttcacaa gggtacgact gcacttttcg ttccctcaca cagccagcca
481     ccttcttgcc ctgttctctc agtgactctc tctgtctcac cttccaccag gagcctttcc
541     tgcccccccca cccagcccca ccctctgact gtgccatgcc tgctgccgcg ggtggacatc
601     tttccacacc tctgcatgct tgtctgccat ccgagcctcc ccacaaggag ccaggtgcct
661     gcaggaggcc cccgccgccc tgcccaccct acctgtcagg gtcctggcag ggacccagca
721     cagaggatgc ttggtgacgt cagggagcaa ccacaggtat gcagagacag cacgtcagcc
781     tgtgagccac ccctcccgat gagctgccca cacacgctcc ttgtccccag gccacagccc
841     caagggtagg ggccacatac cgatgtatgg acgtccaggt tctgcacctg ctgctcgaac
901     ctgtccatca ctgaggagac cttctgcagg tccatggtgc tcagggcctt gtccagggct
961     ttggtcacct gggccatatt cttggtcacc tgagacagga gagagcgcag gagggaacag
1021    gatgaaaggc aagtggagct cacgcaccag ggacgggtcc cctggactct gacaggagag
1081    ctggggcacc ccaaccctga cccacaaaac cccaactctg ggctgagcca tcatctgggt
1141    cctatggaaa gaccaccaac tcgacggaaa aggccatgga gacccagtgc ggggtcagtg
1201    gagaaaaggc cgccgacgtg gagacccagt gcggggtcag tggagaaaag gccgccgacg
1261    tggagaccca gtgcggggtc ggtggagaaa aggccgccga cgtggggacc cagcgcgggg
1321    tcggtggaga aaaggccgcc gacgtgggga cccagcgcgg ggtcggtgga gaaaaggccg
1381    ccgacgtggg gacccagcgc ggggtcggtg gagaaaaggc cgccgacgtg gagacccagc
1441    gcggggtcgg tggagaaaag gccgccgacg tggggaccca gcgcggggtc ggtggagaaa
1501    aggccgccga cgtggagacc cagcgcgggg tccgtggaga aaaggccgcc gacgtggaca
1561    cccagcgcgg ggtcggtgga gaaaaggccg ccgacgtggg gacccagcgc ggggtcggtg
1621    gagaaaaggc cgccgacgtg gggacccagc gcggggtcgg tggagaaaag gccgccgacg
1681    tggggaccca gcgcggggtc ggtggagaaa aggccgccga cgtggggacc cagcgcgggg
1741    tcggtggaga aaaggccgcc gacgtgggga cccagcgcgg ggtcggtgga gaaaaggccg
1801    ccgacgtgga gacccagcgc ggggtcggtg gagaaaaggc cgccgacgtg gagacccagc
1861    gcggggtcgg tggagaaaag gccgccgacg tggagaccca gcgcggggtc ggtggagaaa
1921    aggccgccga cgtggagacc cagcgcgggg tcggtggaga aaaggccgcc gacgtggaga
1981    cccagcgcgg ggtcggtgga gaaaaggccg ccgacgtgga gacccagcgc ggggtcggtg
2041    gagaaaaggc cgccgacgtg gggacccagc gcggggtcgg tggagaaaag gccgccgacg
2101    tggggtctcc aggactgctg tgccctcctg gcccacctgc actgtgtgaa ggaaatgcct
2161    gcaacagcca aggctctgct gtgacgtccc tgacccagca gatgagcctg gccatgcagg
2221    ctctgcctct tgtgggagtt gccaagaccg aggcctggcc aggtacagtg acagtgagtg
2281    gttcacgcct ataattccag cactttggga ggccgaggtg ggaagattgc ttgaggccag
2341    gagtttgaga ccagagcggc caacatagac accctgtctc tacataaaaa tgaaaaaaat
2401    cagctgggca tggtggtgga tgcctgtggt ctcagctact tgggaggctg aggcaggagg
2461    atcgcttgag cccaggaggt tgagaccaga gtggccaaca tagacaccct gtctctactt
2521    aaaaatgaaa agatcagccg ggcatggtgg tggatgcctg tggtctcagc tacttgcgag
2581    gctgaggcag gaggattgct tgagcccagg aggttgaggc tgcagtgagc tgtgactgca
2641    ccactgcact ccagcctggg tgacagagca agacagtctc taaaaaatat atatttaaaa
2701    aaaaaaaagc ccaagtctta tcaagaggtc cttcctgggg catcagtgca agctcagggt
2761    gcagcctcac ctgtgtccct gccagcattt cccaccccac gctgatccag cttaactcaa
2821    cctccccacc ccacgctgat ccagccctca acctccccac cccacgctga tccagcttcc
2881    ctcaacctcc ccaccccRcg ctgatccacc ttccgtcaac tctgagctgc cccagatcca
2941    gaccgcagag cccattcctg cttcagccag cgaacgccac ccatccagca ccagggccca
3001    gcactcaccc ccttcatagt cacagctgtc tgcaccttgg aggccactgc gtctacgcgg
3061    gacgccatcc gaagccagtt cacaccttcg ttcttcttgc ggatggcgtt ctcggcatac
3121    acacgggcac actctacatt tttctgcaga agggcctgaa acccgSgggg gaaagcagct
3181    ggaagagctt ggtggtgtgt gtgccccctg ctaggagccc agtttttgtt ttgttttgtt
3241    ttgttttgtt tgagacggag tcttgctctg ttgcccaggc tggagtgcag tggcacgatc
3301    tcgactcaac gcaagctccg ccccccaggt tcatgccatt ctcctgcctc agcctcccga
3361    gtagttggga ctacaggcgc ccgccaccat gcctggctaa tttttttgta tttttagtag
3421    agatggggtt tcaccgtgtt agccaggatg gcctcgatct cctgacctcg tgatctgccc
3481    gcctcggcct cccaaagagc Ygggatcaca ggcgtgagcc accgMgcccg gccctaggag
```

FIGURE 1-B

3541 cccagtgttg aggcggtggg cgggcctctc cccagaaatg tttgagctaa aaatgcaaac
3601 acccaggccc cagcccagcc ccccaagcag gcttctgctt ccccccgcac ccctccagca
3661 ctccactggg cacgggacac agcgggtgac actcagagcc tgtggcaggc agttctccga
3721 gctccattct ccctgggagc ctggctgtgg gtgaagagtt accaaagtcc aatacgctgg
3781 gacctacttc accgattacg cagttttaag agctgcacaa gatcctacct tctttttctt
3841 tttttctttt tttggagatg gaatctcgct ctgtggccca ggatggagtg cagcagtgtg
3901 atctcggctc actgcaacct ccacctcctg ggctcaagca attctcccgc ctcagccttc
3961 cgagtagctg ggattatagg tgtgaatcac tgcgcccggc ctagatccct cctctccttc
4021 tgccctgtcc atcatgggga ggggacccct cctggagagg cacccctgta agcctccagc
4081 cccatcccac cccatggggc aggggcatca tgactctgcc cagaccctga tgccctagac
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4321 aggtgtggtg gcgcatgctt gtaatcccag ctacccagga ggttgaggca ggagaatcac
4381 tcgaacccag gaggcagagg ttgcagtgag ccgagaccgc acctctgcac tccagcctgg
4441 gcaacagcga gactccatct caaaaaaaaa aaagatagga tcgtggcaga cagctagcta
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4561 aaacaatgaa ggcaatgcac tcatctctgt gctctggacg ccctcagtgg gctgggaagg
4621 tctggcaggg gctgtagggc agggacRgaa accattctgg gctgcaccac acacagcacc
4681 tcccttcctg agtgcctgtt tgtcttatgt gggaagcaaa tactttgagg ctcagaaatc
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4801 caaggcaggt gggtcacttg aggataagag ttcgagaccg gcctggccaa catggcgaaa
4861 ccccatctct acaaaaaaat taaaaaatta gctgggtgca agcctgtaat cgcagctacg
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5041 aacaaacaaa caaacaaaca aaatatatat atatatgtac ctcaaggtga cgattaaatc
5101 atgatgtaga aagtgccctg cccctcccca aaaggcatca aaacaaaaca ggacacaaaa
5161 ataagggcag aaaaggacag aagacaaacc aggagagtca tgaccccaca gcccccaggg
5221 tctcaccttc ttcactttgg cctgctccgc cttggagtcc ttctccgcct tcttggccag
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5461 aagcctgtgg gcgtgcatcc tgggcggcga gagatggcac cagctggagg aggaagctgc
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5761 tgctgtggat gcaggaggtt gctgggcagc acaagcagct tccggggatc taactgctct
5821 gccagcacca cacggaaaca gggcctctgg caacaccaca aggacacagg acctctggca
5881 acccacccgg aaccacagac gccctggtac caggtagccc tggccaccag cacctcaagg
5941 aaacagggcc tctggcaacc catctggaat cacagacacc ctggtatcag gtagccctgg
6001 ccaccagcac ctcaaggaaa cagggcctct ggcaacccat ctggaaccac agacgccctg
6061 gtaccaggta gccctggcca ccagcacctc gaggaaacag ggcctctggc aacccatctg
6121 gaaccacaga cgccctggta ccaggtggcc ctggccacca gcacctcgag gaaacagggc
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6361 ctgtgcccaa cagcaactga caggcccacc gtgatgggaa aacatcccaa agctgcatac
6421 ggtagctccg gcacatcact cctgcccagt agctcagagc cagcgacaag gcaagataaa
6481 gctggccaca gatgagcagc caggagcaca tcccagggaa atgcacggaa acctgccctg
6541 gattaccgga agctgcaacc tccaccccac gtgggaggaa tactcagaaa gctctccttc
6601 aaatgatctc aaagaatgag tccacacagc ggaacaccaa ggcctaatgc ccaagttgtc
6661 tttttttttt ttcttttctt tttttttttt ttttttgag acggagtctc tgtcacccag
6721 gctggagtgc agtggcacaa tcttggctta ctgcaagctc tgcctcccag gttcacgcca
6781 ttctccggcc tcagcctcct gagtagctgg gactacaggt gcctgccacc gcgcccggct
6841 aatttttttg tgtgttttta gtagagatgg ggtttcactg tggtctccat ctcctgacct
6901 tgtgatccac cccacctcgg tctcccaaag tgctgggatt acaggcgtga gccaccgcgc
6961 ctggccccaa gttgtctttc ttaagataac actccgggcc aggcacagtg gctcacgcct
7021 gtaatcccag cactttagga ggccgaggta ggcggatcac gaggtgaaga gatcgagacc
7081 atcctggcca acgtggtgaa accccgtctc tattaaaaat gtaaaaaaaa attagctggg
7141 catggtggtg ggcgcctgta gtcccagcta ctcaggaggc taaggcagga gaatcgcttg
7201 aacccgggag gcagaggttg cagtgagccg agatcacgcc aatgcactcc agcctgggcg
7261 acggagtgag acgccgtctc aaaaaaaaaa aaaaaaaaaa aaaagataac actatttctt
7321 tcatggcttt catggatgac cctaaggatc tgcctccact tagcctcaga taagaaaaga

FIGURE 1-C

7381 gctaatatgt caccaaggtg gctcaataat cccctccttg gtcagcagtc tgagccctgt
7441 gtggcggtca ctcaactgtt atataatctg cccgactgtt tctgtggctc tgagtgagcg
7501 tggcttatac tatctgtcct caccagaaca gggctggggt gaacggccat tcggtacata
7561 ccttcaactg gaacagggta tctgcaaaga aagagggaat taatggtttg aggattggga
7621 atgggacgtt acacttctgg caggcaggac tcactaggtt ccttctagac accaggagct
7681 agaacacaca cacagaccac acctgcctgg ggccttcggg gagcccccccc caacagggga
7741 ggcacgagac agattcgtgt gccagccctg gctccttgct agccacaggg cccagcaaat
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7861 agggttagtg tgaggacaga agaggtcatg gacgcagcat cttttggcca tggttagaat
7921 ccaaaagatg gtggtttata attaatgcaa ctttgcaaaW gtcccttggg attctttccc
7981 aatttaaaag ttcacctgta atcccagcac tctgggggtg ccgaggccag tggatcactt
8041 aaagccaggg tttgaggcca gcctgggcca atttaaaagt Kcagtacttg acagtttact
8101 ttttacagac tctttctcct caaaggtaaa tggataaaaa tagcaaggtg gtaactctta
8161 gacatcaaag agctgatttc cagcggtaca gtcRctcacg cctgtaatca cagcactctg
8221 ggaggctgag gcgggcagat cacttgaggt caggagttcc agaccagcct agggaatata
8281 gtcagacctc atctctatta gaaaaatata tattttttg ccgggtgcgg tggctcacgc
8341 ctgtaatccc agcactttgg gaggccgagg ccggcggaac atgaggtcag gagatcgaga
8401 ccatcctggc taacacggta aaagcccgtc tctaccaaaa aatacaaaaa attagccagg
8461 cgtggtggcg ggcgcctgta gtcccagcta ctcaggaggc tgaggcagga gaatggcgtg
8521 aacccgggag gcagagcttg cagtgagccg agattgcgcc actgcactcc agcctgggca
8581 acagtgcaag actccgtctc aaaaaaaaaa agaaaaaata tttttttaa aaagtaggat
8641 tgatctcaat tcattcaact gctaaatttg gagagcgacc ctgaccccag attcctgaaa
8701 gggctttacc acactagcca caacgaggaa atggagcctg taaaagaatg aggttactga
8761 gtgttcacaa atgcacacca aggctccaag atgagatctc ccggggttcc agaaagctct
8821 gggcatcgtt caatctatcg cctgtcagtg caggcgtggt caaggccaag ttcaacctgt
8881 catctatcag ttcaggtgtg gtcacggcca aggttatctg tgactggaaa acagccagcc
8941 tgacccagat ggcacagtgc aggccaggcg ggccgtccca cccaactcac tgtgggatgc
9001 tggccaaacc gccctcctca tctcagcttt ccctcacctc agctttccct cacctcagct
9061 ttccctcacc tcagctttcc ctcacctcag ctctcctcac ctcagctttc ctcacctcag
9121 ctttccctca cctcagcttt cctcacctca gctttctctt ccagccgtgt gtggcagcac
9181 aaaaacccag ctaaggcaaa atctgactct gaggaaatct gacatgggct tgagagaagt
9241 cccctcaaaa gagttgagtg agctgtggag tgaaaagcca caatttttct tttttttttt
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9781 ttttcacact tctaactaaa agaatttttt ttgagacgga gtctcgctct gtcgcccagg
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11041 ggatcggggg acgacgaccg ggaaaagggg tcccaggtcg gtggtcgagg ccctggggat
11101 ggggtcccgg gggatcgacg gtcgaggccc gagctctcct gagtcctgcc cgcggcccca
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FIGURE 1-D

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11341 acccggcggg gacttccggg gtcgccgccc cacttccggt cgcacgggat gctctcgcga
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11461 tggtgacgca cgccgctggc gcgaggacct tttgtgagtc gctcccggct ccgcggccgc
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14761 aggtttgggg taagttacta tgaagcagta gtgagaagaa cagaagggcc atgatgggga
14821 gaaagtttgg ccataagtta atcaYtgtgg cagctgttag gatattgatg tggcttggct
14881 gtgtcctcac ccaaatctca ttttgaattc ccacatgtgg gaggaactgg gtRggaggtg
14941 attgaattat gggggcaggt ctttcctgtg ctgttttcgt gatagtgaat gagtgtcacg
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FIGURE 1-E

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15181 tgtctttatt agcagcatga aaacggacta atacagatag atgtattata ctgttacccc
15241 tactacttct gtatatgctt aaatttttgc attacaaaat tcacaaacat acaaacatta
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15361 caaataaaga acttgaaaaa aaaggagggg atgttagaag gaaatctgag cgacctagac
15421 ctgggctcag tcacgcctga gacagtcaga tggggtatct gaggatgagt cagtgttaat
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15661 actcagaatg ccaggcatgg tggctcatgc tgtcatccca gcactttggg aggccgagac
15721 gggtggatca cttgaggtca ggagttcgag accagcatgg ccaacatggt gaaaccctgt
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16801 aaagaagaga aatggaacac ttcKattggc tattaaaaaa taccatgctg agtgaaaaaa
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17641 gtggagtgtg cctgtagccc caactaatca ggggcctgag ataggaggat cccttgaccc
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18721 ttggctcatt gcactcttga cgttctgggc tcaaacgatt ctcccacctc agctccctga
18781 gtagctgggg ccacagtgca cgccaccacc cccagctatt ttttgtagtt tttgtagaga
18841 tgcggttttg tcatgttgcc caggctggtc tcgaactcca gaggccaagc aatctgcctg

FIGURE 1-F

18901 cttcagcctc ccaaggtgct gggattacag gcgtgagcca ccgcacctgg cccaagatta
18961 atatttcttt tttttttga gatggagtct tgctctgtcg ccacccaggc tggactgcaa
19021 tggtgcatct ctgctcactg caagctccgc ctcccgggtt catgccattc tcctgtctca
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19141 tttttttttt ttaagtagag atggggtttc actatgttaa ccagaatggt cttaatttcc
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19321 ttgttttaga ctagaaaatt tcaatagtgt aaatacgtta acttctgtaa aatcagtcaa
19381 caccaagtca aaacacaaaa gatcttttgg gaatatgagc agattattca aaggttcatc
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22081 Rcatgaccac tgtagttacg tttctgtaaa aaggtgactg agtcttctaa ccctgaccac
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22441 caggctcagc agtttcacag gtctcaggcg ttccttgtaa ccttaacagg tttaagaaaa
22501 tgtgagcaac atcagacatg tccatttcta gaacattcta atggatgaag ttctgtacag
22561 agggctttag cagaattaga gacctttgga gtggaaatga tgtctctgaa ccttgagctc
22621 tgaggcggtt cctgcctgga cgtgtgccct ccctccttcc tttgctggtc gccctgacac
22681 catcctgcca cggatagtgg aagtgtttct cctgttttct tccctgaaaa agggtgtcca

FIGURE 1-G

22741 gcatcagcaa ccttcatggc tgagttgcac atcccttaag ccctgtaatg ttcatggaca
22801 gttttgatca cttttggact cacccatttt ttctgctaac catacatctt aattccttta
22861 ctctgaccaa tggcaggagg tgtgtgcatc gtggaaggag ctttccacac atctactaaa
22921 tgcctggatg ttttttcctc tagagaaacc tgatgtaaag caaaagtcca gcaggaagaa
22981 agtggtcgtt ccacagatca tcatcacgcg agcgtcgaat gagacgctag tcagttgcag
23041 ttccagcggg agtgaccagc agagaaccat tcgggagccg gaggactggg gcccctaccg
23101 gcggcacagg aaccccagta cagcagacgc ctataattca catctcaaag aataaacaag
23161 cacctttgca tggcactcgc tactccctgc gataggcgtc tcgggaacag ccgcctcacc
23221 ctgtgagaag ccgaggcccc ttctccagtg ctctcgggga ggttgcacca ggcccacccc
23281 accctgtgag aaactgcagc ccccttctcc agtgctttcg gggagggtgc accaggcccg
23341 ccccaccttg tgagaagccg tggccccctt ctccagtgct ctcagggagg gtgcaccagg
23401 cctgcccccg ccgtgagaaa ctgcagYccc cttctccagt gctctcgggg agggtgcacc
23461 aggcccaccc caccctgtga gaacctgcag ccccccttctc caatgctctc ggggagggta
23521 caccagggtt gccccaccct gtgagaagcc accgccccct tctccagtgc tctcggggag
23581 ggtgcaccag ggctgcccca cgctgtaaga agccgccgcc cccttctcca gtgctctcca
23641 gcccgcccca ccctgtgaga agccatggcc ccttctccag tgcttttggg gagggtgcac
23701 cagggccacc ccaccctgtg agaagccgtg gcccccttct ccagtgcttt cggggagggt
23761 acaccaggcc cgccccaccc tgtgagaagc cgtggccccc ttctcccgtg ctctcaggga
23821 gggtgcacca ggcctgcccc cgccttgaga aactgcagcc cccttctcca gtgctctggg
23881 ggagggtgca ccaggcctgc ccaccctgtg agaaactgca ccccccttctc cagtgctctc
23941 ggggagggtg caccaggccc gccccaccct gtgagaagcc gcagcccgtt ctccattgcc
24001 atttggtcct gccttcccca gagctgctag cagctcggtc gaggcaagag tgactggctc
24061 agagagcgag ctttgtggta ttgataaatg aataaattag tatgttcatg ttggaagtgg
24121 ctggctctgc agagtgatgg acagcaggtg gcatcttaca ttgtgatttg tggtgcacag
24181 ttaaaacact tcccttcgtt tcagaaggag acaatgtgaa tacttggaaa ttatagtgaa
24241 taagatgcct cccaaacttg aggaaaaggt cagattctaa gagctaaacg ttaagatgta
24301 atgttccaga acaaagaggc ccagagtcac tgaacggggc cccagggctc ctagcttgag
24361 tgtaatctga gtcagcttat gaaaaggccc caaagaagaa agtggaatgt gtgctgggca
24421 catgggacag ccatggcact gagactttgg aagtggcctt gccagcgctg tcctgtcttt
24481 ctggcccaca gatgagggct cctgattgtg gaaggccacg gaagggacct gaacacgatg
24541 gcacgagaca agttatctcc tgtgactgct cctctccagc aaccctcagc tcaggctaga
24601 ctttccccct gtgttgagaa tgccctgccc tgtgtggaag cctgatgcat ttagtgacag
24661 tgtgttagct ttgttagttt ctagtctggc cagcaggctt tccatgtgat ctgccattgg
24721 cttgcttcag tggccagtgg agccaggggt gtccaccaga gtcttggaca cagacttctg
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24841 gcctatgtag tatatacaca catacgcaga gccttaggaa ttgtgaaagg ccaatcaaaa
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24961 ccaagaaact gcttcctttt tgttcctaag cagagagcta ccaataaaaa gttaaagttt
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25081 tactttaagt tttagggtac atgtgcacaa cgtgcaggtt tgttacatat gcatacatac
25141 gccatgttgg tgtgctgcac ccattaactc gtcatttaca ttaggtattt ctcctaatgc
25201 tttccctccc ccctcccccc taccccacga caggcccccag tgtgtgattt tccccttcct
25261 gtgtccaagt gttctcattg ttcagttccc acctatgagt gagaacatgc ggtgtttggt
25321 ttattttact tgcgatagtt tgctgagaat gatggtttcc agcttcaccc atgtccctgc
25381 aaaggacatg aactcatcct tttttatggc tgcatagtat tccatggtgt atatgtgcca
25441 catttgctta atccagtcta tcactgatgg gcatttgggt tggttctaag tctttgctat
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25561 atcctttggg tatataccca gtaatgggat ggctgagtca aatggtattt ctagttctag
25621 atccctgagg aatcgccaca ctgtcttcca cagtggttga actagtttac agtcccacca
25681 acagtgtaaa agtgttccta tttctcccca tcctctccag cacctgtttc ctgacttttt
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25801 tctgatggcc agtgatgatg agcatttttt catgtgtctg taggctgcat aaatgtcttc
25861 ctttgagaag tgtctgttca tatccttcac ccactccatc aaaaagtggg tgaagtgcca
25921 atttactgag cacgagacaa atacatcatt gacttctttt gtcttgtgga ttcaaggatg
25981 tgtccacgcc cgccctcctt cccctccagc tcctcccctt gaaatactga agccctcaac
26041 atcatctttg gaggaaggta cagagttggc tctcacgcgc acatccttaa ccttggccta
26101 ataaacctct aaggtggctg agacctgtct cagatacttg ttggcttaca aattgaccac
26161 catgcaggga ctcagagtgg aggtggccct gccctttggc aggtttcctc ctggtgctta
26221 ggaccagttt gggccttctt tattgctcag gacagtagga caatttgctg agatccggga
26281 gccctaccac cctccagaga atctctgatc tcccgaaact tggttgaggt cgaaagttta
26341 ttttgcgcac aatgcctttt ccttttccgg tgttttactt gcttccaaca aagaaggcga
26401 gttttcctgc ttccgtgatg atggggagca ggagacttcc ctggagtttc agctcggaaa
26461 caactcgagt ttttcctgat tccacgatgg gggagagcag tctaaagcct gggccccatt
26521 cctaggtaag tggctgaatt ggggttctgt cttggaagtt ctccttaatg actaaagcta

FIGURE 1-H

26581 acattaacga ctggctggtc ttaacttctt actattagca tgctcagtaa gtgtataaat
26641 tgtgggattg tttgttttgc ttaactgctt tttgtttgtt tctgtgtttg ctatttttgc
26701 tgtttcagtc tttttcccgt tggatttgac gaattctgtt agacttggtc aaatctgaag
26761 caaacttcca agttgtggga aacaagcctc tgaattagct gaattcccac agctgggaaa
26821 aaggaaaaaa agccagaaaa agggaaaaaa gattttgacc acgtgatggg ctttatttgc
26881 ataacgaggc cacgtttttc cagccaagcc acactcgaag agtaagtgcc gtcacctcac
26941 gctgcagttc ggtaggtaga gtccgccatt tttccaccag gacagcccgg gtttggttcc
27001 tacatccttt ctggtttgaa atttgtgtta cttttgaaat atcagcagtt tgtcccggct
27061 gaaataaggt agtgagattt aaagatttaa aaggattttc tttttttttg agacggagtc
27121 tcgctctgtc gcccaggctg gagtgcagtg gcRcgatccc agctcactgc aacctctgcc
27181 gcccaggttc agccattctc ctgcctcagc ctcccaagta gctgggatta caggcacttg
27241 ccaccgcacc tggctaattt ttgcattttt agtagagacg gggtttcacc accttgacca
27301 ggctggtcat gaactcctga tcttgtgatc caccctcctt ggcctcccaa actgctggga
27361 ttacaggcgt gagccactac gcccagccaa gaggattttt aaaagggctt aatggtcaaa
27421 agtaaactta actaaaagct aatatcggat atattccaac atagtagctt aattaagtcc
27481 gtatgccaca tacacatata cagacccctg tgtagaaaag aaggcaccag actcSttttt
27541 ggggagaaac ttctgttttt cttatggaac tccaagagtg gaaacagaca cgttcctctc
27601 agatcttaaa ttgcttgcta ttgtattgtg ttacctgatt ttttttttact aaaatagttg
27661 acacaggact ttttggggtg ctgcttctct agctggaggc ctctgtggcc ggtggtgccc
27721 ctacccgggt ctcctgggct ccagggttgg ccctggagta ccccgcccac ctagcccggc
27781 cgtgggatcc gccctcagcc catggctgga ctgcgcatgc gcacgccgca acccgcttca
27841 gccttgagca ctggagtcYg gacaagagga gtgtggtggc gcacaaaacg cccaaagatg
27901 ccaggaacgg cagagcccca agggtgtcac agctcgattg ttccccccgc ctgcggtctg
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28261 ggttcaagcg attctcctgc cttagcctcc tgagtagctg gaattacagg catgcaccac
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28981 gccactacac ctggctaatt ttttgtttgt ttgtttgttt gtttttttgag acagagtctt
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29161 caccacgccc agctaatttt ttgtattttt attagagatg gggtttcacc gtgttagcca
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29461 ctccctctgt attttgagat gtaaattttg ctatctgatt tttcacctaa gagttcttcc
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29581 tcaagaaatt ggaagtttag gccgggcgca atggttcacg cctgtaatcc caacaaattg
29641 ggaggccaag gcgggcagat cacttgaggt caggagttcg agaccagcct ggccaagatg
29701 gtgaaacccc atctttacta aaaatacaaa aattagctgg gtgtggtggc acgtacctgt
29761 aatcccagct acttgggagg ctgaggcagg agaatcgctt gaacctggga ggcggaggtt
29821 gcagtgagct gagattgcgc cattgtactc cagcctgggc aacaagagca aaactccatc
29881 ttaaaaaaaa aaaaatacaa aaattagccg ggcgtggtgg caggtgcctg taatcccagc
29941 tacccaggag gctgaggcag gagaatctct tgaacccaag aggtggaggt tgcagtgagt
30001 tgagactgtg ccactgtact ccagcctggg tgacaaagtg agactccaac tcaaaaaaaa
30061 aaagaaaaag atcgaaagaa agaaattgta agtttaaaat agtagaaaaa aaagaagggg
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30181 ttcactacca aaaatatata aaagagtttt aattaattgg gttaaaggaa aaaaaagcac
30241 ttaaatactg tatcagaaaa atataaactt tttttttttt tttttttttt ggagacagaa
30301 tgttgctcta tcacccaggc tggagtgcag gggcacgatc tcggctcact gcaagctccg
30361 cctccagtgt tctcacgcca ttctcctgcc tcagcctccc gagtagctgg gactacagga

FIGURE 1-I

30421 gcccgccacc acgcccggct aatttttgt atttttagta gagacggcgt ttcaccgtgt
30481 tagccaggat ggtctcgatc tcctgacctt gtgatccccc cgcctcagcc tcccaaagtg
30541 ctgggattac aggtgtgagc caccatgcct ggccagaaaa atagaaactt taagcccaaa
30601 tgctttttca ggttcatgtg acttaagtaa atccttaaaa aataagctag ttttaaaatt
30661 attggtaaaa taaaatagaa atgccttcag aattgtcaac atacattatt gtttagattt
30721 attggtaaag gagttcaata tttatcatta cgagatactg taagttgtca aaatttggca
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30841 aaggcattta atattgttta atggaaagag ataaatcctg agttgctggc aaaaaaaaaa
30901 agaggaacat ttatttaacc ataaggttct tacttaggta aacacctaaa attcacaggc
30961 tataaaaatg gttaggccag gtatggtggc tcacgtctgt aatcccagca atttgggagt
31021 ctgaggtggg cagatcacct cagatcagga attcaagacc agcctggcca acatggtaaa
31081 accccgtctc tactaaaaat acaaaaatta gctgggcatg gtggcaggtg cctgtaatcc
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31261 tcagaaaaaa aaaaaaaaag aaaatggtta acagagaaat aactttaaat gaagactatc
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31621 cctcctgagt agctgggact acaggcacct gccaccacgc ctggctaatt ttttgtattt
31681 ttaatagaga tggggtttca ccgtgttagc caggatggtc ttgatctcct gaccttgtga
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31981 aatttcatat gagaaagaat cttgtgtggt aaatttttgt tctaaaatgg ctagttattt
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32821 ctcaagtgat ccgcctgcct tggcctccca aagtactagg attacaggcg tgagccacca
32881 cacccagcct gaaaattata tcttgtgctc aagatgatta caatttaata gatttgttta
32941 taaaatttta gagagattta attggcctta tgctgtcttt atcttttgag aagaaattcc
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33061 ggaaaggtaa aaacagaaaa aaaaaaagaa aataaaaaaa gaaatctgtg agttatcact
33121 gtggctaagt gaatgactta ttttacaatg acctgtgatc ctatttagtg atagcaactg
33181 ttttaaaact ttttctaggc caggcacggt ggctcacacc tgtaatccca gcactttggg
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33601 cccagctgga gtgcagtggc acaatctcgg ctcacttcaa cctccacctc ccaggttcaa
33661 gcgattctcc tgcttcagcc tcccaagtag ctggaactac aggtgcccgc caccacacct
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33781 gagtgcagtg gcacgatctc agctcactgc aagctccgcc tcccgggttc ataccattct
33841 cctgtctcag tctcttgagt agctgggact acaggcgcct gccaccacgc ccagctaatt
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34021 agtcacctgc ctcagcctcc cacagtgctg ggattacagg tgtgagccac tgcgccaggc
34081 ctcccaaggt gttgggatta caggcgtgag ccaccgctcc gggcctccca cagtgctagg
34141 attacaggtg tSagctgctg cacctggcaa ttttttgata ttaggtcccc tgaagtccaa
34201 aaagagatat atggcttatt tggtataatg aaatcataca ggaagcattg ttaaaggtga

FIGURE 1-J

34261 aatggtgttt ttcttgggat tatatttata taaatgtgtt gttagtgtgt gttccaaaat
34321 tgtatgagat gcctgtgatt ctgatacatc ttagtatatg gtattagtag taattatgat
34381 tattatgtaa aattgttgta tgccacataa gtaaccaaat ttgcttgtca attatgtctt
34441 tttttttct tttttctgag acagagtctt gctctgtggc ccaggctgga gtgcagtggt
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34861 tcctgacctc aagtgatcca cccgcctcag tctcccaaag ttttgggatt ataaatgtgc
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35281 gcaaaatgag agttaatttt atggactaaa ctaatataag actgaaataa tctttttatg
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35701 tttaactttg agctatttgc agcttttagc aattgagtaa agtacactcc tgtgaggaag
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35821 ctttctgatt tctccaaaaa ttgggaacta tctgtgagca ctatttaaaa aaaaaaaaaa
35881 aacttttccc tctcccttcc cctatttgta ttctaatgtc aatataatga tgtgtgcacg
35941 tgcagtaaca atctgttttc tcttgtaata ggacatagag acactgcata ttttaccaag
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36061 acctatagtg cccatcaaag cccttgggaa aactggcttc atactgtatc cacccagtgg
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36661 tggggagggg ctattatcat gtaaactata aacatctccc aaagctagcc caagaataac
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FIGURE 1-K

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41821 gctcactgca agctccacct cctgggttca cgccatcctc ctgcctcagc ctcccaagca
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FIGURE 1-L

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42481 cccaagaggc cgggtacggt ggctcacgct tgtaatccca gcactttggg aggccaaggc
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FIGURE 1-M

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49321 ccagccacct ccgagggcca gagcaagcgc tgtaaaccct gacggtgggc ctggcacacg
49381 cctgtattcc cacaccaggt cttccgatca gtggtgtctg tgaagggtgc cgcgagccag
49441 gctgaccagg cgcccgggat ccagctcatc cccttggctg ggaacatcct ccactgactt
49501 cctcccactg tctgccctga acccactgct gcccccagaa aaaggccggg tgacaccggg
49561 gggctcccag cccgtgcacc ctggaagggc aggtctggcg gctccatccg tggctgcagg

FIGURE 1-N

49621 ggtctcatgt ggtcctcctc gctatgttgg aaatgtgcaa ccactgcttc tYgggaggag
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49741 ggcccagaag accttcgtat cccctctcag tcgcccgggg ctgtcccgtg catgggttgg
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49981 agcgaagcta taggctcttg ttggataaaa gctttttaa cagacatggt ttcaccagcg
50041 tttaatgtgc tctgatgttg accgtccctc tgagtgttct ggggaggagg gggtggggcg
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50281 gacccaccaa gaccccgccg cctgggcggg ctgtccacag gcccttccgc ccagcagcag
50341 tgacgctcag ggccttccca gctgtcagcc actgcccgtt cctgcgcctc tcgtgcacct
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50461 aggggagggc cggcgYcccc gaagccaggt cagccgtgca cccggcagag ccccgcagat
50521 tggcYccagc agagcttggg gtgggggag ctcggtgtca ccaacaggcc cttgaggaca
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50641 tactgcaggg agcaggccag gagccacggg ccttggggca cagggtcctt ctcagggaca
50701 ggttcaggca ctggctggaa caggctggac ccctctaccc agcacatgtg ggcatgcgtc
50761 tgggttccga gggtggggaa atgtggaaag gctcctgctg gccggcttag gcctgctgcc
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50881 acccccctgct gtgcccagga ctcccccagg gacaaggcaa ccagaggccc agacccctcc
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51121 gggcagggct gcacagtggg cagcatgcag ctggcgacag gtgtcgcagc agagggtggg
51181 cagggcgcca ggggacaggc agctgtgtgc ctggtagcct gggggctccg agacagacct
51241 ataggctgag gctggtaccc cctctgcccg aatacgcctc gggctggccg ctgcagagct
51301 ttcaggggtg gccaggtccc caggcctact cagctcacgg cgcagagaga ggaaggagaa
51361 ggcggaaggt tcaggttcca gcccctcctc caaggcccca tatggtgggc tgctggcctg
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51481 ctgctcccag agtggtggcc tgtaggccag ctccgccggg ggcgagtcag ggcctggtga
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51601 gtccagtggg gccctgtaag cagcagggga gcctcggggg ggcaggggtg gcggctcctc
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51961 gcccccagag aaggtctgca agggagcggc caggtcagtg actgcccacc ctcccatagg
52021 ccagacccta gggtacagtg ggtccgggat ctgttggctc aggccttggc agcttctgat
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52441 gccactgtgc ccggcctaga atttttttt tttttcttt tttgagacag agtctcgctc
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52621 ctaatttttg tatatttagt agagacgggg tttcaccatg ttgaccagga aggtcttgat
52681 cccttgacct catgatccac ccaccttggc ctcccgaagt gctgggatta caggtgtgag
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52801 gctcacaaat cagaacaaaa tgaagagccc ctgtactgag aaattccact gtcttctgtc
52861 ccaccgctcc cttcacccct ggagatggcc tcatctaatt agttttgaat gtacttgccc
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53041 cgtgttgttc tgaactttgt ttttttccac tacagtcttg cagacaagga cagaagctgt
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53221 ctctttttt tttttttttg agacggagtc tcactctgtc accaggatgg agtgcagtgg
53281 ctcgatctct gctcactaca acctccacct cccaggttca agtgattctc ctccctcagc
53341 ctcctgagta gctgggatta caggcgcgtg ccaccacacc cagctcattt ttgtattttt
53401 taatagagaY ggggtttcac catgttggtt aggctggtgt caatctcctg acctcgtgat

FIGURE 1-O

53461 ctgcccacct cggcctccca aagagctggg attacaggcg tgagccaccg cgcccggcct
53521 ggctgagtgc tttctagcct acacttaggt gaagaactaa aggagctcag gacaatcact
53581 gcgagcgtct cctgactctc aaattcccta actccgggac tcctagcatc taatgcctgg
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53701 tcctctggcc ccatgaactg gactgttccc gtgtcgctgt ctcaggagga aaggggctga
53761 cagagattag ctaatttggc caagtcctcg cggccaggaa gcagcagaac taagtccaaa
53821 ccagggctgt ccSgcactga agccggttat tcccccgccc cgccccctgg gaggcctcaa
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54001 ccacgtgccc agtgacgtca tcggcttcct actcttccga attagctcag agctcccggc
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54121 agcctcccgc cccaggccgt ggagttcact aggtctgagc ccagccctga gacttcacag
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54241 cataacctgg aggaattagg atgaccatgg gaactcaagt cccttctgtg cccccgtcct
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54361 cagggcagga ccccgtaggc agcacccaag cctgccctcg cccaccccat gttctcagcc
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56461 actttgagag gccgaggcgg gcggatcacc tgaagtcagg agttcaagac cagcctggcc
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56821 agtgccacca tgggtccaca ccagtcctca ggacagctaa cttcgtaagt ctcatcttta
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57001 ggtttttgca cctgcctcaa cccatggaat agaactgatg tggaatgaat tccaaggcta
57061 aatcataaac atgccatacc ctggccttgt cttgagatcc ttggcctctg acatggtttg
57121 gttctgtatc cacacccaaa atctcatctt gaattgtaat cccacaggtc tggagcagga
57181 ccaggtggag ataattaaat cttgggggca gcttcctcca tgctgttctc gtgatagtga
57241 attccacgag atccgatggt tttataaggg gttctcccct ttgttcagtg ctcattctcg

FIGURE 1-P

57301 ctcctgtcgc cctgtgagga gacgccttct gccatgattg tgagtttgct gaggccttcc
57361 ccagccatgc ggaactgtga gtcaattaaa cgtcttttct ttataaatta tccagcctca
57421 ggcagctatt tacagcagca tggggacgga ctaacacacc ctcagaaccc agccactaga
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57541 ttcacctgca gcctattctt gggacttttt tggaaatagt ttttccagac aaaaatcaag
57601 atgagtttgt tctgggccga gcgcagtggc tcacgcctgt aatcccagca ctctggaaga
57661 ccgaggcagg tggatcacga actcaggaga tcgagaccat cctggctaac acactgaaac
57721 cccatctcta ctaaaaaata caaaaaatta gctgggcgtg gtggcgggca tctgtagtcc
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60721 ctcagcggcc tctgccatgg gcagcagggg tggttgtgct gcctggccag tggggtgggg
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60841 cagcatgtga cagtcaagag ggctgaccct tgggctgcac ggacctagat aagatgccca
60901 gggtcccgga atgttcacag cccacagcca aggtgagtaa ggggcaggga atgtcctggg
60961 ctcagagccc gagaccctgc aggggtgtcc ctgcccatca gcaaacagca taccctgaca
61021 ccagctgcac cccaggcccc agccggccct tgttcctgac ccagacaaga aactagttca
61081 tggggctaca actccccttc taggggtcag aggggagaga aactggactg ccgtctccac

FIGURE 1-Q

61141 tgctggccgg ctcatggccc cctcttccct gatgctcccc aggagctgcc ccagccagat
61201 gttcatcgct gagcctgcac ccaccgaagc ccaaagcttc ccttcttggc ctctctgagg
61261 cctacacagg agagcagggc ctggttcctc ctggagctga ttcagcccca ttctgtcggg
61321 gcagaggtgc caaccccaag ctccagggtc agatgtgagg tgaggaaggt gaagagctgg
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62461 ctcccgtgac cattgccttt ctagggccct tcctccctgg ccacacctcg ccctcctggg
62521 actcacatgg cagctgcagc gatgggcggg ggcccggcct ggggtgtggc ctctggggtg
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FIGURE 1-R

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FIGURE 1-S

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FIGURE 1-T

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75961 gaagttgctt cgctggagag gccttagagg cctttgaaat ttgaaagatt tcttggacca
76021 gcggccacat cccccacagg gcggcttgtc ccgccgagag ccgcgcgccc gagccgcttg
76081 ctgtgtccgg gagccgcgcg aagggcgctg caggcgctgc cctcggacct ggagtccggg
76141 acgccctgtg ctcaggagcc tcctttgcca gctgctaaca cttcctgccg ctctgtgcag
76201 gagcaggccg ggctctcgcc atgggtcact gtcgcctctg ccacgggaag ttttcctcga
76261 gaagcctgcg cagcatctcc gagagggcgc ctggagcgag catggagagg ccatccgcag
76321 aggagcgcgt gctcgtacgg gacttccagc gcctgcttgg tgtggctgtc cgccaggacc
76381 ccaccttgtc tccgtttgtc tgcaagagct gccacgccca gttctaccag tgccacagcc
76441 ttctcaagtc cttcctgcag agggtcaacg cctccccggc tggtcgccgg aagccttgtg

FIGURE 1-U

76501 caaagtacgc cctagtctgt tcagagcacg ttcaggctgt cagtactgca gtgtgacggg
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76621 gcccgggttc agtgccaaca gccctgggac tgttgtggag agatgaactg ggaggagctg
76681 gggtgaggga agagaaagtt gcctatgggg accgctgagg tttgagatct cgagagggtc
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80161 cagctcaatt ttttgtattt tttgtagaga cggggtttaa ccatgttagc caggttggtc
80221 ttgatctcct gaccttgtga tccacccgcg tcagcctccc aaagtgctgg gattacaggc
80281 gtgagccact gcacccggac tgagaatagt aatttttaat tattttattt ttttgagtcg

FIGURE 1-V

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84001 cccactccgt gaccctcYgg gttgagtctg aatcccagga cacctgagaa tgtgtctctg
84061 gcttgctgcc cagaaggtct ggggctgctg gtgtgaggag ggctgggagc tgggatggga
84121 ggagccaggc gagcctttc cggatcgagg cagattcagg aggggagggt cctctctgct

FIGURE 1-W

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84361 gtagcaagca tggcctcctg actgcggcga gtaccagggg cacttggttc cccagctgcc
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87901 tgatggaagg aattcctgac ttccccagga tctaggcagt ttgtcaaaac taatagccaa
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FIGURE 1-X

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FIGURE 1-Y

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FIGURE 1-Z

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FIGURE 2-A

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3301    ttgattttat tatatgtaga tctagataat tttttctga cagttgcatg gtattccatt
3361    acctgcctat aatatatttt atgtatctgt tcctctagtt atggagaaat aaatatattg
3421    cctccagctt tttacaacca caaaaaactg gaaaacattt ctttactaat gcctttgtaa
3481    atgtttactt accaaataat ttaagtttct ttggtattat tttatatttc atttttcct
3541    ttagcatcac aaaacaatta ttctttatta ttccaggaca gtggtcctca accttttttgg
3601    cagtagagac tggttttgtg gaagacaatt attccatgga ttgggggctg tgggggatgg
3661    tttcaggatg aaactgtttc atctcagatc atcaggcatt agattctcat aaggagcaca
```

FIGURE 2-B

3721 caacctagat ccatcacatg cgcagttcac aataggattt gcattcctaa gagaatctaa
3781 tgccactgct gatctgacag gacgcagaac tcaggaggtg atgctcgctt ggctgccact
3841 cacctcctac tgtgtggcct ggtttctaac aggccacaga ccaatacagg tctgtggtcc
3901 tagggttggg gacccctgta ctagaagaaa taaagctttc aaagttataa gctaagaaat
3961 tattctatat atttctatag cccactatct tcccatctcc caatcatttc agctcatagt
4021 tttgcaaaag agatagaact taaaaagatc attacaatta cagggtgatt ggcgcaatga
4081 tggaggcact gacaggagca agagaaaact tccttaacag agccagatgg agagcgccca
4141 cagataggtt cttgaaaaag taagctgagg ggtgggtctc aaaggatgaa aaggtgtttt
4201 ccaggatcaa gcattttggg aatgggtgat catattaagc aaagagaaca gcaggagcaa
4261 acttaacaag agaaactgca gagcctgtgt ggaagactca acacaatttt gatataacca
4321 gatgtaaatt gggagaaagg acatgtcagg agataaactg gagaagtaga aagaggggct
4381 ggttgtggta aaacctagct agagttatat ggttcatgag gtccacagaa atattttatg
4441 ctagagagtg acaaagtcag attagatagt ggctgtaaaa gagatgtgaa gatgatgata
4501 attcatcttc aaaaacttct aaggtagatt aggagatcag tgtggacact aggcatttct
4561 tttggtgaaa tgtgatggaa acctaaagtt aggcagtagt tagaatgaaa aaaaggaaag
4621 agatttaaga aatcctgaag aggtaaaatc tgcaaggatt tggcaattgc ctaaccgtgg
4681 aaatgagaca gtgattagaa gaataatgta actaaaacca aacctgagat ataaaataca
4741 ggaggagaag aaatttacag gttaagagcc atagtatttt cttctatcct ctagcaaaac
4801 aaacaaacaa aactacaatc tgatatattt ttctatacca ataaatttgc atatttagag
4861 ttttaaatct taaaagtttg tttaaatcgt taacaaatta ttcttaatta gttaaacaat
4921 tatgtttaag gaacataaaa ttgtatattt ccatatctcc atattatcat gtttgccatt
4981 acaacaattc aacctagatt gattctagat cgtattttgc aaaatgaata attagtgact
5041 cattaattaa taaagacaca actttttgtt ttgatacttt aagttctgag gtacatgtgc
5101 agagcatgca ggtttgttat aggtatacac gtgccatggt ggtttgctgc actcatcaac
5161 ctgtcatcta cattaggtat ttctcctaat gctatccctc ccctagctcc ccaccccccca
5221 acaggccctg gtgtgtgatg ttctccaccc tgtgtacatg tgttctcatt gttcatctcc
5281 cacttatgag tgagaacata cggtgtttgg ttttctgtcc ttgtgttagt ttgctgagaa
5341 tcatggtttc cagcttcatc catgtccctg caaaggacat gaactcatcc ttttttatgg
5401 ctgtatagta ttccatggtg tatatgtgcc acgttttctt tatccagtct atcactgata
5461 ggcgtttggg ttggttccaa gtcttttcta ttgtgaacac acaataaaca tacgtgtgca
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5581 tgggtcaaat ggtatttcta gttctagatc cttgaggaat aaccacactg tcttccacaa
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5701 tctccagcat ctgttgtttc ctgacttttt aatgatagcc attctaactg gcatgagatg
5761 gtatctcatt gtggttttga tttacatttc tctaatgacc agtgatgatg agtttttctt
5821 catgtgttta ttggctgcat aaatatcttc ttttgagaag aagacacaac ttttaaaagc
5881 aggtttttaa ataactcaat aatttcatct cattctattg ttttaaccca tgccacaatt
5941 atttatttcc aggagcgttt tagtagaata ttttatttaa aatatattta aatactttat
6001 taagaaaact atgaacaaga aaatgattaa ctttagttct acaaaagttt aaaatatcac
6061 atgacgtgct agacaaatct caatctgaga ctgctaatcc atgttcctaa agtcattgga
6121 aaatgacatt ctggaaatag atcatattca gagctctaaa acacccataa accaatgagc
6181 aacagctcat attaatttta ctcagataaa ctcacggctg actatttaaa aaaaccctgt
6241 aaattggctg aggaataaca cagcagtctc aacatcaaac taaattgcaa aatttgacct
6301 aaattttgac ctagccaagt catcattaat taaaaggaaa tgaactcaaa ctatcagact
6361 atcaaaagta ataaacactt gaagaaaaag ctgtcttgaa aataaattgt tgagaaatag
6421 ttcctgttca tttggcctct tgcagtaact gaagtcatta taaactacct tttccaccaa
6481 ctaaaataga agtcaaatag agcatgcctc tggttagcta aacacagaac catagaatgt
6541 gaaatggact caggcacttc agcactaaaa gatggcttca accaataagt gtatttatct
6601 gatttaattt aatcaatctg atttaaattt ataatttata tatttatgat ttaaatttaa
6661 tatatattta atatataatt aataattata tataatatat aatttatata taattaataa
6721 tttatattag tatataaatt taatatatat aattgatata gttatgattt aaacttaata
6781 atctgattta aaaagcatta atgaatgaaa taaatatttt ttaaaaacca aaataataac
6841 tcagttaact gccttactct agaagatgta gtattttgat aaattacatt tcttctggtt
6901 caagaaattc cttaatgttc tcagcgaact ttgtgaaatg catatagcaa catttaagtc
6961 ttcccaaaat agaattgtaa tttcttttga ttaagcctgc ttttcatacc ttatggtagc
7021 attctgaatt tctgatctct ttgtataata ccatagatgc ataaaataaa aagtattaaa
7081 ctaattctcc tactattttc aggatatgcc caaaatgttt taattaaaaa cgtcaaatcc
7141 ttcttctaga cttgtctgcc agagattttc tgcctttact gagagtgctc cacacacaca
7201 ctcacatact aatcagaatg tggaagagtc gaattgaatc aattctttaa gtaacataaa
7261 attgtgtatt tccataacac gtctccatgt tatcatgttt gccgttgtaa caattcaacc
7321 tagactgata ctagataata tttctgcaaa ataaatagtg actcattaat taataaagac
7381 aaattttaaa agcaggtttt aaaataactc aatcattcta tctcattctg ttcttttaat
7441 ctgtatcaca attattttca ggaggatttt agtggaatat tttatttaaa atatatctaa
7501 atactttatt aagaaaacta tgaaaaaaaa tgattagtta tataaaagtt taaaatatat

FIGURE 2-C

7561 aatgaaatgc tagacaaatc tcaatctgag actgttaatc catgttccta aagtcacaat
7621 cctaaagtca caagaaaacc acattctgaa aatacataat attcagagct ctaaaacacc
7681 cataaatcaa tgagcaacag ctcatattaa ttttactcag ataagcttgc ttgtaactgt
7741 aaaaaatagt tgaatcaatt agattgattc aattagattc ttaaatcgaa gaagcatcaa
7801 ttagaataac ctaattgaat tagagtcttc catatttgaa acaacaggtc aatgtcatta
7861 tctatataaa gctaagaaag caaaatgtgg ccaggcacag tggctcatgc ctctaatccc
7921 agcattttgg gagactgagg cgggtggatc acctgaggtc aggagtttga gaccagcctg
7981 gccaacatgg tgaaacccca tctctactaa aaatacaaaa gttaactggg cgtggtggca
8041 ggcacctgta atccagctac tcgggaggct gaggcaggag aatcacttga agctggaagg
8101 tggaggttgc agtgagtcga gatcgcacca ctgcgctcca gcctgggcaa taaagtgaga
8161 ttctgtctca aaaaaagaga gcaaaatgca aacattctac ctaattcaaa ctccaaatta
8221 ctcttttaac tcatctttaa agtactatat tgtcttataa agcatagtca atttatttct
8281 tcaaaatccc gtgaaggttt gcttttcatc atgttcgaac agtttcccta acttttaaaa
8341 tcagttttta cattgccctc tgctgttaac atttcttttc tgtttaatct ttctaaatca
8401 tacttgtgtt tagtgatcat tttacatgat gaccattatc acatcatttc atctttatga
8461 tgctggtgcc cgaagctgtt ttatttgcat tttgattctg aatcattttt agaacaaaga
8521 acctcatttg tcttcctaga tcactctcag agctgtctgt cctgcttttc gcacctctgc
8581 ccctgcttgc attccagtcc ttatctattg aattgcctcc aaacgagtcc cccaacttca
8641 gataagatcc tctctaaccc atccttcaga accccaaatc tgtgtaattt tccttcttaa
8701 aatcaatcta tatcttccaa ttgcctattt acagtgtgga gtctaagttc ttcctgacag
8761 cttcagatat ttcaYaattt atctgaactg tgactgctct caaatcctat cttgcactac
8821 tccctccagc gcagaactat gctacagtca ggcaacttgt ccacaagttc accaatatca
8881 cgtattttct catgttgcaa aggctttgac aatgatgttt ccccatattg gaatccttgc
8941 cagcattcct tctactatga atacatatta cttttatttc aagaactatt taaaaaaata
9001 ttcctgccag gaaggctttt cttatccttc ctacagcaga gtaccttaat attcaatata
9061 cattcacatc tgtcagaact ctatgccaat tgttcatgaa catgtttgtc tgtcctacta
9121 cactggttct ttttggcaga gacactgcat taataatctt ctgtagatcc agctgcgctt
9181 gtgaaaagag aagcacagtc aatataaatt cagagttact atacttttaa gtaaattatg
9241 tagtttttaa ttgaagtaat aatctctctg agttcagttt tagggtggta aactccttaa
9301 aacctgtata acaacataca ggattaacaa gacttttcaa ggtgtcttag gtatggcagg
9361 catatgcaaa aatctaatgt tttaacacac tctctcaatg tttttgtgta aacatttatt
9421 tcagtttcgc aattatgtta ttaaggttgg tttagccttt ggtttctctg agtttttatt
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9781 actgctactt agcattccat aacaccaaca atagttgtct gggctccaga gtgcaatgta
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9901 taacagccta aaattgcatc tgcttagtgc aggacaaaac atgacttgag tagatagcaa
9961 gtccttttc aaagtaaaag atttaaacag aataatccac ctccacagtt tttagtggta
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10381 aaaaattctg aatttttttct tcctgaacat ttataaattt atttttaaac tttcagtgaa
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10621 gtaataccta ctactgaaga gttttaagag aatggatatt cataataatt taggggaatg
10681 gtagaaaatt atttacttca aataatacca tttttttctt cttattatta tgcagtttga
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10861 agctcactgt aacctctgcc tcctgagccc aagcgatact ccctcctcag catcccaagt
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10981 tggggttttg tcatgttgcc taggcttctc ttgaactctt ggactcaagc aatctgccca
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11101 tatttttgac ttctttttta aaaaaataaa atctcacatc tcacatatct caacccgtta
11161 ttttaccgaa ctcatagtca aattgctaag agaaacccac tgccaattat tttttttaaa
11221 tctgtttcct gggttcttta cattcatatt tcttaaaata attttgtatt gcctttataa
11281 tatatgggct ttttaaattt tggtatatga agatttagct tttctcatcc ttgtcatata
11341 ttacgatctt ggttaaacta acatttggaa tttatattaa cttgcctctt taatattcat

FIGURE 2-D

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11401  ttttgagaaa atttggttct tatatggcaa gctttactta attttctttt tttccttaag
11461  ttattaattg ctttttttt ttacaattcg ctcagctttc tgcgtaccta tctctaactg
11521  ttctcaacac ttccaagagc acctctttca atactatttt tcacttggcc agacacatca
11581  tgaattttgt caatgctctt ctctcctgca tgagcacccc attcactgcc cacgtgcagc
11641  ctagaactct ccatatattt ttgtttttga aattcgtgtt atggtggaga tgtcaaagac
11701  aaggaagagt cacattctat gccagtgcta tccctggctt tgaccttccc acctggggtt
11761  tttaagggta gtacctatgt gtgtggccga cgctcaggtg aagatgcaaa gcagtatcag
11821  ctctggtttt gagtcccagc caagttgatg gacactctgc cgcagttgca cccatatgtt
11881  gagaaaacaa aactacaggc tggctcttct gctagtgctt ggtcacagtg tataccagtt
11941  cacctccctg gagacaaacg ccattcgaaa ttgggttttc agggccctgg aagtattgaa
12001  ttaatctcta aacttctcta gtttctgtgg agggccaatt ttttttattg ggctactaga
12061  aatgtctgta ccccaaaata catgggaatc aaattcagat ttttaataac tgctaatgaa
12121  ctcttcatat ttgatatttg atctccacat ttgatatttg atttccatat ctctatattt
12181  gataagattt tctcaggtgt tctttatgcc tgctgcatgg ctattgtctt tagattctcc
12241  ttatctcatc atggaagtcc tctattcttt gtgtctctgg attcacaaag tattgtgtgt
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12421  atttcctttt acccttacac ttgatggata gtttgtgtta gatttttagt ttacaatccc
12481  ttccatttaa aatttcaaag gcattaatta ttatcctttt ctttttaagc ctctattatt
12541  gctgttgaga tatcgtttga attcttatct tttcttcttt gtagttaacg tacattaatt
12601  aattatctgg agaaaccttt agcatcttct ctacgttttc tgttttctga attattatga
12661  tgtctcacgc tgcaagttta tttatttctt gtctttctaa tgtggagatt tgttttcttt
12721  agtttaaaga aatgtgttgt attttgaata acgtttcttt tcatctctcc cttttctgtg
12781  gaattactgc tagttagaat ttgagcctga taggttaatc acttaattgt tttttaataa
12841  ttataagttt ttttgttgtt attgctaatt tctcttcagt gaaaagccat tgttactgac
12901  atgctagttc ataaattttt tttctttttt tttttttttt tttttttttt ttttgagaca
12961  cagtcttgct ttgtcatcca ggctagagtg cagtggcacg acctcggctc actgcaccct
13021  ctgcctcctg ggctcaagcg atgcccccta tcttagcctc cctagcagct ggaaccacag
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13321  gatcatttag tgatcataca agttacaata ttttaatctt atttatcatt tgctcattgc
13381  ttttattttt ggtttatttt actatatgtg ttattattat ttatagacaa aaatgtttat
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13681  gaatgaaata tctgttccat tggaatttat aataatcatt tactttaaaa ccatatatgg
13741  actggttaag ttatccattt gcccatttat ctatttgtct attttgtgta atttaatgtt
13801  gttttgaata cagaaatttt taatatctga taaaacaaga tttttaattt tggcaagcta
13861  catagcacct gtaatgtaaa tggtgttatt agttgattgc ctatcatcat taagtattgg
13921  atgttttcct gcccaaacca attaagatag tcttatgaat ttaaaatgtt ttttcatgaa
13981  atagctctgt aaccttcaat atcaaaataa aaatgttggt aagtacaatg gtaagagtca
14041  ggtgatgtta gattagctat ctgtagattc taactctttt taataagttg actataaaac
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14281  gttaattttc tacatctata ctaagaaaat attcttggct tatattcgtt gtgttatttg
14341  ctaagtttta gtattcttat cttgattcaa aagcctctct ctcataagta aatcagagca
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14461  gaaaactact atttcagata ttaatctctg aaagtctaaa atattctggg ctttcatcaa
14521  gcaattgaca atgctttgat gtgtgctaag acgaagaaat acccaagatc gcttccagaa
14581  atttaattca tttaactttt tagtggtcaa tcgataccct ccagagatga atctggctta
14641  gatttaagac acagattttt aaaaaatatt tcaataatag ggtattttgc agtaaatgcc
14701  attaatttta aattcccagt gaataatcca ggactagaaa taagtgacac tggattttag
14761  attcacgtaa tttaggaaaa tgtgataagg tgataaggtc cagggaaatc acaccccaaa
14821  taggaggagg ctttcccctt gcacccttttg ctctagcttc actgaataac ttctcttcta
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15061  caatgctgaa attccaaagc atataatttt ccctctggct tatatatttt tattgtaatt
15121  agtcattgca tcatggttat taaagcccct tctcaggatg attgttaaaa tatacaatag
15181  gtgtggtaca gtcaccaacc aatctgaatg gatcctggct gtacacacct ggttcagcaa
```

FIGURE 2-E

15241 gcatgcttac tggctgctga tgaaatagaa ccagccatac tagatggaca gtatgctccc
15301 tcagatcagt atatgtactg aattgatctc tgtaggatcc aaagttttaa tatagtgttt
15361 tgcatataat agatacactc atatatagca ctaatcaact ttggaaatat aagaaaggta
15421 gcctaagtat tgggaaaaat aagacagcaa ggtcacatat ttgtggagtg aattattgga
15481 tgctataata atagctgtta ttatactcta attgaggatc ttccataatg gtttcatatt
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15601 aactgaattt ccattcttac tgaaactaaa ttggatttta taaagatact taagaaaata
15661 aatgatttat taggggtatt tgttcttcaa aggtatacag ccaagaaaat taagcttcat
15721 ggaaagttgt gattgtaata ctttttaaag atgataaaca cctggtttag gagacttaat
15781 ggatcaaggc agctactaca tggatgctca ctggcaaaaa ataactatta aatacatcca
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16141 tatgcactta attaaattgt ggaaattcaa tgattgatta gtggagatag tctgaaaaag
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16381 gaataaatgg acttgcttaa taagaataac aagaacatgg ctatttaaca ttaaaaatac
16441 tcaatgacat tctcaacaga aattgtaact ccctaaaaca ttacttttta cattctgaac
16501 cccataaagc aaaaacaaga ataaaaattg tatgtgaaca aaccgtctaa aagtgattac
16561 ttaaaatcta tgatatactc tggattaaag tatgctgtcc taaagcaaat ctttgtagat
16621 gagtatttct tagagtggac taaggtattc ataaaacaaa gtgcttaaat gaataatata
16681 agtaatcgag atgaagtgga acatttcaag gatctataat ttcaagaaaa ctgtgcttat
16741 ctacagagtc acagtttttc tgatgtcctg gtgaaggatt gaatggagga aaaatacaat
16801 aaaagaacta tatattttgt ctaaaaaaaa ttgaattgac tcgtttgttt ttgttccccc
16861 gctaaattgg ctgtttatgt tcactgacaa caaaggcaaa taaagataat tatttggatc
16921 actcaaaaca aacaaaacac tgattaaaca tatatctcaa gtacaacaca aagttgattc
16981 catatttcta cgtggacaaa acaaaatctt gcactttgca ttgatgtgtc ctcctatctg
17041 catagagcaa atacattctt aatcattttc tcctcactct gtttatatat tctttctaat
17101 ttaaaattgc ctctgaaagt ctaatattat tgcagttttc ttctccatat tattaacttt
17161 ttaaaatatt ttgcttatag tgattcatgc ccaattcata tagataYgta gattataaat
17221 ttgattattg tcaaatgtta atagcaactc agtgaaaaac aacttgtcca aaatgttgct
17281 accaaaaggg cacttgacta taaataactc acattatatt acatattctg tcttgttccc
17341 atcYtcaacc cccgcccctc tgctcaataa ctaatctaag atcaactgtt gatcagggtc
17401 agttcgctaa aggggaaaca tattgactca taagtttaaa taaaaataaa gtcgcctctg
17461 attggctcct tcttggaaag caagcaagtt ttgtgtggga ctgatatgaa agaagaaagc
17521 agtattagga tgaataattt ctgttcattg acagctgtta acatttatac taaaacaatt
17581 ttatttataa actttaggat taaagaaagg taaaattaag tagctaaaac tatgcatgaa
17641 ttgcttcact atatatctaa attctagact aatacgaaaa tcaatagctg ctaattgtat
17701 agatgatcat atttgttatt catttgctca acaaacattc tctaagcaac tctgtgggca
17761 aggctgtctg ctaagtgctg ggataccaag aggaataagc gctatctctg gtttgagagt
17821 tgttcagcct tatggaggag acaaaaatag aaataggtaa tttaaatcaa agaacaatga
17881 taaaatatgc aaattctgtc aactgtgttt taagagcata gtaggaaaag gaggcaaaat
17941 tggggagagg gtgaattaag tgcagggcat acgtagcttg atgcatccat gtaaaatatt
18001 gtgctggccc tatacttata tgctctcaga tgcattcttc ggtctcttcc ttcctttctt
18061 ctcagagtag ctgccctgta cagttttcca gacctctccg tcaactggct tccagttggt
18121 tttgatcagg cactggcaga gattggagaa tgggaggaag agagaaccag gatatttctc
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18361 gtatatcatc aattgctagt catttgtttc ctctatttca aatattcaga gccatttcta
18421 gtttcctggt tggacacaaa tgcctgacat actgagtcta aattccagga gtttgggcag
18481 caggtttggg actaatcaac atataagaga gagttcatga gtgtacacag agatacggta
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18601 acatagcttt tgaaggcgtc caaagattaa tttacaattt cgaatagaac aagaaaaatg
18661 tggcattcac ttaagcccct gagaaaacct aggtatcact tagacccagc atttgtcaga
18721 tgaggtttct gaagRtagag aaattaggtc acatatctaa taaagaccag aattgaaacc
18781 taaacctgtt tccctatgta gtgctcttgt gataacacac ccattatcat ggtaatagtg
18841 tgacatttgg tgtcattttc acttgttctg tccttgttcc atgtgtgcac ttcagtttcc
18901 ttttatataa agccaatata tgttattagt tacctcatag gtaattgtaa gaattaaatg
18961 agacagtgca tgaaaagtac ttagaataaa ctacttagaa tagttaaatg tatagagaga
19021 ggttggaatg acacatgaag gactataggg ctactaKatt ttatttattt tatttttga

FIGURE 2-F

19081 gatggagtct ccctctgtcg cccaggctgg agtgcagtgg cgagatctgg gcttactgca
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19201 caggtgcgtg ccaccacgac tgtctaattt ttgtattttt agtagagatg gggtttcgcc
19261 atgttggtct cgaactcctg acctcgtgat ctgcccacct cggcctccca aagtgctggg
19321 atttcaggcg tgagccaccg tgcccagcca gggatactag attttatcac agtattatga
19381 aaggtaagct tgtcatcgta aagcttatag atactccttt tatatgtttg ctgacgtcaa
19441 ggatttttca catttggtaa taatttatta tttgtttaat aaaacgaaat ttgaacttaa
19501 atttggtttg tctttagaag ttagtttagc aattaatttt tctgtaaaat gatttttaca
19561 ccattaattt cttctcagct tcgtatattt aagaatttct atggacttaa atgaggttcc
19621 atgattgatt ttctatttgc atgatatttt aaacaaaata tatgttatat ttttaagttc
19681 aagatttccc tcccaccctg ggaaagtctt ctgagtcttt ttcatgtcat ccttctcatt
19741 tttctttctc ttttaatttt tcagtacccc aagttacttt aatgttaaac acaaatgaga
19801 aaattgggga attgtaaaat gaatacagtc attctcattt aatagataat gatatcttac
19861 tacctattgc ttttgccatt agtttgtaac atttaaattc atgttaaaag aaaaacaact
19921 gaaacactta tactgtagaa tgcagattca gccaaaatcc aatattgtaa atttttactt
19981 accttcagtg tctgctagtc ctactcctac ccctggctgt tttacaggct cttgtccatt
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20281 tattcaggcc aaacaatata cctcaacatt cagtagtttt tatttgtaga ctatttatca
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20461 ttttggtaaa aagagcaata ttgaattaaa taatatataa aaatgatatt ttaataaaat
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20581 aactggcttt tgtagtcagg ctgcttggtc tctgtttctg gctttgctat ttcttgctat
20641 gggtaatgta aggcaaagta cctggtcaag actgtttctc cttttgtgat ataaagataa
20701 taatattagc tacattttga ttatgaaaaa aaacacatga aaaatgcgtg aaaagggtta
20761 acagagtgcc tgagaaataa taagcattca ataaacatgR catattaaca ggtaggcatg
20821 Stcgtagtag ccttagaatt caaccaaaat ctgctaatca cttttagttt tcagcttcaa
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21361 tatctcaaaa gccattacat tgttccatta taataattct aggttaaagg tttaagtaca
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22141 attttataat ttatattttt aaataatcgc tagatattta ttaaacactt ttactagccc
22201 aagctataat tttattagat acaatggggg atataaaaga actgccaaat actacttctt
22261 acacatatcc tataatggtt ttcaaaagta aatattcgtt gtgctcatat ggcaaagcaa
22321 gagtctccta gacagttgtg agaagctttg atttacaaga gaaacaggaa aatgggaaaa
22381 atcaaaatta gaatgtggta tatatataaa atacataatc tacttatact gcagacattc
22441 aaatattgac aaaatgacat atttactttt tggaattata actttaccat cagtgttaaa
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22561 cctttctaaa ttcacatgac atttacagct tagaaagaaa tttaaagaat ttgtagaaat
22621 tcttttctgt caaattggat catcagaagt caaagaccaa tgggattaga tttcttttag
22681 gaagaatttc caataaaata taactgatta agtacaaata actctattga atccatagac
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22801 atttaaattg aaaaaaatgt agttcaaaac aacaaaatga actcgttttt cactgtaaaa
22861 atctattttc actaatgctt tgcttttata aactgaacca ttatcaaaat attataattg

FIGURE 2-G

22921 ttgtggacat cagaaggaaa gatttataag aacctttatt ttaaaacaaa gagaaataga
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23041 aacccagctc agggttggca agctctgcaa cgtgccagtt agtaaatatt ttagatgggc
23101 tgtattctaa cgacttaatt ctgccctgca gcacaaaagc agcatcaggc aacacagagc
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23281 atggaaatgc catttttagc tcacaggtct tagaaaacca ggtggtagac tgcttttgcc
23341 ctggcgtaaa ccctgggacc tgggtggccc agtggtattt tcaaaatcca gaagactagt
23401 taatgggcag gaaaaggaaa agtcaggaag tttggatttt gttattggaa cagacataat
23461 ctacatattt atcttaaatg ccaccaatat gaccaaggcg attctaacac attaagtatg
23521 ctaaagtttt gcatttgatt tgcaaaatga ctttttttt attttgaggc ttaacattat
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23641 tagaaagtat ggaaacactt cgaaaccttc aatgttaatt gtagaaggat ttatagttga
23701 aaagtctgta tgattattca ctatgtcctc tatttcaaat atgatatatg gattctttga
23761 atatgtttaa atatctcctg attcaaggta aattaatata tgtttgtctc aaataccagt
23821 aatgtttgta tttggtcatt atgtgattaa aacattactg tattcctgct gaactttatt
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24661 gaatttagaa agacttgggt agatagaaat ggcaagataa agaaaattgc ttatttttt
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26461 aatgtaaagg taatgtgagt aggatgtaaa atgatggaca tgtataaagt agattaaaat
26521 gcataaccta cataatgagt cagattagtc aattgattat aaacaaaaga aagctgtcat
26581 actttttgat gggattctat aatccaattc ataattttta gtatgacatt gaatggaaga
26641 cattaatttc atcaattgga aaatcacaat ttactatttt caaagataaa ccttaattat
26701 tagacactaa tattcaatca atttatattt attaaattaa aataatttta attcaagagc

FIGURE 2-H

26761 aaactcacaa tgaacaaaaa tagctacatt ataaaaatga tttattatct atgtttcaaa
26821 atcgtccatc ctttgttttg tcaactttgg ttttacctga tgcgattttt agttctattc
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30121 ttttttccaa atctacttca gtataattat tatctatttg ggaaaatcta aagcaaactg
30181 gacactagaa aaatgggcta gcttcaatag agctatttgt agttttcaca caccaccaaa
30241 tcacaagttt tcacaaatac aggtgttgaa actctgatat ctctatcagt catttgtaag
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30361 ttattagatg actattagtc attacagata tattttatat atatatgtaa acaatatatc
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30481 ataaaaatat ttcccttaag atatgtcata ttcacatagt agctcctttt agagaagaag
30541 atgaagacgg gttgcctcca tttgctgtgt tccagaaaga tggtaaatct cgtatattca

FIGURE 2-I

30601 cagttttctc tctccatgca cattggcctt atgactgaat tcttaatgac atcttaatga
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FIGURE 2-J

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FIGURE 2-K

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FIGURE 2-L

```
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44581  gttaatgtaa aaattgtttt tattgttttc tcctacttgt agttttgctt cttaaaatgt
44641  tttcagtgat ttttctcaga atacttaatt ataaataaca atgcaatcaa tatgtcacat
44701  caaatcaatt aaagaacctg taaatgcatt tttaaaagtc caggccattt tataatataa
44761  taaatttgtt acttcaaatc tcatttggac tcacagtatg attacatatc ttcctattga
44821  aagaaaattt catcttagaa attaattata aagtacatca agtgatagag tgaaaaccat
44881  ttcttgaatt ggtattaatc tactcaaata gtaaatcagg aaataaattc tatctgccag
44941  aagatttttt tcagaaacgg ctatcttata aacttcagaa acatgctttg catcgtgctt
45001  taattggtgg tttaccatag cagcaaataa gggaaaggaa gtcRgaggct tacctcccca
45061  aggaagtcgt tggatgaaaa tctatcataa tcccaaactg tcacctccag tgttttcttc
45121  ttgagctata tagttcaaat agaaatctaa ttaaacctat ctttccatca tacattttca
45181  ttacacacat acagtagaca tatttatttt tttccttaaa ctccttccat ttatgtgaaa
45241  atacttaaaa ttttaccgaa aactatgtag tttaaatatt aaatattatg taaaatttga
45301  atgattttgc actctaaact agtgtttgat catggggaac attattattt tgtgaataaa
45361  atgataattc ttacttattt attgtatccc cacctcattt tcaaaaatag aaatcagaat
45421  ttataaatac tctaaatata agaaattcat agattgcaaa aatgtctagt attatctaga
45481  tgaagtattg gattaaatgt ttcagcaatt tccaaaaaac ttagtagcat tgccttattt
45541  ctgcaggtga gtttatttta aattcacaaa cccagattat aatttatatc cagcttcatc
45601  tttgtaatga aattaatcta ctagaagaca aattaagaat ctcattttga aagacagttc
45661  acttgtaaat tggtttatgt gggaactgtc tttatagttt tctctctgaa ttcaacctta
45721  tacatttcag ttattgtctg ttaagcaaag atataaaaat gcagattttc agaaatataa
45781  taatgtaatt tttgcctaca gttacttatc tStggtgata atcctttata ctagtcatca
45841  ttttgccttc ttctgtagag attagcacca caatgccaga ttcttaggag gcctcaattt
45901  agcaaagaga tgagatccta aaatattgtc tagtggagta atacagttct atgcactgaa
```

FIGURE 2-M

45961 tcttattttt tttgtgtatt gtgtatgaaa gtcaaaatat agccagttgg aaaatgtgtt
46021 tctctctcaa atatgataaa tgtggcttag tctattaaaa attttaaatt ctgaaataac
46081 aaatggaaaa tattccacta gttttcttat tttatttgtt tatgttttgg ctgctttgtc
46141 aaaatgtgca catttacttt caccctgtgc ttaaatgtca ctcatttttt tccattggct
46201 acatttctta catgtatttt actcaacttt ttttgtttga ttggcaaaat gtatacagat
46261 cccaattttt gaataattgt gttatcactg tacttatatt agcctaattc tgtcacctag
46321 aaataatctt gacatacctg ttccatggaa atacttttat aaattactgt ttgattccac
46381 tcaggattaa gacttttctg gacatgttta gtccttctct tgtactcagc actgaattgg
46441 gagaaaagaa agagttatct tgattattca ccttagttta tgacttcaca gttaaactaa
46501 aggacatgca gactattcaa gatattttat ttcaaatcac tatataatta tctcatcatc
46561 ctcatgtctt aaaccttagt ttaagttgaa tgcacagtga caatttaaaa atatgttgga
46621 tgcttgtagt tttctttgcc ctWatgattt ttttttaaag aaatgcttgt aggtgttcta
46681 aatatactat aatttcagaa atcttgctca ttcctgaatg taggagataa ttacatgaac
46741 taaatagtaa catcaatgtt actgccccat aaacaataat ttggtgttta accttactat
46801 agttttgtac atacRgaaaa gcaaaactaa aacattgtaa tgagtgtact gagaaaaaga
46861 tgaagaatgg ctgttgctgt ggctcacatt ccataaacac ttgttactga tatctaaagt
46921 atattccaac actcttggta aagtatattt aatgcagtta taaagcaatt ttaattaaat
46981 ataaattttt ggtttatgtc aatatgYtat tttacaattg atgaaccaaa taaaaatctt
47041 tcctcaatta ttagaacttg ggacatctgc attaatcctt gactttccat ttcctctgag
47101 caccaattag aagcttatat gctacacatt taaaaacaat ttattttcaa agcctatcct
47161 aatgaagtct ggcagaacat ctatagctgg caccaacctg ctgatggggt tgaaattaga
47221 ttactgttac ttgctattac caaatggtgc ccacacagac aaggcctttc tctaactctc
47281 actgcttttt tctgaatttt ctgcccaagc ttatgtctca cgttctaaat aatacttcat
47341 ctgtggtggg cactagagtc ctgtaaacca acctctctgt ctgggggtct tgacatgtgt
47401 ctggatttca caagttgcct ttccctaaaa gggggctgga ccctgactct tgtaatctgt
47461 agttctattc caaactatag ccagactaac tcttgctaca ttcctggtct caagtattgc
47521 catatcctgg atgcctagaa attttcccca gccactaatt tacctataca ttgtagagaa
47581 agctattgag gatcaaactc cagctcacca ctcactttta aagatgggcc tgcaggcaag
47641 tactttccct gtatctctga ttttattttc ttaccagtca gatacaaggg aaataacgct
47701 caacattgac tgcataatgg gatcacctga gttctggtgg tgggaggtgg gtcagtcaac
47761 cctccaccca cttccctctt gcccctgctt actccccgaa ggaaagtctg acttgattag
47821 tctgggatga ggcttgagta ttaggatttt tgaaggctcg caggtgaatc taatatgtag
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47941 ctgaatccaa ctgaagaaat aaagcagcat tcctcgcact tcaacctatt tgaatgtaca
48001 caattaaggg cagaatttga cagctgtcac tcaagataaa ttacaaagaa ttttagggaa
48061 atatacagac aatgatttaa agaaagagga gctctcatag actatggata ggaagtttct
48121 atatatactt tttagataaa tttgtcaata tctagtgaag tttaagttta tatacccaaa
48181 catccaaata ttcaatttct actaattcca cttctgccat agagaaattc tcctacctgt
48241 gaacaagaaa tttgttcaag aacattaatt gcaacattat ttcaatagta agccaataga
48301 agaacgaata aatacattgt gatatattca tttcaatgaa atagtaagtg gcactgaaaa
48361 tcaattaaat tttaaaagcc tccatatgtc aagatagata catcttgaaa aaagttttga
48421 tcaaaaactt aatatggtat ggtataatgg tataaacata aaatcatgtg aaataaggtt
48481 acacattata tatacatgta tatatgacat acatatatat taatatcgta agaaaacttg
48541 taaattatga atattaaatt caatttagtg agtttttaa tggataggga agtgatttca
48601 gagggcttca gggtattatc ttttaaaaaa tctaaaacaa atatagcaaa atcttaaaat
48661 ttgacaaaat tggatagcaa gcacacaggt atttgttagg gtattttcta taatttttag
48721 taaacttgaa atattttata atgaaaaatt caaaaatttt tagtaagata tgttccttta
48781 aatttagttt tggattcttt ttttgatggt gacttagaac taatgactta atttgatggt
48841 gatagaatta gtgtctacaa aaaagtgtct acatagaaat aatacatata aattaataca
48901 tagaaagagt taataacttt aatttgatag tgacatagaa agaattagtg acgactttta
48961 agttaatagt aaacttggat tgctacttta gaatcatggc tattctcata ggtgaatata
49021 cataggaaac aaacacatgg tagtatgagt tttaaagcct ctgttttgga cttacttatc
49081 aaggtggtga ggttatggaa accatattaa gatttataat acactgaaca gtaataaaat
49141 tatgtttttt aagttctaaa aaatacataa tttgtttaac aagatgggaa ttaatatcaa
49201 atgcaaaccc atgtactatc actaaaattc tgggtctgcc aatacatatt aaaatagtct
49261 gaagtagtat taaaatacct ttgaagggat ttatcagtca ctatcttttc ttaatccata
49321 catgtgaata attgttattc aaatttttca aatccacatt tagtcttttt ttcacttata
49381 cacctagcaa aaattagtga atgccaactc tgtatcagga attgtagatg tctatcaact
49441 aaaaaaccct taattgtatt gacatatgag tatatattta attcatgcat gaaaagcatt
49501 tttaaaagta agcatattaa aatcataact aacatttatt aaatgcctcc tttttcctct
49561 ggtaaagttc taagtgcttt tcatgtgtta actcatgtaa tactcatatt aaccccatta
49621 tacaggtatt acttcttact ccattttata ggtgagaaaa cttgaagctc agaaaaatta
49681 aggYgtattg tcaaagttgc atagttatta actggaccag gatccaaaca taggtaattt
49741 gatttcttgc ttttaaataa atgttatatg aactcaattg attaggccca tcataaaatg

FIGURE 2-N

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49801  tgacatccat ctattttctt aattgcaggc ttcactacct gaagtatcta gtttgtcttc
49861  tttataatct aaaattctcc atctcaattt aaatacataa tttttataca tataatataa
49921  attatgtata atgtgtgtag acacgcatta taaacatcgt gaacaagtta ggccttcttt
49981  agagttgcct agggaaattc tgaatagtac atccKaagtg agtgttgtgg aacaattacg
50041  cctacttatt gtaaatactg atgtttggcc agatacattt agaaataacc taaaYtgatt
50101  ggacaaaagt taaaatgttc attttaatag agtatcttaa tcatagtaat gagtttgatt
50161  ctccaattct ctccagacct aaaacatcct ttagaattaa tgaaagtaaa aacagcttgc
50221  tcctaaacac caatgaaagc ctttgcagta ttttttgccc ttgcatttcc tgacatgcag
50281  agctggtcac acaaagccat tcttcaataa cagttgtttt ataactacca tgctctgatc
50341  atatcataca caatttcaat gaactgtgtt gccacctaac acaatttaaa actctacaca
50401  aaatagtcat atcaaaatct gtggagttga aggtaggcag gKaaacaggg ggattcttaa
50461  atgtgagcat aaagtcaggc tgagaaataa gtggagttca tcctcccttt cctttcttgt
50521  ctagtaaaca cactatattc tcttgtggga agattacatt aatgatttaa cattaggaca
50581  attaggacaa ttatatctaa taattaaaga agtttattaa taagggaaaa taaaaaggtc
50641  aatacataaa gatgggacat ggtgcttatc aaaaaatatc taaaacttca ccctcttgaa
50701  gttttgcctt gtttgttggt ttgattattt atttttgag atggagtctt gctctgttgc
50761  tcaggctgga gtgcagtgca atctcggctc actacaagct ctgcctcctg ggttcacgcc
50821  attctcctgc ctcagcctcc tgagtagctg ggactacaga cacccaccac catgcccggc
50881  taattttttt tgtattttta gtagagacgg ggtttcacca tgttagcccg gatggtcttg
50941  atctcctgac cccatgaacc accctccttg ggctcccaaa gtgctggtgg tttatttttt
51001  tatttgtttt tattggtcat tttgtcatgc ataggtatat atacttttaa ggctgtctga
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51301  cacacacacg tttttcaaaa ttactcctct gaggttattt ctcttaattt agaaaaaata
51361  caacttgcat cccattttgt aagctctgtt taatagtgcg atggtgtgct tattgtctat
51421  cattttattt tcctctttgc tctctgatgg cagagactat atggctacat tgtcaattgt
51481  aacccctgca cctggcacag tgtctgacac atagtctgtg ctaagtaaat attcagtgat
51541  ccttagaaca tgcttgtatt ttgttttcct ttaaaatcta ctgaagtaaa ataaattttg
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51661  tagtttgata ggataccaat gttgtttaga gaaaggtcca gccaggaatt gggcttccag
51721  gtataaagat agctaaaaat aattatattc ataacaaaat ctcagtaatg agaaaatatt
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52081  taaagaaaag ttgtttaatt ttctatatag tattttaaaa taatttagta taattcagaa
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52261  tccagacatt atgcttatca cttttgatgt atttatttca tgtatttcac agaaggcctg
52321  ggaagggagc tgttattatt cctattttgc agaagataaa atagttttag agaaatctta
52381  aagcttctaa gtgacagggc taaaattcaa acgcaagttc ttaaggacct cacttattgg
52441  cttccacagt ctaacttaca atgtcagtac cttgtcaata taattccctc ttacattgac
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52561  gatcttttaa atagttattt aagacatggt attatttata atttataaaa tattctctct
52621  tttataagtt aaatacaatc tctatcattc tgataatttt ccccaagttt ctatatataa
52681  aagataggga gattctgaat aatgtgatta ataatatctg ttctaaaaat aacactattt
52741  ctttgaaaca aaactaattt tgcatatcag cctgagatac ctggattgtg ttctgtgatg
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52921  ttgtttgaaa tatttacgta tttatgcttt taaaaatcag aaacagcctc atttgggaaa
52981  cagttcattc gtagtaaata tgtgaaattt taatgtcata gacaaaaacg aatgctgtac
53041  cattaataat ctgggtggga ttaaaattcc catcacccta ttgctacaga tcatacatga
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53161  atgcttttgg ctatgtacta agaaattgtc ttagttgaca gtgtaatgat gcaacttgtc
53221  atgagctgta ttagaaaacg ctcctactat tgggaacaaa ggaagattaa cttattgcta
53281  atatactaca gcaagccaat tatggcatcc tacattgcat agcagaaatt ttgtggggca
53341  gaagttacaa aggcatgaaa atgtttcaac attaggttca agtgagggac caagttcaaa
53401  cacctattat cttttttttt gtttgtttgt ttgtttgttt gtttgttttt tgaggctgga
53461  gtgcaggggt gcgatcttgg ctcactgcaa gctccacctc ctaggttcac gctattttcc
53521  tgcctcagcc tcccaagtag ctgggactat aggtgtccgc caccatgcct agctaagttt
53581  ttgtgttttt agtagagacg gggtttcact gtgttagcta ggatggtctc gatctcctga
```

FIGURE 2-O

53641 ccttgtgatc tgcccacctc ggcctcccaa agtcctggga ttacaggcgt gagccaccgt
53701 gcctgatggg atatacacct gcactggaca tccagaagac ccattaatta cttttgaaaa
53761 atggctacag atatttttaa tagaagactc gagaacttaa atcatgatta ttatgtgaga
53821 agctaaatga gttttagtga atagattatg agactttagt tatgtctaat ttcatggtaa
53881 taatattttt ttcattgttt ctatgctttt aatattttct acttttctgt gttctattgc
53941 acacatctgc taaagctatt tagaaatatg ctcagaacaa tttgtcgcag tgctgattca
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54181 agtgaagggg taaaacagga aagtagaaaa gacaggaaga aaatagttag gaacagaaat
54241 aagaaagaaa acatgaaaat aataactaga ggagctatcc cataacataa atgacatgag
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55141 ttctgagtat tatctaattt ggttctcctg acaagctaaa aatgatgatt ctgcctacct
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55261 atataaatac taagcagcag attcaagggc agtgtatagc tctaatttgg atcctgttta
55321 aacaaaccaa ctacagtaaa agaatacact tcatataatt aaaatgcttt taaatttgcc
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57061 aggaaaatca taaggtagaa tgctggttat ctttttttaat taaattgcta ctcttaggaa
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57181 ctaattggta aattattata aagtattatt tgcattttgc caaataatta gcagtggggt
57241 ggaactgtca tttaaagata aagctgtcag cactgaaatg taagaatatt taagaataca
57301 cagattatta ctttttaatg ttatattatc tgWtattaaa cctatagata cctttcggta
57361 ccagctttcc taatagagtg agatactaca atactctttt tttcttttaa ttttagaagc
57421 tgaaaaaaga agagacattg ctttatagat gcttattggc tgctgcacaa ttgtggctga

FIGURE 2-P

57481 atactaaaag acataattca aacaaatatt tgagaaaact gcRtaattca aaataattga
57541 gttaagcatt tttttcttct acaattgaaa gactcttttg gcatcattta gaataaagct
57601 taattctgtt tgatgttact tttgtttgtt aaataataga gtggaaggga tccatatttc
57661 aaagggcaaa tccatataga aagatactaa cttttaaaat aatccatata aaacagatat
57721 gctgcattta tatttaaaat aggataactc agatgagtca tactttcctg taaaacttca
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57961 ctatgccatc atgcagcaac tgtatgctat aatctggtac tgaaatacag aatataaaat
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58321 ggttgtctac ataagatttc atttgaaatg agcctttgct aaaataaaat aataataata
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FIGURE 2-Q

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FIGURE 2-R

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FIGURE 2-S

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72121 aaatattttc tttatcagaa atatggttta tgagccacct tgctgttggt agctgactgt
72181 tgacatgttc ttttcaccct aattgaattg tgttcacatg tagtttggtt atttactagt
72241 tgttgtgccc ttgagcaagt tggttaatcc tccttcatcc ttgactccct caaggggatt
72301 atacttgcta ggtgactgct ctagttttat ttccatccta tgatagagaa tacaatatga
72361 cagaatggga aacacaaaac agctgcttgt ttacaacttg taaatatgca ttttttgagc
72421 tgaaggttta tataagaaat ttaaaaaata ctttaggatc ctaaaacttc cattttgttc
72481 ttaattattt tccttatcta tagctgttct tgacatatac agtaaaactt ccccaagcat
72541 agaaatcatg tcatctaatt tttctttttt gcacttccca catctcctct catggccctc
72601 tcagtggcag ttgtccaggt tctttggctt tgtctttgct cccctgggtg ccaatggtgt
72661 ccccccttact gagtttcttt tctctcggca ttgttacatt gttatatttg taacatttgg
72721 attggttaac tctgcatggg acatccaatc tgcagtctga atctaaattt ggtttaaatc
72781 tacatgccaa gcagacaaat atttatcatt aatgccacta acccaaagtt gatttaaatg

FIGURE 2-T

72841 caaaatacca aaattttact ccatcataca cttaaaaaac atgtgatacg tcataatctt
72901 atctcttcat aatataaaga taatataatt ttaaactcat taaaaatttt aatgcaaatt
72961 ttataaatga atattctttc aaattttagt agtattaaat atacatacac aggagatttg
73021 cagtatcatc ctactctttt gctttaagtc actgtatttt tatattgaat ataaaatgaa
73081 tgaaacagat tgttatgcaa acttatatgc tatgataata tactctgttt ccatttttgg
73141 gcaggactgt tgacaagaat tctttagata aatgttatac agcatggata tctttttaaa
73201 tcgctcagag ttagagaagg taaattctgt atttgaaact ctcattgatt tgggatgtga
73261 tcttggacaa tttactttcc atgtactttc tttcactctc aaattttgtg aagaacaagc
73321 aattaaaatt agcaaagtgt ggcttgcata tataaactcc aaaatgaaat aaatttacat
73381 atttttaaaa cttttcatca cattttgaat aaaagaaatt taagaaatac caaagactac
73441 agttgaatgg tctgagctga ctggtatttc ttttctaggt ctgagtacat tgaaagtatt
73501 tagagtcaat gacttcttta ctcacatatc taaaatagat ttagctccaa tcacaaaaaa
73561 gtataattgt aaaataaaca gattcttact tatatcacag tattaatagt taacaataaa
73621 aatattgttc aaaaggattt catcgtcaaa tgtgttgtaa aagctcaagt cacaaccatt
73681 ttttaggcta atgttatata gtaagcaaga tacttataag tactgtagtt ttaatctgtt
73741 atactatata tttaaaaagt gacacctaag aggtgatata acttgtctaa tatcccacag
73801 aatggtagta cagaaatatg aaccccaacc atctcctagg ccaatgcatg tatcagtaaa
73861 taaaaaaact aattcaactt atgccaacta agcctacatg ctagcctacc tgaaggcaaa
73921 ctatgttcaa atatgtgaaa cttagcaaaa ataacatata ttatttgtaa tgccatttaa
73981 attgcaacat aatatgataa tttggaaatt ttattaattg cctacatgct gatattattt
74041 ggaggcttgg acatgcaaaa actgaagaca ttattgaacg aagagaaagt tgctgtggga
74101 tatatcactt atggtgagta aacagtgaca gaaatgaata aaatttgatt gggtctctta
74161 tccctttcc ccatctcact cccagaagag aagacaatgt cgtatttctc cagggagatt
74221 gatgaaaaat tatgctgaat cttactggga agaaaaataa tgtaagaagg atgaaagaat
74281 aggaggtgca gattcagtgc tagggaggaa atggtggttg gaggttccaa aggaagtagg
74341 gaccagcatc ctgcttgttt atattgccta tggaagatgt ctggcatatt ttttcaataa
74401 aaattgccaa gaggtgcctt tagaaagttg aacactagat tctgtgactc tcaatgtagg
74461 caaaactact cttgtgaaaa cttgggcaca gttaagggag ctactcatta tcaggaaagt
74521 gtgctagctt tgacattgca ctcttagtgg cgtggactga tgtacagagg cccaaactcc
74581 agtgttctag aatgtgtaat accctcactg ggaagttcct caaggcatgt ggtgcaggaa
74641 acaccaaatg atgaatgcaa ttcaatttcc taccaacaga tgaaagaaag attggacttg
74701 attacatttg atttacagaa aaagtaatat ttcttatact caaatatgac tgttgcaaag
74761 atatgctttt taaacatact tagtgtgaat aagggaatac aattagccat gatttgtgga
74821 ccaacctgtt agaagattat catgataaga ttcgatttct aatcaccgtg accactaaaa
74881 caatccagtc cagtatttcc ttgaaggatt ggtatagatg ccaaaagcca ctttatggct
74941 acagttcatt gtatgtctca ttctatgtgt tatttggaac agactgaatc agaaagtggc
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75241 ctggtctgct gtggtttgaa cgcctcctca aaaactcatg ttgcaattta attgccaatg
75301 ttatggtatt ggggggtggg tagggccttt aagagatgat gaggccaagc cctaatggat
75361 ggattaatgc cattatttca ggagtgggtt agttatccca aaagtgagtt ccagatacaa
75421 aggatgagtt caacctgatt tccttactct ctctgtgttg tatgcttact tgaaagagca
75481 tgcctcttca ctattttatg acacagcaag aaggtcctct caagatgcca gcactgtgat
75541 cttagactta tcagcctgaa gaactttaag aaatgaattt cttttcttta taaattactc
75601 agtctctgct attctctcat agtagcagaa aacagactaa aatgctatca aatcttatga
75661 ataccataat catttaacaa taacaaacta aaccaatact atatggattg tgtagaaatc
75721 cacaattaat tgaatggact taggaagcta gggtagttga tgcacttagg aatgagaaat
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75841 acttcagtta tgttgataac ctttatgata ttcatatatt ctgtactgtt ctttttaac
75901 tgttacttaa atgtatctta ctactcagat gatagatttt aacataaaat atcactttat
75961 actaggaaag tgtctcctaa caaatataaa tgctatctga actagtggca aaatcatcat
76021 cactgccacc accatctcca ctgtacatag atataaggac aatataaatt tcattttata
76081 acataatttg acagataaaa tacccagaag tttgcataga ttactgaggt ataactttaa
76141 agcatgtgta aaatgagata aaatggaaat catgtttctg aaaaagaaag ttagaagaaa
76201 gaaatctctc aatcaaaatt taagagtaaa aggaaaattc aaatatattc atcctatagt
76261 ataagaaaat aaaatgtttc ttttgacaaa ggaggagaga ggttttatca caacccaaat
76321 attaaaagta tgcttcacaa gaaataatac aacatggtca attgttatgt ataaaaatgt
76381 taattaaaga ttaatatttt aattgaagag gaagaaatac ttccaaactc attgtataag
76441 gccagtatta ccctgatacc aaggccagac aaggatgcta caaaggaaaa ttacagacca
76501 ttatccctga tgaacataga tgcaaaactt ctcaataaaa tactaacata ctgaattcaa
76561 cagcgcatta aaatgatcat ccaccatgat caagtgggat ttatcattgg gatgcaacaa
76621 ggtttcaaca tatggaagtc aatacacgtg ctacacatta aaaaaatgaa gaacaaaaag

FIGURE 2-U

76681 catatgatca tctcaataaa tgtagaaaaa gcatttgaca aaattcaaca tcctctcatg
76741 acaaaaaact ctcaacaaat tgtgtataca aggaatatac ctcaaaatgt taaagtccat
76801 gtatgacaaa tctgcaacta atatcatact caatgaagaa aagttgaaag tttttctcta
76861 agatgttggt atccattctc actaattcca tcaacatagt actggaagtc ctacccagag
76921 cattgggaaa gaaaaagaaa gaaaatacat ctatactgga gaagaaaagg ttaaaattgt
76981 ctatttgcag atgacacgat gttatatatg gaaaacagtc aagactccac caaaatactg
77041 ttataattaa taaacaaatt cagtaaagtt acaggatata aaatcaacaa caaaaatcag
77101 cctatactat actcagctta tactatgcac ttctaaacac tgacaaacta tctgaaaaag
77161 aaattttgaa atatcatata tgatagctac aaaaagaaac tatttgggaa taaatttagc
77221 caagaaggtg aaaaatctat gcactgaaaa tgataatact gatgaaagaa actaaaaaag
77281 acacaaataa tagaaaaaat actatgcgcc tatggatcag aagactcaat attgttaaaa
77341 tgtccatact aaccaaagtg atctgcagat taaatgcaat ccctaccaaa atttcaatgt
77401 aatttttcat agaaatagaa aaaaatcttg aaattcatgt ggaaccacaa gagatatggt
77461 gtctatgggg tgaggcttgg ctcctctgaa aaggcaggga agagtgggaa ggattgcgtt
77521 tggttgtttg agggccagct cagctgcaat acaatagaac accaggtaga cttctaagat
77581 ttttgactct ggttcctgac tcctggatgg cacttctgga cccacctggg gcctggtgga
77641 cctcaccacc ctgaagggaa agacaggcct ggctggcttt gccacctgct aattgtagag
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77761 aagatccagt gctgtgctga ctttaggtct tacccagtgt agtcacagtg atgttgccca
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78001 cagcattact gggcttgggg tgccccctaa agcagacata gcttagacca taacaccaag
78061 tcatttgaaa tatctggaaa gccttcccaa aaggacagtt acaaataagc ccagacagta
78121 aagactacag taaataccta agggtcttca atgcccagac aggaaaacat gacctcacct
78181 aatgaactaa ataaggcacc aagaaacaat cctggagaaa caaagatatg tgacctttta
78241 gacaaagaat tcaaaatatt tgtgttgagg aaatgctaag aaactcaaga acacagagaa
78301 ggaattcaga attctattag ataaatttaa tagagtatga aataactaaa aggaatcaag
78361 cagaaattct ggaggtgaaa aatgcaatag atgcaactga ataatgcatc agaggtcttt
78421 aatagaagaa ttgatcaagc aaaagaaagg attagtgagc ttgaatacag gctattttaa
78481 cgtacaccaa gaagacaaaa aaagagagaa ttttaaaaat aaagcacacc tacaggatct
78541 aggaaacgcc tcaaaagggc aaatctaata gttattggcc ttaaagagga agtagaggaa
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78781 gaaaaaaaaa taacatacaa tacagctcca atacatctgg tagcagactt ttcagtggaa
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79081 tggtccaaaa ttcattggta atagtatgta cacagagaaa cacatattat tataacgctg
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79321 cttgtttgtt tatgcaaata gtgttaagtt attatcaggt taaaataatg ggttataaga
79381 tagtatttgc aagcctcaag gtaacctcaa accaaaaagc atatgatata tacgcaaaaa
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80221 aataatggaa atcaccaagt attttctctt actacaatga aataaatcta gaaataacca
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80341 gtggatcaat aaagaaattt agaaattgta aaatttcttg aaacaaacga taatggaaac
80401 acatactaaa acccatgcaa aagcagtact gagagggaag tttatagcta taagtgtcta
80461 aatcaaaaag agaaaaaagt tgaaatgaaa aatctaatga cgcatcttaa agaactagaa

FIGURE 2-V

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80521  aagcaagagc aaaccaaacc ccaaattagt agaagaaaac aaataataaa gaacagagtg
80581  gaaataaatg aaatcaaaat gataaaaata caaaagctca acaaaaccaa aaattggttt
80641  tttgaaacag atatatgaaa aggtgcttaa catcattgat catcagagaa atgaaaatca
80701  aaactacaac aaaatataat ttcaccccag ttaaaatggc ttatgtccaa aagacaggca
80761  ataacaaatg ctgatgagga tgtggagaaa agagaaccct tgttcactgt tggtgggaat
80821  gtaaattgct acagtcaata tgcagaagag tttggaggtt cctcacaaaa ctaaacattg
80881  atttatcata tgaacccaca atcctactgc tgggtatata tccaaaagaa gggaaatcag
80941  tttattgagg agatatctgc actcctatat ttattgctac actgtttaca acagctaaga
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81061  agcaacctaa ctgtccatca acagatgaat gaataaagaa aaggtgacat atacacaatg
81121  gggtactatt cagccataaa aaagaacaag atccagtcat ttgtaacaac atggatggaa
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81241  cgattatttg tgggatctaa aaatcaaaac tattgaactc atggatatag agagtagaag
81301  gatggttact agaggttgga aatagtagta gggagttgga gggaaggtgg ggatggttaa
81361  agggtacaaa aaatagaata aataagacct gctattcgat ggcacaatag tgtgactata
81421  gtcaataata acttaattgt acatttcaaa ataacctaat gagtataaat gtattgtttg
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81661  attatactac atgattatta tgaatgatat aatcaaaatt aaaagggtaa agttgatgca
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81841  atgtgtcaag ttatttcata aaaagtgcaa atattctgtt ctttatatca caatgaagaa
81901  ttagcaaata attcactttg acttggtaga tgtttaataa ataacataaa aaatcaaatg
81961  tcatttgatc cctgaattcc atttgaaaag ttatcaatct ctttaataaa tagaattcaa
82021  tttcaaatgt tatcaatgtt agagtgtata caatatcctg caataattga ttttccattg
82081  aaaaataaga attgactaag aagaaaacag tttaacagca atttctgcca actgaataga
82141  ataaaactta actatgttcc ctccagcttt ctaatattca tgtagagaaa ttctttctct
82201  aattgtaaat aggattacaa ctgtaaaagt aatggcaata tagttctata tgaattatag
82261  agggttttca tatgtatacc atctgattgg tggttatttc agttaaaagg agtaaaattt
82321  aacccatttc acttgtggta ataccttcgg tattaataag gagcaccaat acaggactca
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82681  ataaaacatc acatcaagtc cacaaatatt tagtcagtaa gtgccaaaga gaatactaaa
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83281  aaataagaca ggaattcaaa attgcaattg attattaatt cttacatgaa ataaaatttt
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83401  tagtacttaa attcattttt tccacagttt attaatgcaa actgtctaag cactctaaaR
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83521  ttttcttaaa taaagaagta ttacagaatg attttccttc ataaacatta aaactgtggc
83581  tcttggctgc cttttgtcct actgagatgc aaattacaaa tgatagaaat aaaaaaaaaa
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83701  ccagcacttt gggaggccaa ggtgggcaga tcacctgaga tcaggagttc gagaccagcc
83761  tgaccaacat ggtgaaaccc cgcatctact aaaaatacaa aaagtagcca ggcatggtgg
83821  ccagcgactg taatcccagc tactcaggag gctgaggcag gagaatcacY tgaaccaggg
83881  aggcagacag tgcagtgagc tgagatcgcg ccattgcact ccagcctggg cgacagagca
83941  agatgccgtc tcagaaaaaa caaacaaaca aacaaacaaa aaacMcacaa atatacattt
84001  atatggtata tttcctacta aaatatatgg atttattgtg ttaatttaaa ataagatgca
84061  agacttagat acaaaatact ctgttggctt gctgtattat gcagggattt aagtttttaa
84121  aaaatggtga agggattttg gcttataaat atgaatacct aataaatgaa tgaacatatt
84181  gagatcattt tcattaacta aattaaatac acatattgtg ttgatacata tgtatatcta
84241  ttatacatat atataactat ttcttaacac ctccctgttc ccaccttggt cttaacttac
84301  ataggttctt accaactctc cttgcttcta ctctttacct ctttaaaact attcttaata
```

FIGURE 2-W

84361 cagcagtaag agtgatccta tttaaacgtc attcagctta tgtcaggtca attgcgtctc
84421 atctcacata agtacacgtt aaagtcctta caatggcctg caagatttga cccctgctac
84481 ttttggtatc cgctctttca cgtgttcact cagtttcagc cacgttggct tcctttctgt
84541 cttgctgttc ttggcacaca acaagcatgc tcttgctcag gatatttgtg tccttgtcac
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84721 atcctcctac gtgccatacc caccctcctt gctatatttt tctccttagc gtttattatc
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85681 atggcaacac tcctgtctct acaaaaaatt taaaagaatt agcatatgtg gtagtgcatg
85741 cctttttact acttacaata ttctaagcat gacattatgt ttcctatatc ttattcctaa
85801 atttgataac aattttgcca actattatcc cWgttatcca gctaagaaca cctgggtact
85861 aaaagtttta aaaaatccag gcaataagta ccagatctga atttaaatcc tgatctaact
85921 ctaaaagcat ggctgtctac aaaccactgg agatactaaa gcattggctg gtggaagatc
85981 tggtatggat attaaaaaga gaggttagca tccttgcttc caaagtaacc actccaagct
86041 tacgaaaaag tgcagtctat tccaagaaat attggttaga caaatccgga aatctaactg
86101 taggaacaat tgttccttat gaagcaatat cactgaacac agaaatacct caaagtatgt
86161 caaccttgat gaaggcaatc aaattaggat ttggggcatt gtaccacata aaacaggaca
86221 ttatttagtt tccttcatgt ccctatcaca aagattataa tgtaagcata attctcctct
86281 gataaatttc aaaataaatg gataaagaag agaaatatgt ttctttgtac tggcaatgta
86341 tctaatcact agtatcgtga tgtggtgtga tatcactaca tcttgaaaat aatatattag
86401 aacctatcag cccagggacc agtaatttgt atttttcttc acagaagaga gtttcctaaa
86461 tatatattag aaaatcttca tatcaacatg aWatgtggtc tgtgtcatgt gtacctaacg
86521 caccagcttt aaggaatttt gagaaatctc atgctaatga ccaatccgta cctggtaatc
86581 cccctggaac aagaacaagg aagctcactc atctgtgtgc tgtgtttctt gatctccaac
86641 cttgatcact gccatgccat ctgtaacata tgccaaaaaa gcataagcag aaatagagac
86701 tttcttgcct aggagcattc ttccttatgt tatgctggag tgcgtcctct gtcctctagt
86761 aatgctactg gaattagctc ttctaccaaa gactttttca tgacaaggaa ttccagaggc
86821 caacttctaa aatcaaaacc accactccaa aaacagctaa tttcatcctt acttcaatcc
86881 ctgattctca gcattacatc caacagcatt ttcttgccag aaaccctgtc agttcatctt
86941 taagaagaag agcaagctag ctggaccaat ttcactcacc tactctgaaa caactaaaaa
87001 ctaagaatat aaaagtatgc atgaactata attcatgtca cagaggcatt tcctcacaga
87061 atacctatgg acaaacaatg aagtttctct catttcatta caagtcttat ggccttggac
87121 gtgcttactt gccatgtagc tctggctaaa tctataagca aacataggat atcactggtt
87181 ttagctttgt gctcttccat gctgtgttac cactgattca ttaagaatgt tcttgaagac
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87361 acaaagttga acaacttatc aatataaaca attgttttag gttcattgga tatatgatat
87421 ttagtccttg tggattcatt gttctcttac aaaaattgct gaagttttaa aagtatcacg
87481 atggtaatgt atttcacaat tatgttataa cacagacaac taggatgaaa attaatttgg
87541 agaactagtt caaaaaatcc agtgattaaa taaagcttag aaccaatgat atgtatataa
87601 aagtttagat ttagtccatg atattaacca agtaaaattg attttatcta tattttctac
87661 tctacctttt ctggagatat aatattggca taaattgata aaaccatata atattgttaa
87721 taagtttaac aattgctatg gataattgtt ttaatgtcct aactcttgtt attgtattaa
87781 ttcagaatac aatgactaag tctctaagta gagcaaaaac ctgcattgtg aacttattga
87841 agactcaact ggacatgatt atatgtctaa tttttttcca aattaatcag tctcttcaat
87901 gaaattacta tcaaatctca acagagattg tcatgaaaat tgaaaaacag attccagaat
87961 ttatatgcaa aaccaaaggg tcaagaattg ttccgagagc atcctgacaa acggctctag
88021 gatggatcca cctacgaaat gccaggattt aatataaaga tgttacaatt aaaacagtgt
88081 gatatcggtg tagggataga aaaatagacc agaacagaga acctggaaaa gatctgtgca
88141 tgccttttaa aacttaatat atgacagatg ggactagcag atcagtgtga gtaataatac

FIGURE 2-X

88201 actattcaaa aaatggtgca cagtagtagt aaagaaaaat aagaaagcaa tcctatttaa
88261 aacagctaca gtataatgaa atacctaaga ataaatttaa ctaaataaat gaaagatctt
88321 tacaatggaa actataaaac atgaaatatc ttttcattct tatgtgtcct cttcaatttt
88381 ttcaatggat aaaaaataga aaggacacat aaaaaatgga aagatatttc atgttcatgg
88441 attgaaaaaa ttaatattgt taaatgtcca cactatgcaa aatgatctgc agattcaatg
88501 caatctctat caaaatatca atcaatgtca ttcttcacag aaatacaaaa aaatttctaa
88561 tagttgagtg gaaccacaaa aggccctgaa tagacaaagc aatcttaagt gaaaagaaca
88621 aagctggagg catcacactg cctggcttca aaatatacta caatggtata ctaaccaaaa
88681 gagcatggca tggcataaaa atagacacat agactaatgg aacagaatac agaacccaga
88741 aataagtaca tgcatttaca gccaacacag tttcaacaaa ggcacaaaga atatacgctg
88801 gcaaaaggat agtcttttta agaaatggtg ctgacaaaac tggatattca tatgcagaag
88861 attaaaatta gagcattatc tcttacatat caaaataaac tctaaatgaa ctaaagactt
88921 aaatttaaga cctgagctta tgaaactact agaagaaaaa cattaaaaga atactccagg
88981 acattggtat gggcaaaaat gttttgagta agacctcaaa agcacaagca acaaaagcaa
89041 aatttgacaa atgggattac gtcaacctaa aaagcttctg catggcaaag gaaacaatca
89101 acaaagtgaa gagacaacct acagaatggg agaaaatatt tgcaaactat ccatctgaca
89161 agggatgaat aggtagaatg tataaggaac tcaaacaact taatagcaaa aaaaacccca
89221 aataatttga tttaaaaaat gagcaaaaga tctgaatata catttctcaa aagaagacat
89281 acaaatggcc aacagataca ttaaaatgct caatatcact agtcatcagg gaaatccaaa
89341 ttaaaaccac aRtgagattt cacctcaccc cattaaaaat ggctcttttc aaaatagaga
89401 tgctggcaag gagatgagaa tagcagatgc tggcaaagac ttgaagaaag agaaatgctc
89461 atacactgtt tgtggccatg taaattagtc caaccactat

FIGURE 3-A

>1:74048401-74143400

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121     gttgctagag aaacaagaca acatccaagt tctccaSatc atggttttcc gggcgccagc
181     caaggcgctc cgggggcgtg gttacgtggg cgacgcacgg agggggcggg tcagaaacaa
241     ccgggcggag gcgcacccca gggcgcatgc gtgctgtgcg gcgcggtctc agggaaggtg
301     gggctatggc agctgctagg gaccctccgg aagtatcgct gcgagaagcc acccagcgaa
361     aattgcggag gttttccgag ctaagaggta ccagagaagg caccggagtt ctcctgggca
421     atgcagaggg agggtgcttt tacgtgccag gaggtttgct ggactgtcac ttcccgttta
481     cttctcatct gYaggcctat gacgctcccc aggagtagct agctaataat ccttttgagt
541     tttttattct tttcactgtc cctgcttgac atgcttgttg cttactttat tcttagtagt
601     atagatatta aaaatgaggg cggaggaaga agaagaaaat cttactagtg aagttatgca
661     ttgattagct cattaataaa agttgcttta aataaatcta aaagatacga agcacagtat
721     tttgaacttt atgagtagat gccagccccc tatctacttc acgctttaca ttacgttcat
781     ctacttctgt aatgtaaccg tttgttgagg gagtaacaga acatggagga attatggatt
841     aaaaattaaa aggaagaaat ttgttatcaa aaaattggct atgacactta atccctgtac
901     acctgtctaa taaaagtgat tatatttgtg ttgcagtgac tgcttaaaaa atactgggac
961     taattcttgg ataacagtaa aactttcagg actattagat tctagctgac aagttctgtt
1021    tgttaactaa ttaaaatgct aaatcatttt gtttatcaat aaagagattc caactgtcta
1081    ctaaaagtgc acactgtctt ttaaagatgt catcagagag ttgggacctt ctgttatcca
1141    gaattttatg ttatattcta acagcctatg taagtttgca tggttcatct taaagtaata
1201    gaaaataaag tacccacatt tataaacagc aacattgagg gaagggatct ttgggttgtg
1261    tctttcttag tcacctaaca ccaagtgtcc Stgatacata agaattgatt tgcaaagctg
1321    gagatttgtt tatgtttatc tcctcttctt attgaagaat tgaggcaata gtctttggca
1381    agttaaaagt cgctctctta atcaagaaac attatgtcat tcagaattta taattaaatt
1441    ggattgcaaa ccataaaagg agggagtgat ctaaaagaaa aaaaaggaac ttgtgaacag
1501    tcttcattat aactattttg aatcgtatta atgcaccact aattattccc taactttcaa
1561    aagccaaaga tacattttgg aagatgataa tggatattac cttctttatc atctttctca
1621    ataggcaaac ctgtggcaac tagaaaattc tgataatttt tgttttcatt tccttgcttt
1681    ttccaaatag gcaaacttgt agcacgtgga gaattctggg acatagttgc aataacagcg
1741    gctgatgaaa aacaggaact tgcttacaac caacagctgt cagaaaagct gaaaagaaag
1801    gagttacccc ttggagttca atatcacgtt tttgtRgatc ctgctggagc caaaattggt
1861    acgcgcttta tggtcagttt tataatatag gtcctaagca gaataatcat tgaagaaaag
1921    gtttctgtga cttacagtgt ataagctgca tatctctacc cacagcttta caaactttaa
1981    aatttgaaca taaattgact ttttttagaa agataaaagg aatagcaact gttcttaccc
2041    attatgactt accttgaaaa acttccagaa tgttacttaa aagaWaattt tattagtttt
2101    aatgaaattc acactattca gataggaata ctcctttgga ccttatcagt agaacccttg
2161    aggtcctctc cactccagag ttcctccagc aatttacatg aagaaagcaa ttagtgggaa
2221    aaaatactct tgacctctta gggacataat gcagaatgca aaagaacact gtcacatggc
2281    ttaaatataa tacatatatt tgaaaaccct agtttaggtc aactttgccc tttgaccgtc
2341    cattgcaaat agaaataaat gctgtttttc tgaatgctct tttctatgtg atacttaaag
2401    ttgaagcccc ctgataccag agataagata tctgtatatg acattaatat gacattagca
2461    ttattctaat tagccaacat tattttaatc cttacaacta tgaggtcagt actgttatta
2521    tttctttttt tttttttttt tttttttttg agaaggagtc ttgctctgtt gcccaggctg
2581    gagtgcagtg gtgcgatctt agctcactcc aagctcYgcc tcccaggttc aggccattct
2641    cctgcctcag cctcccgagt agctgggact acaggtgact gccaccagcc tggctaattt
2701    tgtttttgta tttttagta gagacggggt ttcaccatgt tagccaggac ggtctgtatc
2761    tcctgacctc gtgatccacc tgcctcggcc tcccaaagtg ctgggattac aggcgtgata
2821    ttatttccat agatgagaat ctgaggtact caagagttaa gtaactggcc caagataact
2881    agtgtggtag ttatatttaa gatttttttt tgggaatcca agttctaaaa atctttttc
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3001    ttgtgatttg taactctgta tgaatgttta tatttatcag tcttctagtg ttacagattg
3061    tgtaattgat tcttctttct tataattact attttgggga gaatattacc tcatcattta
3121    ttactgaggg ttgttgtctg ggtttcattg ctaatttatt gattggttgt ttgctatgag
3181    atgtttttaa ttttgttcta ttgccaatac ctttgatgtc catctattta cttattcctg
3241    aaaggcaaat ccttaaggtt atataacacc taaatttact gtcatgacaa agttttagta
3301    ggtttctatt aaataaattg tgctttttta actttgtttt taaggaaatg gaggatcaac
3361    actttgtgcc cttcaatgtt tggaaaagct atatggagat aaatggaatt cttttaccat
3421    cttattaatt cactctggta atgttatact ttactaattt acattttctt tttagtcttc
3481    cacctttaat actttagaga ctttttttctt tcttgcaaac actttccttc ttttttaaaa
3541    gaatctttga agttattctg ctttgaaaac aaatatttta tgattttcat gactttttt
3601    aggttgtaag tagtatagtg attttcacaa attttactcg taaaattgta gatcacgtat
```

FIGURE 3-B

3661 atcgtcagtc ttttatgaat attgttttgt tttgggtatg tatatagaaa attattttcc
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3781 taattttaat ttgtatttta agttccaggg tccatgtgca ggtttgttac ataggtaaac
3841 gtgtgccatg gttggttgct gcacctgtca acccatcacc taggtattaa gccagcatgc
3901 attagctatt tttcctaaca ctctttctcc cttaatgggg attcttgctt tgagggaagg
3961 gtggtttaac actgtcatta ctagactttt gccagtactt tttatcttgc atttttgtgt
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4081 gagtggacaa gtaaatatat aaaagagaaa tcacacacac aaaataagac attttaaaac
4141 agaaaagtag gaaggacatg gtctcagaat Raagaatagc tttttaaatt gaatacattt
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6961 gtgaaataga tgcctatggt gactttctgc aggctttggg acctggagca actgtggagt
7021 acaccagaaa cacatcaaat gtcattaaag aagagtcaga gttggtagaa atgaggcaga
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7381 ttagtggttc ttacatccta acaaaagctg ccctccccgc acattctttt gtatgttcct

FIGURE 3-C

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7861 gRtattttaa atattgtaca ctttgccttt ttgagtaaca ttccagagat aggtattttt
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10021 caaacgtacc accaataatg tacctaattc aactgaagtg acagtcatat acgcagatat
10081 gaccaagttc acatgtgagc aagtaacaac tccatgactR ttgctgcctg gctaatagct
10141 aYtatactat catttgtaag gcacattctg ttttctgggg tgtcgaaatg tggataaaaa
10201 aagatgaatt aggaatgatt ctaacctaag tatgtgtttt aataaaagga tctaggcaaa
10261 aaaaaaaaaa gtaagtcact cctaaattta atccctgaat aatgcagtgt acatgatgat
10321 agaggagaag tgtgtttttg ataagaagtg actaaatttt gtgacaatct taatttttta
10381 ggcttttcat ttagtcttcc aataaagata atttttttct gagttttatc agcagtagaa
10441 aaataagacc tacatggata agtttgaaat taaacatttt gtctcatttt ataattttta
10501 tttttatgaa atcatggcRc ttacatcata tactcaggtg tgtaaaagcc tgctatttgt
10561 aactataatc cataaactta ttgatgattt aataactatc aacaagggca tgggaaaaat
10621 tcaacatttg ataataatct tttaccttag gcatttattc tctaagcaaa gcagaaataa
10681 aggatatgta tcagtgtata ctgattgaaa taaagcttta aaaatccaag tgatactctg
10741 aaattgtcaa aagtttaatg gcatgaatcc aggattaatt cccataacct gtgatgatct
10801 agtcatcttc tgtagctaca tagtactcct aatgttaaga ttaccaaatt cagcaataaa
10861 gccaaaatca aaactgcctt ctgtcacata tagctgttaa gtaaactaca caaaaKcaga
10921 gttgctgttt acatacatca tgatgccgtc tggacttgag caccttggcg gctcaggatt
10981 aaggcacctc agtctagcct agcagagtta caatggagag aagtgaaaac tcattagtag
11041 ctcaaaacaa gctaaaggat ttcagatgct ctttttcttg ttcatctaaa tcaagtcttc
11101 atctgtgtca agaactaaat tgttaaagac ctttttaatt tgcttagtgc aagaaaaata
11161 atagcaacca tatatctagt taacttgagt cttctgtgcc tctaaaattt tgtttagaga

FIGURE 3-D

```
11221  aagcctattt ctattgaggt tgaggaacac aattctaata cttagtaaaa ttattaacat
11281  tcattgcatt taactttgtc gtattttcct tcctccaata ctagtgtgcc aaattctgta
11341  acatagtagc atttttcatg ctcccattta tctgtatata cagaaacttc tgcttaggtt
11401  tttttttata tataaagaaa gtctagtcat accagtttgg ttgaagaata ctaattctgt
11461  ccctggaaga gctgtctacg tgagccacaa caaaccaaac ttgccacatc attcaaactt
11521  gccaatttgg ccgtagttta gtagatgaca actttgggtc aggttaatat ttggggaaat
11581  ggaataataa aagctgctga ttttcctact gtattgctac ttggaggatt ggaggtgtag
11641  agggaagatg cctgtaaatg agtcactgtt atcacctacc tgcacatcag cttgattgtt
11701  gacacttatg tctaaagatg ttcatcccRa gagtattatt gtgcatgcaa gtaactgatt
11761  gatactaacg agttaacatt ttattttggg ctgcttggac aaaaagtctt atctttttga
11821  agcctctggc tgcagggatc tcttagccgt tgcacatata aatttcaacc attcacacag
11881  agcaattcat ttctgattgc tgtagactag tgcaatccat ctgctagtgt catttcctag
11941  ctatctgtgc cagaattaca ctccttcaat tgtgcttcag tgcatttctg aaacaatcta
12001  aactaaaatg tctgtattct ttggccactg gcttatgatg tgttactgat atgcttgttg
12061  aatctccagc ctctttaaca ctttttaaaa tctttgttac aaccaacaca tcatagctaa
12121  gtaatctgca catgtaaatg atttttttaa atttcttttc ttaccagtat ccactgtttt
12181  ctctctgtag cacattcaga tggttcaagt gagttttaat ttaccacttc cttgtaggag
12241  agtgtcacat cgcccagaat agaattaaag catttacatc ttgaggcaaa aaaatctttt
12301  aaaatacaac tatgtagaaa tcaagtaagt gttcatttca tttgcaggtt tagaaatgtt
12361  gcactgctta atgaagtttt acgtgagtgg tttcttacct attattttta gccttggggt
12421  ttgagaaagt aaattatgtc catcaatttt ctgtacttta gagaagtttc aaatatttct
12481  agaactagaa aacttgggac tacacaaaga aataattatg attatatcag gtggcccaag
12541  tgcagatttt aaatgtacag gcacactgac aaagtcataa attaaaaatg cactaattat
12601  atatcactgg gatcaatctt taatgaattg aataagaaag atcacttatg actggttaaa
12661  gttgatagag cttctaatta agcattatcc agtcaaataa agagctgtgt atggaagcca
12721  gcctatgagg aaggaaggaa aaagttttag agtaattctt ttttacttgt tgcaacagct
12781  gattcttcaa tacaaaagaa atatttactt tgatttgcat ttctctgatg gccagtgatg
12841  gtgagcattt tttcatgttt ttttggctgc ataaatgtct tcttttgaga agtgtctgtt
12901  catgtccttc gcccactttt tgatggggtt gtttgttttt ttcttgtaaa tttgtttgag
12961  ttcattgtag attctggata ttagcccttc gtcagatgag taggttgcga aaattttctc
13021  ccattttgta ggttgcctgt tcactctgat ggtagtttct tttgctgtgc agaagctctt
13081  taattagatc ccatttgtca attttggctt ttgttgccat tgcttttggt gttttagaca
13141  tgaagtcctt gcccatgcct atgtcctgaa tggtaatgcc taggttttct tctagggttt
13201  ttatggtttt aggtctagcg tttaagtctt tagtccatct tgaattaatt tttgtataag
13261  gtgtaaggaa gggatccagt ttcagctttc tacatgtggc tagccagtta gaggatgtgg
13321  agaaatagga acacttttac accgttggtg ggactgtaaa ctaattcaac cattgtggaa
13381  gtcagtgtgg caattcctca gggatctaga actagaaata ccatttgacc cagccatccc
13441  attactgggt atatacccaa aggactataa atcatgctgc tataaagaca catgcacacg
13501  tacgtttatt ggggctctat tcacaatagc aaagacttgg aaccaaccca aatgtccaac
13561  aatgataggc tggattaaga aaatgtggca catatacacc atggaatact atgcagccat
13621  aaaaaatgat gagttcacgt cctttgtagg gacatggatg aaattggaaa tcatcattct
13681  cagtaaacta tcacaagaac aaaaaaccaa acactgcata ttctcactca taggtgggaa
13741  ctgaacaatg agaacacatg gacacaggaa ggggaacatc acactctggg gactgttgtg
13801  gggtgggggg agggggggagg gttagcatta ggagatatac ctaatgctaa atgacgagtt
13861  aatgggtaaa gcacaccagc atggcacatg tatacatatg taactaacct gcacgttgtg
13921  cacatgtacc ctaaaactta aagtataata ataataaaat aaaaaaatta aatatttacc
13981  atgagttcag tgagaagaag caatttacaa aattagccat gtttctagtg tctttgagta
14041  tgtatctcta agactacaaa cgtgctggaa ttttccataa cataaaaata aacaaaaaca
14101  aaaaacaata cttctcttag ccatattatt tcatcaggaa tagtcagcct agtttcatct
14161  acaatgaaac cgaagtttta ctagccatca tacccaacac tgaattctag attcagatat
14221  gtacctccct gcttcgtatc cctcccttac tggaaaaaaa tacataggca tctctatttg
14281  gagagctcta atcttctatc aattaaggta atctttttca tctagataaa tgacacagcc
14341  attcaccaaa ttgctcaagg aacaaaccag gaaattttcc atgactcttc aggtacttcc
14401  cctcatcctt ttcatcctgt tttcaacaag tgaagtctat gtatgaaaaa cacaaccaaa
14461  atccatcaac ctctctcaac ttgttgagct accactgttt tctagactaa tggaatagtt
14521  tttttttttt ttttacatcc cacaatgcct tattgtgtgc agtaataaca atgatMtgac
14581  ttttataatt gcacatgaac gcaaagttgc agaaagcctg caaaggaRag atttagaaga
14641  ttggcattgg ggtgtatgag gcattgaaag aaaaaggaat actgtggcca tctcaacctt
14701  acttcactaa tttggtactg tttttgtatc ccattttgct cccctgaaga ctacctttta
14761  ggacaaagat tcatactact ttctaacatt ctacacttta ttttctccat gaagttttgc
14821  ctggtgatag tctgcaatct ctttaccacc cacattgttg ttttttacct ttttcatatt
14881  tgctatgtgt aatcagatgt cagctggaaa tctgctttcc ctttagatgt aggcaacatt
14941  agttgagcct ctattctaaa ccccagagat gatgtcaaaa acttctctca aatatctgtg
```

FIGURE 3-E

15001 aaattcctga agatcatata tctccataat tgctttggac tgtaagcttc catttctggt
15061 gagttagttc tgtttgggct tgcatgtgat tttctcacaa ttctatgagc tgagcgccta
15121 tttttcacta tgtgagtctc aaacttttcc tctttcctgc aattagggca tcaccatatc
15181 ctctccagaa aaaggccttc tcacacaaat tttgtgtgta gcaaatttct ctgaatcatt
15241 ggagctaggg aggaagKtgc tggaaggaaa gagaaggata catatcagag cacagcatta
15301 agtaataatt gttcttagaa atcctttggc atcttcatct ccaagacttt cttcactagc
15361 tattttttt ataatccaaa attatgtcta actttttttc tcttcctcag accaacttct
15421 tccatcccct tacgagatat gcacacgttg tttacattgt agacatatag catttatctc
15481 ttctttctct tgtgtcatta gttttcttcc ttcaatgaat tattctcatc agtacactaa
15541 tattctgtga tttttccagt ttaaaaaaaa aaaacccttc actacacttc cttcaggtat
15601 tactttattt ccttgttcct tttacactaa aatttttaga atacattgtc tgtttttcca
15661 ttcttcagtt cccgtcttcc tatttactct tcaacccaat tcaggctttt agcacccctc
15721 tccattacca ctactccatt aaacttgttc tgaagatttc cagtgctctc gactttgcta
15781 aatccagggg tcattcttgg tctcatcttc ttgcccttta aacagcattt atctcaattg
15841 attacttctt tgacttgcat tctttacctg gatgcaagga accccacatt actggttctt
15901 tttctaactt tctggtcaca ctttttaagt ctctttaact gatttctcct catcttcctc
15961 acctcatatc actagaaggt cacagatatt tgtRtttgaa tttctctatc cacattcact
16021 cctttggaat accatccatt ttcatagcat ctatgtgtta tcaattctca aatctgtatt
16081 tctcattatc aaaatgtaac tctcaaattg ttaaaatatg aatccataaa ttgtgaacat
16141 gggtcagaat ttaatcagtg aggaagccag caggattatg aagttgattt ttatattgtt
16201 ccRgatgcta caaggaagaa aatttatata caacattata aagaattttt tccaataaca
16261 gagtacattt tcttatgaga taataggctt aaaagacaat ttagcaagag ttttctcaag
16321 aagttcttat tttagataag aggtaggatt gaggcaggaa aatagggcct ggaggcaggg
16381 aacgtaaggc caattcacac ttaagctatg acaggaaata tccttttcat agggtgtatg
16441 cagagtaaat aactttgtaa ctttacttct tcctctccat ttacatatgg catacaccaa
16501 gtaaccagtg gaaatctcta gagggtattt aaacccccac aaattctgta acggtgtcct
16561 tgagccccta tgctcaggcc caYtcccaca ctgtagagtg tactttcatt ttgaataaag
16621 ttcttcattc tttctttgct ttgtgtgttt tgtccagttc tttgttcaaa atgccaagaa
16681 cctggtcact ctccaccagt aacaggatta gataatgact gtgggttgga tttcctgaaa
16741 accagaatct gagatgtact ttagaatgca aaatattttt aaggagggcc tgtgggatta
16801 atacttgtac aaggaagggg agagagcaaa acagagtaga agaaagtgaa gctgagatgc
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18001 gagttttcct ttcatttaaa tctgctgtgt cccttttttaa agtttcctgt tctctggaca
18061 tctgtcatca ttgctgtccc caccttccat cttctgtttt tttccttcaa atgtggtaat
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18301 actctcctgt Rgaggctttg catttgcttc tatcaggaga ccagagaagc attgccactt
18361 aagagcaacc tcagattaag ttcaagagtg agcttttctg acttagaagg ctctgtataa
18421 atccaaagtg aatatttttg tagcaataat tgctcaggaa ccttatttta ctttcttctc
18481 ttttttcctt tcttcttctt tttttaaatt tcttctgctc tgcttaacag caaggcaagc
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18661 atttccgacc tgaggaaaca cttggctacc ctctggttcc ttagaaccta agtttaaatg
18721 tgtgcttttg gaaaattcct cagggcagaa acttactcca tacgacctac atttcttata

FIGURE 3-F

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18781  caaagaaata tccacttata tctctgtgtt taagcatttt cctgaaatgg tttgtgtata
18841  caactttatg gtttttagtt cctcattgtt ttttgcgatt atgactttta tacttagcat
18901  ttaaaatcag tccattattc tcacttatgt gaaacataac tctagttctg tattatctta
18961  ttgacttatt atccaacatt ttcactagtg atatatttta gttagtagag ggtatggtat
19021  gttagtgggg gggatagtac tagtagatga tatattttta taatgaatgt tacagtcatg
19081  gaatgtaatg attatgaaaa tgctaaacat atgaagaaaa aatgaggaat aaagtaaata
19141  tttataccct tatccctttt atcccccatc ccataagcca catgacggag tagacagctc
19201  agcacctagc atgatgctgc tatgagatga taaaccatgt taaatctttt acagagcagg
19261  tcagaataaa cataagcaga caaaagtatg ttaaatgtat actttttgaa ataggaaata
19321  agcctacaaa atttgcttta aaaaagttac catttatagt agatagaaca catagaccag
19381  tgttagaccc cctctgactt caaattatca caatttgaag ttaattatgt gccaggatat
19441  ttgatcagca ctaagaatat tttatccctt gctctcaggg ttcttccagt ttagttgagg
19501  ataagatagg aaaaaaaata attgcaataa ttcctaggta gagctaccat aagtaaggca
19561  tttgaatagt cagccaaaga gactaacaaa agctacatga tgaggaaaga tctcttagtt
19621  tggtacgcga gagtgctcgg tgcataRcaa agtctgaaag aaacccagtc aaagtgtagt
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19741  ttaatttata gtattttata taaatatgca gataatttca tatttatata aatacacagg
19801  taccttagaa attaaacctc tgaccaaatt atgattaaca atttatttca aagaagagga
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20161  atagtacaaa tattgtacag cagtttattt actttgaacc tgaaaaaatt taattagatt
20221  tcaaaacctt ataaaaacct tattttatRt tctcgttaaa acacatattt cttggaaatg
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20401  atattattat atcagtctga tttaaagagc tgaaagaagg tgtttatgga gtaaactaca
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20641  aacaaaggaa atgtataaaa atgaaaaaac attttagctt tgttcctagc actgctatta
20701  actcaccgtg atattcatta aaccaaaagt caaatatatg aacagcaagg gccactgggc
20761  attgcaagtc tgaaatggtg tgctagaaag tgttttgaaa tttaaaggaa aagaaaaaaa
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21481  ttactgtgta aaacaataat agagatttta atgaacatca tcttaataag ttttctagtt
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21901  ttttatttct aattcaagga cctaacctca gcagattctg atttagttga tcacgagtag
21961  gttcttgtaa ttgtagtttg taaaatctcc ctgaaagtct ggtttgtaag ttattgctag
22021  aacatcaaat cccttgtata aattactaat gctagcaact ccaactaatg caaaaacctc
22081  ttaaggatta catatacagg aagatgagga aaacaaagag actaatattt gtgtgaattt
22141  tccttgcata gaatttcaaa agcctgtagt atttaggctg cagaattgca atggcctact
22201  ctagtttcac tttacctctt ttccgacctt agcaatattc ctcttactga aggaatgtat
22261  tctaagcaat tcaattggtt cagtcccttt cagttcagtt caattttatt cagttcaatt
22321  cattccaaaa caattaaatt tatgtctata cttataagga actgtggtgg gctatttcaa
22381  atgcaaagat gcctgcattc aagttactta ttgcctggga ggagggataa aagcattaat
22441  tctatattct ataataaatc ccttaataga agcagatgct gcatggatag caacttagag
22501  taggatttaa atgtgtttaa tttcttgcct attcttaaac tacatatatg tattgtatat
```

FIGURE 3-G

22561 atgtatatat atttatgtaa tgtatacatt gtattatata tagtatatat gcacacatat
22621 aaaattatag tataaactta ccaaatataa atatgtttag tcttcaaaat gaaatagtta
22681 ctaacagcca tcttcagtaa cattaaagga tgcagccctg atagatcatc tcaaggtgac
22741 tttgtaaatt agtacatgtc cagactctgt agaagaaatg agttttatat aataagtcaa
22801 agagagaata tatagtcttt aggggacccg aacataacta ttgtagttca ctaataggtt
22861 aactgttata tagctgcacc gagcatcatg ggcaatgaga gtttcagaaa gataatgatg
22921 gagttaattt gtgaaaactc tcatgtgata atatgcattt ctctctcgtt ctgatatgct
22981 taaggcctac acattttcca aatgccgtgt tacccttttac cataggccct atcatttatt
23041 ctctggctgt atatatgaac tagggaaata tgggtgataa ttttaggtaa ctatttgtgt
23101 actcagacct agacctcaac ctgggaaact ccggccagca gttaggaaat gataacacat
23161 ggtgagccaa cttaaacaaa tagactcaag acttgtaatc aaatccagta tattctatta
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23341 cccccggaca acacRgaggt gcttctaaca cctttgcatg tacaatttcc ttatgtaatt
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23581 aatgttctgt gaagttggta aagactcctc agaacagctg acattttgaa gcaggaatat
23641 gactttcctg gagataaagg caagaatact agagcaatca ctctccatat taccagacaa
23701 ggaagtacaa tttaggctta ctagtagcaa gaactcctaa aaatggcttt ctgtgaaaac
23761 aagtggtctt gaaattcata ataattatag tctactcttg ataatccatg ttgaagaagg
23821 ggagtacagt tgtaaggaaa acatgaagtt tttcacaaat tgtaattaaa atgtaaatct
23881 ttttgtatat acttagatac taaacttgaa ttctggttgg gaagggtata ttatttggat
23941 gccaataaaa tgagatataa atctatgagg acatatgttg aattggaagc actcaacttg
24001 ggtttattat taaaagtctg cctggcatta aggatgcact caaatattac ttgctataac
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24121 tgtgaccata caaactgcaa ctttctatta attcaccaaa tgaaatgtgt tgatccacta
24181 atggggttat gaatgaaagc tgagtttttt tttttttttt taccccaaca gcattatact
24241 aactcctagc actcctttaa attttatgca agatgttaaa gattatatat gtggaatttc
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25981 agtaggacac aaacctgatt ggctttcccc tcctcctgct gattatagag cccagagcct
26041 tgagtgaaca taggcggtag ccaggtagag gttatagtgg atcttgagtg agacccagtg
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26161 agctcaggac agagagaaag attttgttag tttgtgagaa agtaagggaa gagaacaaga
26221 gtctctgcct aaaaattcag agaattattc cagatcttat ccaagactat caaggtaata
26281 cctccacaag tctccaacag ttatagcatt aataggcttg gggtgcccct gaatacagat

FIGURE 3-H

```
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26461  aagatgaata tccacaaaca tcaaggcttt tcgggaaaac atgatgttgc caaatgaact
26521  aaataagaca cgagtgacca atcctgcaga gacagagata tttaattttt cagagaattt
26581  aaagtagctg ttttgaggaa actcaaagaa attcaagata acacagagaa ctcagaattc
26641  actcagagaa atttaacaaa gagattgaaa taatttttta aaaatcaagc agaaattatg
26701  gagtttagaa atgcaattgg catatattga agaatgcatg agagtcttaa tagcagaact
26761  ggtcaaacag aaaaaagaac taatgagctt aaagacaggc tatttgaaaa tacacagagg
26821  agacaaaaga ataaaaaaga atgaagcatg cctacatgat ctagaaaata gcctcaaaag
26881  gaaaaatctc ggagttaatg gccttaaaga ggaggtagag aaggagctag atagtgataa
26941  aatatccaaa gggatcataa cagagaactt cccaaatcta gagaaacaca tcaatgtcca
27001  aatacaagaa atctatagaa caccaagcag atttaaccca aagaagacta cctcaaggca
27061  tttaacaatc aaacacccaa agtcaaggat aaagaaaaaa atcctaaaag cagcaagaga
27121  aaggaaacaa ataacatata atggagctcc agtacattgg ctgaagactt ttcagtggaa
27181  accttacagg tcaggagaga gtggcataat atatttaaag ttctgaagaa aaaaaaactg
27241  ttaccgtagc atagtatatc tggtgaaaat attcttcaaa cttgaaggag aaatactttc
27301  tcagacacac taaggctgag gaatttcatc aacaccagac ctgtcctata ataactgcta
27361  aaggaagtac ttcaatccga aataaaaggg agttaacgag cagtaagaaa tcatctgaaa
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27601  agtgggggca caagttaagg tgtagagttt ttatttgttt tctctatgct tatttgttta
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27901  ctatttatca ataataatat tgaatgtaaa tgggataaac tttcaaatta aaagacatag
27961  actggctgaa tggatggaaa aaaagactca ataatctgtt gcctacaaga aacatacttt
28021  gtctataaag atacatatag gctgaaaata aagggatgaa aaaagatatt ctatgccaat
28081  ggaaaccaaa aaagagcatg agtagctata cttatatcag aaaaaaatag atttcaatac
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28201  gaggatataa caattctaaa tatatatgca cccaacactg gagcgctcag gtatataaaa
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29101  tatatgccaa taaattggaa aatatagaag aagtgaatca atttcaagac acatacaacc
29161  taccaaaatt taaccatgag gaaatccaaa acctaaacag acgaataaca agtaaagaga
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29461  gatgcaaaaa ccttcaataa aatacgagca atccaaattc aacaacacat tgaaaaggtc
29521  accatcatga ccaagtggga tttatcttag ggatgcaaga atggttcaac atatgcaaat
29581  caattaatgt actacattgt atcaaccaaa ttaagtacga aaatcacatg gacatttcaa
29641  ttggtgctga aaaaccattt gctaaaattc aacatctttt catgataaaa atcataaaac
29701  tggatatgga agaaacatac ttaaacacaa taaaatccat ctatgacaaa tccatagcta
29761  gtatcattgt aaatgatagg ctttcctcta agatgtggaa cacaaggatg cccatttttc
29821  accactgtta ttcaacatag cactggaact cctagctaga gcaatcagag aagagggaaa
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29941  cttatatttg gaaaaaccta aagactccac aagaaaacga cttgaattga taaatttagt
30001  aaagttgcag gatacaaaat gaacatacac aaaaatcagt agcatttctc tatgccaaca
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```

FIGURE 3-I

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FIGURE 3-J

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37441 gaagaactgc cctggagaaa ggaagaaact tataataaat gggaaattat aaatctagac
37501 caacccaaac ttgtactggt aattattcta attattctta tttccttaag tgtaatatgg
37561 ttcaattata gttactgata actaacaact cattggaata tgtgttaatt tgtatacgga
37621 agataaggca gcatgttttg tgaaagtctt tgaaaaacta tctgaactca aattattttt

FIGURE 3-K

37681 ttctgaagat ctttatagga aacaagaaat ttcttacaaa aatattattt tagttccttg
37741 gtataatgtt acagaaaaaa atttggaata ttgctgaatg tagggatttt agaattatat
37801 cttaagtatc tagtatttaa aaactaaaaa ccgtcttgca actagagatt gctataatta
37861 aaatgcaata aaatcaaatg aaataagtca aatatatttt tctatgtaaa tatattatcc
37921 aatatcgaat gggttcttca ttactacaat tcaatatgat tgcattttaa atataaacat
37981 ctgcatttta aacWcacaat cagtaattta aattaagtat tgtagaatct agaataaaaa
38041 acagttttga ttacttgtat gttatgatct gtgtctacat tttgcaaaac acaactatga
38101 atcaatctca tttgttcttc tttactagat gaatggaaga aaaaagtcag tgaatcatat
38161 gttatcacaa tagaaagatt agaagatgac ctgcagatca aggaaaaaga actgacagaa
38221 ctaaggaata tatttgggta aagttgtaag agtcattatt tctttgtata agtgtcttca
38281 gtattcacct taWtttttaa agtatctgta tatttttaa acccgtagaa cctcagacat
38341 aagcagtcat gttctaagcc ttaggatgtc agattatctc tctttgacca ctcatatagc
38401 tctcaaaatg caaacataac atctcacctc cttaaaatat aaattgtaat ctgccatcat
38461 taaagtttaa aaataaaaac ctaaaggcta gcctttgaat gcaagctatt gttgatctca
38521 gtaatcttct caggaattag atcattcttg taaaccatgc cggcaatgaa aagcaagatt
38581 tttcttccca catagtggtc gcatattggc cacattgttc tctttgaact atgacggtaa
38641 gtccaatttt aacaaaccct ctggtctctt gacattgaaa ggctgtccct taatggaact
38701 gagtatcatt ctgcccctga acaatcatat aacaacatat aatattgcct tcaggatttc
38761 agtagatttt gttccatgat aacaagagaa aaataatcta agtgtcacaa ccttggaaga
38821 cacaaaatgt tcagaaaaga ggagcaagac ccttatatac acaaaaagcc ttctggttaa
38881 attgaatctg acattgagaa actagatgcc cattagaggg tcaagaaagt tacctgcctg
38941 actaaggaaa agttccatat aggccaatta gccatgttca tttatagctg tgttatgtaa
39001 tgcactcatg gcaaagaact ccctctattt tacttagaaa acaagtgtaa agcaatgacc
39061 aaatgacaca tctttaaaat aaaattttag atatagtaaa catataaata tcacataatt
39121 ggcaaataaa atcacccatg tataatatag tttatatgaa attcgtcaat ggatgtaaca
39181 aggctttcac aagtgttcaa cttatggttc aaaaagtagt tggttctctt tatagtttgg
39241 cccaggatga tgaactcaac actgacactt gtgatgagat accactgatc tgacttttgc
39301 aagtagtatc acatgttgag atatggaact acatttgaaa ttcctgtaga aatatgactg
39361 gcatgttagt acagtagaat tataaatatg tatttgtttt gttggaaaag tatgaatata
39421 gaaattaatc ataaacatct agctcttatt gacttaaata aatatgctaa atgaaatatg
39481 attacattga agagattttc ctcaactttt aaaggtcaaa gcctcagtta tttagtatta
39541 ttttttaatt tagaaagtat tgagcacata ggtgaaggct agcttaaact agatgtatcc
39601 aaacctgaat attaggatta acaatggatt taaaatgtag gttctttctg ataccacatc
39661 gacaactaca agctgttttg acaactgcta taatggactt ttcctgtgtt tctactaaat
39721 gcaacaaatg tgaccttctt ttttctgatt agcattgggg gtgagatgca ggaatctgtg
39781 tcagggagct tacagtccag aatttgttga gtgccagctc gtattcaagt gttgttctgg
39841 atacatcaaa tacaagacat tatttaatct atagtcatat gtagattgtt gtcatttcat
39901 gtgtgccgaa taatattaac tccggtggat gataaactaa ggattagaga caaggcagtg
39961 ggagttgtca agtcacatgg tcagtaaatt ctggaatgtg atttgtgtca aggtctgcct
40021 gactccatag atagcgctct tcctaccata ccctgcttac aaaaacaaga tttaggtcct
40081 gatttattca ttgatttttg gaatcattgt agataaaaag catagttaag taaaggtgtg
40141 taggcaagaa tgaatgagta ccatagaaag tttaggaaaa gtgagaaaaa ataatgtctt
40201 caccatatta tctgacttga gtaagaaagc tatgtgaatc aatgtaagaa ttttggagtc
40261 atacaaacat ggttttaaat acagcttctt ctatttataa gctgtatatc catggatatg
40321 ttttttaatc tccttaatcc tcattttcat ctataaaatg aggtgaataa taatcacctc
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40441 gcattgagta gttggaaatt tctattatca tgattgattg gataaataag gacagtttga
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40561 tgaaagtttt tatgaagagg atgatttcaa aattaaaaat gtaaagtatt agcacaattt
40621 aggaagatgc cgaaatctga aatatagctt ttaatgattt tgattgaaag ggatttgaag
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40741 atggtgagac atttttggag agaaagacca atagcctgat gctgatgaca ttaaagaagc
40801 tacagaatgt gatgataagg aagctgagga gaggattatc cagtctagaa tgatgtttct
40861 gcaagaacta ggggcctctt atgttaatgg agatggagac tgtagtactt gctaaaattt
40921 tcgattccat gactccaccc tttatcatgt gaatcagaat ctctggagat gtcttccaat
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41041 aagtttgaaa actatacttc tagaaagata tccaaattgc actgagaact ctttgcctga
41101 ggtgatatta gtgaagggat gaggaatatg ggaacagaaa gtaagcaact ggtgtggtct
41161 aaagagagtc aagagaatca aaaacaagca agcaaaaaca gaataatctg cttttgtctg
41221 atttcgtcaa ggtagagagc ataatctggg agaaaaaagt gaattgcttc cagggcagag
41281 ttctaaggat tttcttttct ttggaataaa atgatggatg aaagaaagaa aagaatagtg
41341 tgctgagaat gtaaattgtc ttactcactc attcacaaaa ttttaaaggt agttgggaag
41401 atcaaaccta acactgtatg aaatgacatt taaatgagta tctagagcat tataggtgct

FIGURE 3-L

41461 aaataaatgt tagaatctca ttactcaccc ttattcattt gtcttataaa gagcattcct
41521 gtgataaaca attatgttat gttgcctgac atcagccttt ctctaaacat ttagatagca
41581 aggagactgt atacaatgcc caaaaaggaa catttaaact agcatgaaac gtaaaggatc
41641 actgatgtaa acagtttttc atttgctaac caatttcttt atggcattcc cggtagatgc
41701 taatttcatt cattataaga gatttttcac cacataatac accattgctc tatcagctcg
41761 aatacacaat cttcctggca tagcttttac ccacaacata ataaacagca atatagtgct
41821 aaatgtaaga cagaaagagc taaatagtta tcctgcttat gccaatttat agcagctttg
41881 gaatgggagc ttgatgtggg agagagggga aatggaaatg gaatgttctt tcatcttctg
41941 ctataaagtt gcattcactc ataactttgg acatttgttt aggtaatgga ttggtgacag
42001 gaagaaatga agaaaaagag aaggcaggag gagaaagaaa gacagaaagg gcaccttaga
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42181 ttcattaaag gcagcttttt ttcttattta gccttattta tatttgtact tatttgtaaa
42241 acaaactaat aacttagggc ttaccatatg ccagaaatgc ttctacgtat ctttttgtgc
42301 atcagcttat ataatcctaa tggtgtatat gtaaagtgct ttagcacagt gtctggcaca
42361 tggcaaaccc tcaaaaatgt tagttaacac ttaatcatta ttgtttatgt taacaaccct
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42961 cccacacccc acaacaggcc cccgtgtgtg atgttcccct tcctgtgtcc atgtactcaa
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44701 gtcaacaaca aaaaaaaccc tcaaatccaa aaggaaacaa agaattcata atgccctaag
44761 tcagtctatt tctctaattc ttttcttgtt tgtccaggta aaactagtta agaaccataa
44821 ttttacagga atatcttgtg aaatcattga gaagcaactt gacctcaatc tctctctgcc
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45001 catgattcct tctttcctat ccctgttttg aagagcaaaa caatacaaaa acagtaaaaa
45061 taatatcaat gccttaatag aaataactat tatagcagct aatatttata aaagctttac
45121 aagctctaac ttatttacac ttcacaacaa tcttataaga taacaataat tatgccaatt
45181 ttatcatatc tgtcactcta actataattg tttattgtat gaatggctga ataaatgaat

FIGURE 3-M

45241 atacttcaca gtattagttt gcagatttta tttgcaagat atcaaacaaa tatatttctg
45301 gatatttctt ggagatatat attagaaaca gatcttattg atatagtctg cttctattgt
45361 ttggagggca tggggcaggg aagaatctgc aatgaatagg caagaagttg caactagcca
45421 tttgaaactt aaatgatcaa tttgggaaac tagacaaccc ataaaaaatc cttaccttct
45481 ttctacattc ttggcttttc cctaagtttt aaccaatgaa ttagctttaa aatatatcta
45541 cctgtctgaa taccttggag agcagtgtgt tactttttgg ccaactgttc aaatgttaca
45601 ttttaataag ttcccacttg tggtcatgtt agatatcttc ttgaaaggat gaggtcatga
45661 aaaagaagtt taattggatc acaaaactgc acacttttct aggtMaaagg taaaggctag
45721 gaaaagaatt cattatgcta caagaaagaa agtaaccttt gggtacagaa ctatcatttt
45781 taatgattaa gaacagcatt tactattaga aatatattca taatagtggc tttattttaa
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45901 agtgtggcat ggcaggtgat gaaaaatgta aggggaaatt aaaaaataaa ttgagcttag
45961 ggtattagaa tacataagtg atgctcaatt ggcagtgaat ttgacataca cagttacttt
46021 agaagaggca aaagaagaga aaatggaatt tctctcctag gaatgattgc ttaaatatct
46081 tgaatatttt aattacatgt ttcaaaacag aaacgtttga ctagaagtta atgggaagtg
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46561 tcttgtattt tctgtttatt ccatgttcat ttgttttgca aagctgatca gagtattaga
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46741 caacctgaag tgagccttaa gagcagaagt gaggcgtata gtaggtgttt agYaggtgtt
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48361 ctttgtggtt atgacttcaa atagtagagg tattcagcgg agctgaactc tgcctttcaa
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48901 tgaaagcctc attcttatag ttataccagg attcaaatcc tatcatgact ctgcctttta
48961 agtagtttgt tctttttttc caacttgggc aagttattta acctatttaa gcttcaattt

FIGURE 3-N

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49021  cttcaattat aaaatgagta aaataatata tgtgacaata tgcatgactt tgtcctgttg
49081  tgtccggaat tggtgggttc ttggtctcac tgacttcaag aatgaagccg cggaccctcg
49141  cagtgagtgt tcagttctta aagatggtgt gtccggggtt tgttccttct gatgtttgga
49201  cgtgttccga gtttcttcct tctggtgggt ttgtggtctg ctggcttcag gagtgaagcc
49261  gccgaccttc gcagtgagtg ttacagctct taccgcggcg catctggagt tgtttgttcc
49321  tcccgtccgg agttgttcat tcctcccagt gggtttgtga tcttgctggc ttcaggagtg
49381  aagctgcagg ccttcatggt gagtgttaca gctYataaag gcagtgcgga cccaaagagt
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49501  gacacaagca agttgccgat ggtggctggg gcagcctgct tttattccct tatttggccc
49561  cacccacatc ctgctgattg gtccgtttta cagagagctg attggtccgt tttgacaggg
49621  tactgattgg tgcatttaca atccctgagc tagacacaga gtgctgattg gtgcatttac
49681  aatcctctag ctagacataa aagttctcca agtccccacc agattagcta gatacagagt
49741  gctgattggt gcatccacaa accccaagac agacacagag tgctgattgg tgcatttaca
49801  atcctccagc tagacataaa agttctccaa gtccccaccc aactcaggag cccagctgac
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50461  gcgagggctg ctagcacgtt gtcacctctc actgtggtga ggaataagta agattaagcg
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50581  cattgccaac ttcactgtga atatacaact ttctttttga agtataactc ttgggataat
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51061  aattttctga tttctgattt cctgatttac ataataatca attttatata tgtattatgt
51121  aagtattccc tactaacagt gactctcagg ttcctagatg atgtctgacc ttggttttac
51181  ttgtctttaa aaagtgccac taaattcgct attgtgacat ctagtagctg tcagtgattc
51241  tggagcaact attggaatca tagtgttatt tctggtgaca tcattacaat gtaaaactac
51301  agaatttcct ctcaatttta attcttcata tagagggttc aagattcttt ctgtaagtgc
51361  aaaataatct tagaaaaaat acatttctga attgatagta acaggatttg catttataat
51421  tttcaaatga aagacaatat gctaaaagat gaattttgtg atcatctgta acatgttttt
51481  ttcagctctg atgaagcctt cagtaaagtc aatttaaatt accgcactga aaatgggctg
51541  tctctacttc atttatgttg catttgtgga ggtgagtact tgaaacttag tacttcttaa
51601  actggttata tgtgtatatc gtcagtgact tgagctgctt aatagtctgc aaaagaattc
51661  tattcatact caattttccc ttctgctttg ccttttccaa ccttgataat ctcagtttag
51721  gcagtaacta tcaggcagaa tattccaatt gatttagctt taaatataag cttcattgtg
51781  ttgctaccgg aaaccaagtc cctcagtttg cttggaaatc aaaaagcact tttcaatatt
51841  gggcatgcca gtcagggatt aacttaaatt cagaagcact taaagattcc ccaaaatatc
51901  atcaagcagt tgcttcacaa tattcaacaa gagtatgtgg aaaagtgata aatgccaaag
51961  ataagatcta aaagtgaaga ttgatcgaag tgaagattaa gagtttaatt tggcctacac
52021  tttagtttgt tttgtttatc aatgtatctc aagtaatttg aatggtgcct ggcctgtaat
52081  agccactcag taaagttatt gaattaatga atgaaccatt aatatttatt ttgttaatcc
52141  aaactaaatt cattgagctt aacttcttaa aatggaacag aaatgtgtaa gtgtcaactc
52201  taaccatatt ccttaaccat ttctcccaaa caaaccaaac agactctgct taacagattg
52261  ttctctcaac ttcaaacgtg ccttcccaac cttggttata tccttcatat ttctttgatc
52321  taaataagct ctactgttaa taatgttcag ataaatcctc tacaattaga ttttttaatt
52381  taagcttttt cactaatagt ttattatggt gaattctctt atgtgtttat gtttcaaaac
52441  catctgatga tgagggtact aaataaaaaa tctaagacag agtcaaaata cacagcattt
52501  gaataaagtt ttataaatgg aaaagaaata tcccctagta agtaaggttg tcaattaata
52561  gaaaacttta caaatggcct gcagaacgca gcttgacatt tttatacagc tgtatggcat
52621  ttatcattag gtcaaaaaga gtctcaaact caccccatcc ccacaatgat ttagcctttt
52681  ttcatttttc tctttaaggc aagaaatcac atattcgaac tcttatgttg aaagggctcc
52741  gcccatctcg actgacaaga aatggattta cagccttgca tttagcagtt tacaaggtag
```

FIGURE 3-O

52801 gacactttaa ttcccataaa cactgcattg gaactaagga tagtgtgtat ctttaggctt
52861 tttttttttt ttttcaaatt agtaatcatg gaaaattttc agtgaccaga ggcgttacat
52921 tactaaagga cttctttctc tttattgagc agatacctgc tgcatactag acacatactc
52981 tttttaatgc tttctgtatt taactcattt aattctcaca agaaccccat gagtgaatat
53041 gattattatc cccaaggtta catggttagc caggggttag ccaggattta agacaaggca
53101 gtctagttct gttgccaaag ctcctcatca gaacaccatg atgcctctgt gcagagagag
53161 atgaggttgt atttaaagac aaaagaagca cactgaagct gtatttcttt actgcaaatt
53221 tttcttaaaa aacctttttg ctttagctgt ttattttctt atattagccc ctggctccaa
53281 cctaatctca gcacctgata gaataataaa tataatagtg gattggacaa actgggatac
53341 ttagtgttgg aattgaacct tgagattttc ataaatataa atttataaaa catacaaatt
53401 atattatgca ttgatcattt tataattata ataacaattt ctactttgta tttattatga
53461 gctaaatatc atactaagtt taatgtattt tagtcattaa aataactgca tattaggatt
53521 tactttacag aaaatgcaat taaagactaa agtagatacc tggacaatat tagaatagtg
53581 attaaagtca agtacagttg gctcattact cccagaatct tatttgtata ttgcgtattt
53641 tgttctttct cattttcaag cgagtctgtg acagaatttt atttcagttt tgtgtgtgca
53701 cgtgtgggag gagggacaac tttttgcttg tattaggaac cccctgcact atctccctcc
53761 cccaactgct agagagtttg tcattgggag ggaagaggac cttattttcc catgatctag
53821 catcacaaat tcctgtaatt catagcgcaa atactctaaa gtttcatctc ttttcatgcc
53881 cagtcaatgc ctagtcaatt cttctaattc cttctgggag aaagcctcag ttaagtgcta
53941 aattgtcttt agtacctgtt aattatcctg ctaaactatg aaacattctg agtttccagt
54001 gtagaaaaca gcatctgatg ttgacttttc ttctgaaagg caggaggtga aagtagaaga
54061 gctccaagga acaggaaggt agtgaatgat agtcatggca ctgtatgaaa ccatgaattc
54121 tgaacctcac cgtctgggag atttttctg tattagttca ttttgcaaag atttagcatg
54181 acattggcac acaaatgggt tctgaatcat ttagtcctac aatatttaga gaatatattt
54241 cttcaacctc tgtttataat aattaaattt ccacttttag agttttcttt gctctatttt
54301 tatgtttttt tctattttag agaagggtgc ataaactata actttttcat agcaagttta
54361 aatgaaaatt tagattcttg ggaaacaaag caggcaaaaa tattaaaagg ccataagaaa
54421 atgcatagtt attttgcaaa tttcttaaca aaagtgaaaa acaaattaaa gttactattt
54481 cattttaaac acaaaaataa tataaagtag ttgtgtgtcc agaattggtg gattcttggt
54541 ctcactcact tcaagaatga agccagggac cctcgcggtg agtattacag ttcttaaagg
54601 cggcatgtcc agagtttgtt ccttctgatg tttggatgtg tttggagttt cttctttctg
54661 gtgggttcgt ggtctcgctg gctatggagt gaagctgcag accctcgcag tgagtgttac
54721 agctcttaag gcggcacgtc tggagttgtt cattcctccc cgtgggttcg tggtctcgct
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54841 ggacccaaag agtgagcagt agcaagattt attgcaaaga gctgaacaac aaagcttcca
54901 aagtgtggag gggcacccga gtgggttgcc actgcttgtt caggcagcct gcttttattc
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55081 ccctgagcta gacacaaaag ttctccacat ccccactaga ttagctagat acagagtgcc
55141 aattggtgca tccacaaacc ctgagctaga cacagggtgc tgatggtgtg tttacaaacg
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55381 ggcagtcaat gggatggggc actgtggagc agggggcagc acgctttggg taagctcggc
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55621 ccctcactgc ccggagccgg caggactggc cggccgctcg gagtgcgggc ccgccaagcc
55681 cacgcccacg cccacccaga actctagctg ggccgcaagc cccgccgtgc ggccccagtt
55741 cctgcccgtg cctctccctc cacacctccc cgcaggccga gggagccagc tccagcctcg
55801 gccatcccag gaaggggctc ccacagtgca gcagcgggct gaagggctcc tcaagtgcag
55861 ccagagtggg cgccaaggcc gagaaggcac caagagcgag cgagggctgc aagagctgcc
55921 agcacgctgt cacctcttag ttgttcacac taccaggcat taaacctagt aaccattaaa
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56101 ttcaaactta caaagacaat tgcaagaata gtacaagaaa ctgcttatcc aggttcatta
56161 actgtttgca ttttgtccca tttccattat tttttttWag aaccatttga cagtaaattg
56221 tataaaacat gccctgttgc cacttcagtc ttcatttcct aagaacaaga aaattcactt
56281 acataactcc aatgcaatta taaaattaaa aagaacattg agatgatatt aacattgata
56341 agatatgata atctatagtt caaattcaag ttttatcaat tgtcccaatt gtgtcattta
56401 tagattatat tttcttgtcc aggataggat tcaatccaca atcatgcatt ttcagttttc
56461 ttatttctgt aatctccctt actctgaaag aatttctcac ccgatccttg tatttttta
56521 tcttaatatt tttcatgcat accagttatt tatacatatt tctttgaatt tttttggtat

FIGURE 3-P

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56581  tgcaatcgaa ttttattttg ttcataacac tcacaaaatg aataatgtaa ctctcccatc
56641  cttttgttca ctacatcaaa tagctctttc aattatacac cctggcatgc tgggcctgac
56701  tcattgttag aggaaagggg tcccgatcca ggcctcagga gagggttctt ggatctcgcg
56761  caagaaagaa ttcagggcga gtccacagtg caaagtaaaa gcaagtttat tatgaaagta
56821  aagtggtgaa aggacagcta ctccatagac agggtaggat gttcctgaaa gtaagaggag
56881  gagcacatcc accctaggta caatgctcat atacatgggg agatgtgttc tgctgcaagg
56941  gtttgtgata acatattaat tttcttaatt gctatatttt gcaagaatcg atattattat
57001  ctttaaagca aaattaggaa tgcctttgtt ctacagatat caggatatct ggacactccc
57061  aagtctgggt ctgttcagta aacattatga acttgttctt taactgtaaa catctagagg
57121  ttaaaaatgc ctaacttttg ggaggccgag gcgggcggat cacgaggtca ggagatcgag
57181  accatcccgg ctaaaatggt gaaaccccgt ctctactaaa aatacaaaaa attagccggg
57241  cgtagtggcg ggcgcctgta gtcccagcta cttgggaggc tgaggcggga gaatggcgtg
57301  aacccgggag gcggagcttg cagtgagccg agatcccgcc actgcactcc agcctgggcg
57361  acagagcgag actccgtctc aaaaaaaaaa aaaaaaaaaa tgcctaactt tctgagaatg
57421  taaccccgta agtctcagcc tcattttcct attttcctag ccctcactca aaatggagtt
57481  gttcactctg gttcgaacgc ctctgacatc atgactgtat attttctaat caatagagta
57541  atctctgctt tcattaataa aagtgaagca gatatttagc tatttaatac cacatgaatg
57601  attaatcctc atacatcttt ttgttttagt ttgttgagtt tttcacagtg tttagtttta
57661  ttgaggttta atatatacca aatacaatta tcaattttaa gtctacaatt gttagctttt
57721  gaaaatgtat gtaatcatgt aaccatcatc acagtcatgt tataggacat ttctactata
57781  ccaaaaagtt ccctcatgcc attttgcagt cagtctcctt ctcacctggt ctctggaaac
57841  aagtgttttc tgtcactata gttttctctt ttctagaatt ttaaataaat ttattacatc
57901  cagtatgttt tcttttctat atggtttctt gcacttatca taaggctatt gggattcacc
57961  catgttgtat attctgtaat taatgctttt cttgtagaat tgtattccct tatatggata
58021  taccacaatt taccatttac ctgctgatgg acattttccc agattttgac cattataaac
58081  aaagctgttc tgaacactca catacaggta tttgtttgaa catatgtttt tatttctcct
58141  gggaaatacc taaaagtgga attgctgagt cacataataa gtatatgctt aattttatga
58201  gaaactaaca aactttttaa caaactagca attccttcct acattcccat cagcaaggta
58261  tgagagctgt agtttttca catcctttcc ggcacttggt gtggtcagtc tttttttttt
58321  tttttttttt tttttttttt tttggctatt ctattggatg aattttagta tttcattata
58381  attttaattt gcatttccct gaagactaaa gaggttgaat aggtttttat gtgcttatta
58441  ggcatccttt atttttaat gtagtgtctg ttaaatcttt ttgccatttg taattttgtt
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59221  gttgtttact tttccgttct aggattttta tttattaaga ttaattaaga tataatttca
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59641  ttgttaggct gaaggtattt cagtttgaac ttagcctctt ggcttacctc tttttttttt
59701  tttttttttt tttgaggcgg agtctcgctc tgtcacccag gctggagtgc agtggtgcga
59761  tcttggctca ctgcaagctc cgcctcccgg ttcaagccat tcttctgcct cagcctccgg
59821  agtagctggg gctacaggcg cccgccacca cgcccggcta atttttttgta tttttagtag
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60181  ccttttagca ataaatcagg tgatcttttc tagatcttcc agaatctttc tctgtgcttg
60241  tgcagcccag ctcaacaata cataatggat ctccatgcag atttctgcag tgccctctct
60301  gtgcagcttc ttcttctcgg ttaccctgct ccacaaatac agccccttca taatatcaga
```

FIGURE 3-Q

60361 actctcattt acactcttaa ctcagtgaga cttcctatta tgctttgtgg cagaaaagta
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60481 ttaaaggaca cagctgtttg ctcatgctct tcagtgcttg agaacagtta tgtcatatat
60541 tttgttccat tttgtagatt ttatttgcca gtagagaaag tctatataag ttgttctgtc
60601 atgcccatat ctacttttgc attgcttcca aaatgatcWg aatgaaacaa aaatctatga
60661 tatcattgct cactttaaca cttactattg tcatccattg cctatataat gacattcaaa
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60901 attggtacat ctagggtatt ctaggaatct aaatttttaa caaacaacct aggaattttg
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61861 agaaataatg ttttactagc taactaggca tcccttaacc cagtcaagtt ggcacctaaa
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62761 attctaaaga gatgagaaaa ggtaatccta acaatataaa agaaatggca tctatactta
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63061 aggaaattga tttatatgaa gctcagattg gtagaaaaaa gtaccagctt tttctttgct
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63421 agtgtaaatt tacatgttaa acatgaatga aacttcattt atctttatat ataaatgtat
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63541 catttatatc cctctatagg gcatacttct ttaggtggta tctaaattgt attcctaaaa
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63661 tgagaaagct aatgaacaaa atcctattag accatctaat ttagccttac atgtaactct
63721 cattcaatac acagacaagc cacttagtga aatttcttta gtgagaaaga agtagcattt
63781 tgattcatta acttattttt aacatttcgt atgataaaag cagatattga atggtaatgg
63841 tcatttatcc catcctatat atttcttgca agatttaatt cctatcattc agaaacaact
63901 cattttatat atgtattaca aaagggaagg acatgaatgg gggaaaaatc gaattaaacc
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64021 actctgactt ttctatcagt ggcgattcgt agcctgaatc attgtattaa tatcttttat
64081 cctgactttt tttttcctcc ttagcacata tatttgattg caaagttgaa attttcaact

FIGURE 3-R

64141 atcctgaaac taaagaccca aagtaagtgt ttcatagttt ctaactgctg tcgatttaga
64201 ccaaggttca acagccttgg cactactgac aatttggatt ggataattct ttgctgtggg
64261 aggctgtcct ttgtgttata aaaatgttta gcagcatccc tgtcctctgt tctctagatg
64321 agagcagcca cttccctcat gcccagttgt gagtaccaat aatatctcca gatatcaccc
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64741 ccctttagta atgaaatatt tcataatctc tttctaaatg aacacattct caataaaaag
64801 ttaataggat cctagctgaa gatggtaatt tgcaatttat gcttcaattc ttacaccaga
64861 cagtagtatt tcctggaaaa ccttccctga tccctcccaa gtttgggtta ggtattgctt
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64981 ttagttaaat ctttatatct tcctctatat tagcggtcac aatctcacat attttaagga
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65101 tttttgagat atgagagagt ggcaaagact gtggtaactt agaaaacata tgccccatgt
65161 aaagggaatg gtcactcttc agcttcagct aatcattgtc atgtaaaaat gtagacccat
65221 tatttcccaa aatttcagag aatcataaat tatgtgaagt ttcctaatat ttaaatgctg
65281 gccattaatg cagattttta gtcataaata ctcaacaggc taagccatat atatttccat
65341 tcctcttgta gcctgtttgt aatctctgat agtaattatg agcatcatca aggcagagac
65401 cagatccaag ttgcttatca tcttattctg agtgcttaga acaacgcttg atatatatac
65461 ttaataaatt gatgttttat aagtgaagaa tgaagttata gttctctggt aactgggggg
65521 aagaaaagtg tttcaaagga ggtaggatga ggttgacagt gggcaaaatg gtcctatttg
65581 ggccattaga ataggaaatt aggaaattgt cagatacctc tttaagggat attttagtaa
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67621 taatatatga aaaaaggaaa ttacctatat gtagaattag atcaatagtg tacataataa
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FIGURE 3-S

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68641 ttttctatac tgaaatagag ttgaaatttt tttgtttaat aaataaattt taaaaatgga
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68761 tccatagcaa taatcacaga gctaacaata aggcaggata ttaagtaagc attgttttag
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71581 ataagaagaa atgtgagaag tataagtcag ttaaaaccag tagaattctg aaactgagct
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FIGURE 3-T

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75301 tagtgagatt cattgtaaat ataggtgagt ttgtgttact tatgaggaaa ggggaaattc
75361 cattagattc acctaaatat aaatgttttc caaaaaagaa agaaagaaac tgaggccagt
75421 gataaagtaa atgagtggta aacattaagg gatctgggtg aaataattta tgagttagac

FIGURE 3-U

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75601 aagcaaagtg gttaagagct tagtttcttc atctcctatt caaatagctc tgttttcttt
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78721 atgctaagtc tgacaggact ctttgtctcc acatatcaaa ttcagacctt ccattagtgt
78781 ctcaagtgtg tttgtcctcc cataattgtg aattctatta aacaatctta caataaaatt
78841 tacattgact aggcagctgt cttcttcaat aatagaagag aacatgtgct gcagattcct
78901 agacatgctg actacaattt gggactcaga tttaaattta ctgtgctttg aagagtaggc
78961 aaatattagt tgtcccaggt ctcaatactt ctctttgact gatacatcca tctatcaata
79021 catttgcata tgcttctttg tacaaggcct aagatcctgt cagcaatcaa taaacatgca
79081 ttaaatcctc tttttccctt taggtttggg gaatgtgagt catacgcttt cccaggcatg
79141 gaaaaggaaa aatattagct aacatttggt ggtactttat cattcacata catttgtcat
79201 ttggttgttt tgtgagataa ctactgtcag actcagttta ttagtgagga aactgaggac

FIGURE 3-V

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79261  tggagaagct gaatgacatc tacatgggca ttcagatgat aaataaataa gctggatggg
79321  actccaacct ggggatctac cttcacatct gtagtcttat acataaaaga gcgattRctc
79381  cccagagact cttctgttta ttgctataac acagcttata cccacaagac acaaaaaaag
79441  tatttggaaa gtgaaaaaag aaacggaata tgttactata taaagcccaa gcattactac
79501  atatacgatt aaagcaacat taaatgactc aaaactaatt tcataatgca ttcactatat
79561  gggcataacc tatggaagta taatgtaggt atatgagcac acaacacaca cacacctcaa
79621  gtgtaaaaca ctttatactt aaataactcc ttaaaaagtt gttactctgg tgttacgtgc
79681  tgtagtttct gcagttgcca taagtcaaat cagttttctg cagccgttga caactgtttg
79741  agcagtgaac agaaaggcat gcagcaaaca tgtaaaccaa tgtgtaatgt atagaggttg
79801  tggagtggtt ttcttattac agaaaagtgt actttcatat acaccttgtg aaggtgagcg
79861  tattattcat agttgaagtt attctatcct accatatccc attttcaaat tgtaaacact
79921  tattcaatca ctgcttcaga aatgcttccc agttattttg gaacttattt ctgatttcaa
79981  ggtaatgcac tcagtattgt ttcagttcat tctttactaa atcatccaaa tgtttcagta
80041  gagaattttg tttaccaaga agcctcRgac cctgtgtaag ttatttttta ataatcgctt
80101  tagtttcctc tccaaaggca caaatgacag aatgcttaga attataaaat atggtttctc
80161  tctctctctt atttttaatt ttttagagag agggtagtca tgagtttttt acctaaacag
80221  tagcaagtct gccccaatct tgtgaatagg caatagtccc ttgtgaactc catttggaat
80281  cagaacaaat aatgaaacaa aataatagtt aatgctttga atagataact ttgtactgaa
80341  catattaatt gacttgatcc tcagttgaga gctctctcac tcactgtgct gtactgcttc
80401  tctcctgatc caaacagtaa cctctcagct cacctgacca gaatttaagc tttggacatg
80461  atacacagaa gcttagaata tgtcaggaaa acatgccata tctgcagatc tgaacccccct
80521  caaagactta gcacattaag atattctggt gccttttgt atggtcccca ttcttttggg
80581  ctgtataatt tttctctaaa atttctgcat tacattttaa tagctttgtt gagataaaat
80641  tcatatacca tataattcat ccatttaaaa tgtacacttc aatggttttt agtatagttg
80701  cagagttgtg taatcatcac caaaatctaa ttttagaata tttttgtcac ccaaaaagga
80761  aacttaatac ccattaagta gtcagtccca cccagccctc actgccaaga caaccatgaa
80821  tctactttcc atccctacag attggctatt ccagacattt tatataattg gaattatgta
80881  atgtggtctt tttgtgactg gcttctttta ttttgtgtaa agttttcaag gttcattcat
80941  tttcagtaag gttgatttct atcaaaatta tgttataatt acatatgact ttatttagca
81001  aaacagaaaa agatacagat tcaactgata gtgtaaatgc aatttctttc tactacctgt
81061  ctattttcat tataaatcaa tgctggaagg aaatcttcaa ctaaaacttc aagtccccaa
81121  actacacttc tagtcacaaa aatgtgccta aattatcaga ctaggaacac ccccatgaga
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81481  ctacctcaga cctgcctata attagcattt taagatttcc agatgattca tatgcatatt
81541  caaatttaag aaccctcccc taaagagtat tagaagaaat tagatttaaa agagatatct
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81841  ctaagatata aaatttcata gtagtagtat taaaataaga agaaagttat aatgcaatgg
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82561  aagtgattgt cagactttgc attggaactc aatgatggcc tatcatagtg aaaaacaata
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```

FIGURE 3-W

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83761 tataaaacat attaaaaatc aagaaacatt ggttcttgat atttaagttt aaatcattaa
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FIGURE 3-X

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FIGURE 3-Y

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92221 ttttgccatt ctatatttct tttttttttt tcaagagagc aagtctaagt cctccctgga
92281 gaattgttga aataatgcct aatttaggta actaagcatt ttaagccttt ctacactttt
92341 ataatatttg taattgaaaa aaacccagca ccaatatata aataattaat ttacctttga
92401 aatactgctg tcagaattat gatgcaaact ctgcatcaca tttttgcata ccttttaacc
92461 caggaaattc acttctagaa atttatttta cgaaaataat aagagattga attgcatggg
92521 tgttcatgca aaataaaaaa gtaaaatgct ctaaatgccc agcattaaat attgattaaa
92581 tcaaaacagt gcatggatat ggtgggacac tatgctatca ttaaacatga cattgtacaa
92641 gattatacat tgacatgaaa agacacatat aaagactttg tgaaacatgt ataatgttat
92701 ttaagctttg ttgtgacact caagtttttt ctttcttttt agtttttctt attactagaa
92761 tgaatgcatt ttcttaaata ttcaccttta cagaagtgac tacacaatta atggctacac
92821 acctctcccc acttatttct gcccaaagac aactactgtt gacattttgg tggatattct
92881 cctaggttgt ttcatgtatg tctttttcaa atgtaggatc acactaaatg cttctgaagc
92941 atacttttct tatttaaaaa atacagcaga cagcttctaa gtgtgcacca tgttcttttg
93001 taaacatatg tattttaaat atatgcacac acataaagag agagaaagag gctgtttaag
93061 gagtaattgt taagtggata tgcatgcaac gaccaccagt ttaagaagta atttctagtt
93121 ccccggagaa tcttcatgag aacttctgat ttcatatctg tctccttctt ctagagtaat
93181 ccctctctct ctatggtaac tattcctttg ctttcctaga tattaagtat atgtaaatgt
93241 atgtgtaact ctgtgaatat gtatctctgt ataaaatcat taattaaata tttttaattt
93301 tttctgttct tgaactttat gtaaatgaaa tcaaaggcat atttttgtga ctttattatt
93361 tattgtgact tctttgtgag tgatcactta tgacatttta acaatttttt tatgcatgtg
93421 gctgttacat agccacataa tatatgttta cataggtctt atgtacaagg gaaggttcta
93481 agcacattat acagattatc ttgttttatg tcgggaatag gtatcattat tcgtttcatt
93541 ttacagattg ggaaactgag ttccagaaag gttaaataac ttaatgtagg tcacacagct
93601 agtaagtggt gtagattata ttctatccta agttgactga cttcatagtc tgtgatctta
93661 accatagttc caacctgctt tctgttacag atgagtatgc tacagatgcc ttctgcttat
93721 ttagggttaa tgctttcata tattaagaat cccccaagac tcaatttcat aaagatattt
93781 taaattatta tcttaaggtt tgatggtttg ccttcagtat ttaagtgctt tacctaccta
93841 atattgattc cagtctatgg tacaaagcat gggtttaact taattttttg acatgttcaa
93901 ttgtctcaac accttttatt aaaaagctta tattttcctt attaataata tacaatacta
93961 attctgtcat atatcaagtg tccatttaat tgcaaatctg tttctagatc tctgttctgt
94021 tcatttatct acttatctag tcatgcaaca tcctatataa agttgttcag aatagtctct
94081 taataatttt aattttctac caatagtggc atattctttt ttattcctga tactgattat
94141 tttggtctct ctttttgtcg gtcttatcag aaatcagaag tttagcaatt ttgtgtcttt
94201 gcaaagaacc aacttctggc tttgttgaat ttctctagta ttatatgttt gtctttttt
94261 taatcaattt ctgcttttat ctttcttaac ttcatataat ttcactactg tttttctaat
94321 ttcttaagat ggatgcatag cttagcttat taatatttag cctttttttt ctaacagcat

FIGURE 3-Z

94381 tttaggctac acatttgtaa gttctgtttt tggcacattt aagttgtaat atattttgtt
94441 actgttcagt ttaaaacatt tttccttcta ctagaaattc tttttggacc cataaattat
94501 ttagaagtag gtttccaact ttacaaactt agtgttttta aattaccttg atattgattt
94561 ttaagttagt tgtactgtaa gcaaagaact tcgtcattag ttttccagta tttgaaatgc
94621 attgagtgct gctgtaaggg ccaatattta gtcaattttg tgaatgttcc ctttattctt
94681 gaagtgaata tgcattctgc agttgtttgc tacacagctt ataggtacaa atttgatcaa
94741 ggtcttaatt gtgtccttca tgtctttcat atctttattg tttcttgttg gctttatcaa
94801 ttttgtgtta aaaatttttc accatgattg tagatcttgc tgtttattgt tgtagttcta
94861 taaggttttg cctaatatat tttgatgYta tgtgttattg atataaaatt taacatggtt
94921 tatagtttcc cagggtgaat taatgaatac attacaatag attgaacttc tctatctcta
94981 gcaatggttt actttaccca

FIGURE 4A

>gi|32528262|ref|NM_003674.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 1, mRNA

GTCTGCGCCTGCGCGCAAGAGAGGCGGGGCCAGCGCTCGGCATGGCGGAGCCAGATCTGGAGTGCGAGCAGATCCG
TCTGAAGTGTATTCGTAAGGAGGGCTTCTTCACGGTGCCTCCGGAACACAGGGTGAGCCACCGCCCCCAGCCTGGC
CTGGCATTTCTTTGAGTTCAGGAAGTGTGACAAGGATTTGGACACCCAGAAATAAGCGTGTCGAGAAGAGCACAAG
CAGAGGATCTGGGACGATGCCGGAGTGTGAAGGAGTTTGAGAAGCTGAACCGCATTGGAGAGGGTACCTACGGCAT
TGTGTATCGGGCCCGGGACACCCAGACAGATGAGATTGTCGCACTGAAGAAGGTGCGGATGGACAAGGAGAAGGAT
GGCATCCCCATCAGCAGCTTGCGGGAGATCACGCTGCTGCTCCGCCTGCGTCATCCGAACATCGTGGAGCTGAAGG
AGGTGGTTGTGGGGAACCACCTGGAGAGCATCTTCCTGGTGATGGGTTACTGTGAGCAGGACCTGGCCAGCCTCCT
GGAGAATATGCCAACACCCTTCTCGGAGGCTCAGGTCAAGTGCATCGTGCTGCAGGTGCTCCGGGGCCTCCAGTAT
CTGCACAGGAACTTCATTATCCACAGGGACCTGAAGGTTTCCAACTTGCTCATGACCGACAAGGGTTGTGTGAAGA
CAGCGGATTTCGGCCTGGCCCGGGCCTATGGTGTCCCAGTAAAGCCAATGACCCCCAAGGTGGTCACTCTCTGGTA
CCGAGCCCCTGAACTGCTGTTGGGAACCACCACGCAGACCACCAGCATCGACATGTGGGCTGTGGGCTGCATACTG
GCCGAGCTGCTGGCGCACAGGCCTCTTCTCCCCGGCACTTCCGAGATCCACCAGATCGACTTGATCGTGCAGCTGC
TGGGCACGCCCAGTGAGAACATCTGGCCGGGCTTTTCCAAGCTGCCACTGGTCGGCCAGTACAGCCTCCGGAAGCA
GCCCTACAACAACCTGAAGCACAAGTTCCCATGGCTGTCGGAGGCCGGGCTGCGCCTGCTGCACTTCCTGTTCATG
TACGACCCTAAGAAAAGGGCGACGGCCGGGGACTGCCTGGAGAGCTCCTATTTCAAGGAGAAGCCCCTACCCTGTG
AGCCGGAGCTCATGCCGACCTTTCCCCACCACCGCAACAAGCGGGCCGCCCCAGCCACCTCCGAGGGCCAGAGCAA
GCGCTGTAAACCCTGACGGTGGGCCTGGCACACGCCTGTATTCCCACACCAGGTCTTCCGATCAGTGGTGTCTGTG
AAGGGTGCCGCGAGCCAGGCTGACCAGGCGCCCGGGATCCAGCTCATCCCCTTGGCTGGGAACATCCTCCACTGAC
TTCCTCCCACTGTCTGCCCTGAACCCACTGCTGCCCCCAGAAAAAGGCCGGGTGACACCGGGGGGCTCCCAGCCCG
TGCACCCTGGAAGGGCAGGTCTGGCGGCTCCATCCGTGGCTGCAGGGGTCTCATGTGGTCCTCCTCGCTATGTTGG
AAATGTGCAACCACTGCTTCTTGGGAGGAGTGGTGGGTGCAGTCCCCCCGCTGTCTTTGAGTTGTGGTGGACGCTG
GCCTGGGATGAGAGGGCCCAGAAGACCTTCGTATCCCCTCTCAGTCGCCCGGGGCTGTCCCGTGCATGGGTTGGCT
GTGGGGACCCCAGGTGGGCCTGGCAGGACTCCAGATGAGGACAAGAGGGACAAGGTATGGGGTGGGAGCCACAATT
GAGGATACCCCGAGACTACCAGGAGAGCCCTGGGCTGGAGGCTGAGCTGCATCCCTGCTCCCCACATGGAGGACCC
AACAGGAGGCCGTGGCTCTGATGCTGAGCGAAGCTATAGGCTCTTGTTGGATAAAAGCTTTTTTAACAGAAAAAAA
AAAAAAAAAAAAA

FIGURE 4B

>gi|32528264|ref|NM_052987.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 2, mRNA

GTCTGCGCCTGCGCGCAAGAGAGGCGGGGCCAGCGCTCGGCATGGCGGAGCCAGATCTGGAGTGCGAGCAGATCCG
TCTGAAGTGTATTCCTGGGACGATGCCGGAGTGTGAAGGAGTTTGAGAAGCTGAACCGCATTGGAGAGGGTACCTA
CGGCATTGTGTATCGGGCCCGGGACACCCAGACAGATGAGATTGTCGCACTGAAGAAGGTGCGGATGGACAAGGAG
AAGGATGGCATCCCCATCAGCAGCTTGCGGGAGATCACGCTGCTGCTCCGCCTGCGTCATCCGAACATCGTGGAGC
TGAAGGAGGTGGTTGTGGGGAACCACCTGGAGAGCATCTTCCTGGTGATGGGTTACTGTGAGCAGGACCTGGCCAG
CCTCCTGGAGAATATGCCAACACCCTTCTCGGAGGCTCAGGTCAAGTGCATCGTGCTGCAGGTGCTCCGGGGCCTC
CAGTATCTGCACAGGAACTTCATTATCCACAGGGACCTGAAGGTTTCCAACTTGCTCATGACCGACAAGGGTTGTG
TGAAGACAGCGGATTTCGGCCTGGCCCGGGCCTATGGTGTCCCAGTAAAGCCAATGACCCCCAAGGTGGTCACTCT
CTGGTACCGAGCCCCTGAACTGCTGTTGGGAACCACCACGCAGACCACCAGCATCGACATGTGGGCTGTGGGCTGC
ATACTGGCCGAGCTGCTGGCGCACAGGCCTCTTCTCCCCGGCACTTCCGAGATCCACCAGATCGACTTGATCGTGC
AGCTGCTGGGCACGCCCAGTGAGAACATCTGGCCGGGCTTTTCCAAGCTGCCACTGGTCGGCCAGTACAGCCTCCG
GAAGCAGCCCTACAACAACCTGAAGCACAAGTTCCCATGGCTGTCGGAGGCCGGGCTGCGCCTGCTGCACTTCCTG
TTCATGTACGACCCTAAGAAAAGGGCGACGGCCGGGGACTGCCTGGAGAGCTCCTATTTCAAGGAGAAGCCCCTAC
GTCTTCCGATCAGTGGTGTCTGTGAAGGGTGCCGCGAGCCAGGCTGACCAGGCGCCCGGGATCCAGCTCATCCCCT
TGGCTGGGAACATCCTCCACTGACTTCCTCCCACTGTCTGCCCTGAACCCACTGCTGCCCCCAGAAAAAGGCCGGG
TGACACCGGGGGGCTCCCAGCCCGTGCACCCTGGAAGGGCAGGTCTGGCGGCTCCATCCGTGGCTGCAGGGGTCTC
ATGTGGTCCTCCTCGCTATGTTGGAAATGTGCAACCACTGCTTCTTGGGAGGAGTGGTGGGTGCAGTCCCCCCGCT
GTCTTTGAGTTGTGGTGGACGCTGGCCTGGGATGAGAGGGCCCAGAAGACCTTCGTATCCCCTCTCAGTCGCCCGG
GGCTGTCCCGTGCATGGGTTGGCTGTGGGGACCCCAGGTGGGCCTGGCAGGACTCCAGATGAGGACAAGAGGGACA
AGGTATGGGGTGGGAGCCACAATTGAGGATACCCCGAGACTACCAGGAGAGCCCTGGGCTGGAGGCTGAGCTGCAT
CCCTGCTCCCCACATGGAGGACCCAACAGGAGGCCGTGGCTCTGATGCTGAGCGAAGCTATAGGCTCTTGTTGGAT
AAAAGCTTTTTTAACAGAAAAAAAAAAAAAAAAAAA

FIGURE 4C

>gi|32528265|ref|NM_052988.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 3, mRNA

GTCTGCGCCTGCGCGCAAGAGAGGCGGGGCCAGCGCTCGGCATGGCGGAGCCAGATCTGGAGTGCGAGCAGATCCG
TCTGAAGTGTATTCGTAAGGAGGGCTTCTTCACGGTGCCTCCGGAACACAGGATCGGGCCCGGGACACCCAGACAG
ATGAGATTGTCGCACTGAAGAAGGTGCGGATGGACAAGGAGAAGGATGGCATCCCCATCAGCAGCTTGCGGGAGAT
CACGCTGCTGCTCCGCCTGCGTCATCCGAACATCGTGGAGCTGAAGGAGGTGGTTGTGGGGAACCACCTGGAGAGC
ATCTTCCTGGTGATGGGTTACTGTGAGCAGGACCTGGCCAGCCTCCTGGAGAATATGCCAACACCCTTCTCGGAGG
CTCAGGTCAAGTGCATCGTGCTGCAGGTGCTCCGGGGCCTCCAGTATCTGCACAGGAACTTCATTATCCACAGGGA
CCTGAAGGTTTCCAACTTGCTCATGACCGACAAGGGTTGTGTGAAGACAGGTGGGTGCAACTTGGGCCAGGCCCTG
TCCCTAGATGGCACTTGGTGACACACACTCCCCTCTCTGCTGCAGCGGATTTCGGCCTGGCCCGGGCCTATGGTGT
CCCAGTAAAGCCAATGACCCCCAAGGTGGTCACTCTCTGGTACCGAGCCCCTGAACTGCTGTTGGGAACCACCACG
CAGACCACCAGCATCGACATGTGGGCTGTGGGCTGCATACTGGCCGAGCTGCTGGCGCACAGGCCTCTTCTCCCCG
GCACTTCCGAGATCCACCAGATCGACTTGATCGTGCAGCTGCTGGGCACGCCCAGTGAGAACATCTGGCCGGGCTT
TTCCAAGCTGCCACTGGTCGGCCAGTACAGCCTCCGGAAGCAGCCCTACAACAACCTGAAGCACAAGTTCCCATGG
CTGTCGGAGGCCGGGCTGCGCCTGCTGCACTTCCTGTTCATGTACGACCCTAAGAAAAGGGCGACGGCCGGGGACT
GCCTGGAGAGCTCCTATTTCAAGGAGAAGCCCCTACCCTGTGAGCCGGAGCTCATGCCGACCTTTCCCCACCACCG
CAACAAGCGGGCCGCCCCAGCCACCTCCGAGGGCCAGAGCAAGCGCTGTAAACCCTGACGGTGGGCCTGGCACACG
CCTGTATTCCCACACCAGGTCTTCCGATCAGTGGTGTCTGTGAAGGGTGCCGCGAGCCAGGCTGACCAGGCGCCCG
GGATCCAGCTCATCCCCTTGGCTGGGAACATCCTCCACTGACTTCCTCCCACTGTCTGCCCTGAACCCACTGCTGC
CCCCAGAAAAAGGCCGGGTGACACCGGGGGGCTCCCAGCCCGTGCACCCTGGAAGGGCAGGTCTGGCGGCTCCATC
CGTGGCTGCAGGGGTCTCATGTGGTCCTCCTCGCTATGTTGGAAATGTGCAACCACTGCTTCTTGGGAGGAGTGGT
GGGTGCAGTCCCCCCGCTGTCTTTGAGTTGTGGTGGACGCTGGCCTGGGATGAGAGGGCCCAGAAGACCTTCGTAT
CCCCTCTCAGTCGCCCGGGGCTGTCCCGTGCATGGGTTGGCTGTGGGGACCCCAGGTGGGCCTGGCAGGACTCCAG
ATGAGGACAAGAGGGACAAGGTATGGGGTGGGAGCCACAATTGAGGATACCCCGAGACTACCAGGAGAGCCCTGGG
CTGGAGGCTGAGCTGCATCCCTGCTCCCCACATGGAGGACCCAACAGGAGGCCGTGGCTCTGATGCTGAGCGAAGC
TATAGGCTCTTGTTGGATAAAAGCTTTTTTAACAGAAAAAAAAAAAAAAAAAAA

FIGURE 5A

>gi|37538611|ref|XM_168530.2| Homo sapiens piccolo (presynaptic cytomatrix protein) (PCLO), mRNA

ATGACATCCTCTGGAGCCCAGAAAAAAGTTAAAAGAACTCTGCCAAATCCACCTCCTGAGGAGATTTCCACAGGAACTCAATC
CACATTCAGCACAATGGGCACAGTTTCCAGGAGAAGGATCTGCAGAACCAACACAATGGCACGAGCCAAGATTCTCCAGGACA
TAGACAGAGAGCTTGATCTTGTGGAAAGGGAGTCTGCAAAACTTCGAAAGAAACAAGCAGAGCTTGATGAAGAAGAAAAGGAG
ATTGATGCTAAGCTACGATACCTGGAAATGGGAATTAACAGGAGGAAAGAGGCCCTATTAAAGGAGAGAGAAAAGAGAGAACG
AGCCTACCTCCAGGGAGTAGCTGAGGATCGTGATTACATGTCTGACAGTGAAGTGAGTAGCACAAGACCAACCCGAATAGAAA
GTCAGCATGGCATTGAGCGACCAAGAACTGCTCCCCAAACTGAATTCAGCCAGTTTATACCACCACAAACCCAAACAGAATCT
CAACTAGTTCCTCCGACAAGTCCTTACACACAATACCAGTACTCTTCCCCTGCTCTTCCTACCCAAGCACCCACCTCATACAC
TCAACAGTCTCATTTTGAGCAACAAACTTTGTACCATCAGCAAGTTTCACCTTATCAGACTCAGCCAACATTCCAAGCTGTGG
CAACAATGTCCTTCACACCTCAAGTTCAACCTACACCAACCCCACAGCCTTCTTATCAGTTACCTTCACAGATGATGGTGATA
CAACAGAAGCCACGGCAAACTACATTATATTTGGAGCCCAAGATAACCTCAAACTATGAAGTGATTCGCAACCAACCCCTTAT
GATAGCACCTGTTTCTACGGATAACACATTTGCTGTTTCCCATCTTGGTAGTAAGTACAATAGTTTAGACTTGAGAATAGGTT
TGGAGGAAAGAAGTAGCATGGCAAGCAGTCCAATATCAAGCATATCTGCAGATTCTTTCTATGCAGATATTGATCACCATACT
CCACGAAATTATGTCCTAATTGACGACATTGGAGAGATCACCAAAGGAACAGCGGCATTAAGCACCGCATTTAGCCTTCATGA
AAAGGATCTGTCAAAAACAGACCGTCTCCTTCGAACCACTGAGACACGCCGGTCTCAAGAAGTGACAGATTTCCTAGCACCTT
TACAGTCTTCCTCTAGATTGCATAGTTATGTGAAGGCGGAGGAAGACCCAATGGAGGATCCTTACGAGTTAAAGCTTCTGAAA
CATCAGATTAAACAGGAATTTCGTAGAGGGACAGAGAGCTTAGATCACCTTGCTGGTCTTTCTCATTATTACCATGCTGATAC
TAGCTACAGACATTTTCCAAAATCTGAGAAGTATAGCATCAGTAGACTCACACTTGAAAAACAAGCAGCAAAACAACTGCCAG
CAGCCATACTTTATCAAAAGCAGTCAAAGCATAAGAAATCACTAATTGACCCTAAAATGTCAAAATTTTCACCTATTCAAGAA
AGTAGAGACCTTGAACCTGATTATTCAAGCTATATGACTTCTAGCACTTCATCTATTGGTGGCATTTCCTCCAGGGCAAGGCT
CCTTCAAGATGACATCACTTTTGGCCTCAGAAAAAATATTACAGACCAACAAAAATTTATGGGATCTTCTCTTGGCACAGGAC
TGGGCACATTAGGAAATACCATACGCTCAGCTCTGCAGGATGAAGCGGATAAGCCATACAGTAGTGGCAGCAGGTCCAGACCT
TCCTCCAGACCTTCCTCTGTCTATGGGCTTGATTTATCAATTAAAAGGGATTCTTCTAGCTCTTCCCTAAGACTGAAAGCTCA
AGAGGCTGAAGCTCTAGATGTTTCCTTTAGTCATGCATCATCCTCTGCCAGAACTAAGCCGACCAGTTTGCCAATTAGTCAAA
GTAGAGGAAGAATACCAATTGTGGCCCAGAATTCTGAAGAAGAAAGCCCACTCAGTCCTGTTGGCCAGCCAATGGGAATGGCC
AGGGCTGCAGCTGGACCCCTGCCACCAATATCTGCAGACACCAGGGATCAGTTTGGATCAAGCCACTCATTGCCTGAAGTTCA
GCAACACATGAGGGAAGAATCACGGACTCGAGGCTATGACCGTGACATAGCATTCATCATGGATGACTTCCAACATGCCATGT
CAGACAGTGAAGCCTATCATCTGCGTCGTGAGGAAACAGATTGGTTTGATAAACCCAGGGAGTCTCGTTTGGAAAATGGACAT
GGTCTGGACCGAAAACTGCCGGAAAGATTGGTCCACTCTAGACCACTCAGTCAACATCAAGAGCAAATTATACAGATGAACGG
GAAAACTATGCACTACATCTTTCCTCACGCAAGGATAAAAATAACAAGAGACTCAAAGGATCACACAGTTTCAGGTAATGGAT
TAGGAATTAGAATTGTGGGTGGTAAAGAAATCCCGGGACATAGTGGAGAAATTGGAGCCTATATTGCCAAGATTCTTCCTGGG
GGAAGTGCGGAACAGACGGGGAAGCTTATGGAAGGGATGCAAGTATTGGAATGGAATGGAATTCCCTTGACTTCTAAAACATA
TGAAGAAGTTCAGAGTATCATTAGTCAGCAAAGTGGGGAAGCAGAAATATGTGTAAGACTGGACCTCAATATGCTATCAGATT
CTGAAAATTCCCAGCATCTGGAACTTCATGAGCCACCAAAAGCTGTGGATAAGGCGAAATCCCCAGGGGTTGATCCTAAGCAG
TTGGCAGCAGAACTCCAGAAGGTTTCACTACAGCAGTCACCGCTGGTTCTGTCATCAGTTGTTGAAAAAGGATCTCATGTTCA
TTCAGGTCCTACATCAGCAGGATCCAGTTCCGTTCCCAGCCCTGGGCAACCAGGGTCCCCCTCAGTGAGCAAAAAGAAGCACG
GCAGCAGCAAGCCTACCGATGGAACAAAGGTTGTCTCTCATCCAATTACAGGAGAAATTCAGCTTCAAATTAACTATGATCTT
GGAAATCTCATAATACATATTCTCCAAGCAAGAAATCTTGTTCCTCGAGACAACAATGGTTATTCTGACCCTTTTGTGAAAGT
GTACCTTCTTCCAGGGAGAGGTCAAGTCATGGTTGTCCAGAATGCAAGTGCTGAGTACAAGAGAAGGACTAAACATGTCCAGA
AAAGTCTTAATCCTGAGTGGAATCAAACAGTAATTTATAAAAGTATTTCCATGGAACAGCTCAAGAAGAAAACACTGGAGGTG
ACAGTTTGGGATTATGATAGATTTTCATCCAACGACTTCCTTGGGGAGGTATTGATTGATTTATCTAGCACATCTCACCTCGA
TAACACTCCAAGGTGGTATCCTCTCAAAGAACAGACTGAAAGCATTGATCATGGCAAGTCTCATTCCAGTCAGAGCAGCCAGC
AGTCCCCAAAGCCATCTGTTATCAAAAGCAGAAGCCATGGTATCTTCCCTGACCCATCAAAGGACATGCAGGTTCCCACCATT
GAGAAATCCCATAGTAGTCCTGGTAGCTCAAAATCATCATCAGAAGGCCATCTCCGTTCTCATGGACCATCTCGCAGTCAAAG
CAAAACCAGCGTCACTCAGACCCACCTGGAAGATGCAGGGGCTGCCATAGCTGCTGCCGAAGCTGCCGTGCAACAACTCCGCA
TTCAACCAAGTAAAAGACGCAAATAAATTCCTCAGCATGGCAGCTTAATGTTCATCTGTTGCCTTTCTTTCCTGCTGTCCTTT
CCTGTTTGCTTTCAGTTTTCAACATCCTCTGCTCACCCTGTTCTCTGTCCCTTTGTCTGTGTAAGAACGATATAAATACATTA
ATATGCTCTTTCTTATTTAGATTTTTTTTATTTACATAGACTGAAATAAAACTGGCTGTTTCTCCTTTGTTTCCACCATCCAT
CCAACCTGGCTCATAGCATTTGATACAGTGTCTGTGATGTTTGGAAGCAAAGCAATGTTGTGTGTCCTTTTTGTTTGCGCTTA
AATATCTTTTAGAATACAGAAATTATAAGCACAAGTGGCTGCCAGTTTTCCAGGACTTATACCAAAAAAAAAAAAGTGCACAC
ATATAAGTATTTAGAGCAGATTTGCAATTAGATTCTTGTATCTGAAAACACTCAAAAAGTCTAGGCAGAAGATAATGCAACCA
ACAGTCAACTTCTAGAACCTTGGAGGAAAAGCCATTTCAAGACAGTGCTTTAAAACACTAACAAATTTTGCTTCTGAAATATG
GTAGCTTTCCATGTGCAAAAAATTGTAGTCTTCTGAAAAATCTGTGAAGAAAATCTTATTTCTTACATTCTCAAAAAACTACA
TTAAATTAATATATGTATAAGCATATGTGATAAGGCAATGCAACCTCACTGAGGAGCACAATTGGGTCCATTCTGTTGGATCA
CACTTTGTATGTGATGACAGATTTTACAGATATTTTTTCTAACCATTGGAAATCAAGATATACTATGTCTGGTAGCTATAAGT
CAATCAAAGTATAACAATTGACCTATCTTAACTGCTGTATTTTCATTTCATTTGTGAAAATTTAGTCGATTGATATAATTATA
TAAAAACTTAATATGTGCAAATATTTCACAAATGTAGGTACCCTGTTACTTCTAAAAGGCATTAGCCAGGCAATGGAGATAGA
TCATTGTTCTCTCCATCTCCCTAGTCATCATTTTCAAAGAAACAGCCAGTTTTAAACCCCTTTAGTGCTGTGCATGTGGTGTC
ATTTTGGCATTTGAAAACACAACCTATTTAAATAGAGCAAAAGAGCACTTCTGTTTGCATGAATAACATTTAAGCTGGTTCCA
TCTGAGGATACATACTCTGGGTTTCCATTTCACCCACACTGCCACAGCAGCACATAAAAGCGGTCAGTCTAATCATGCCAGGA
AGCAGCACAGACACAGCATAGCAGGAGTCCTCCCCATTCAAAGAACTCAGTCTGATAATCTGCCTCCACCAGCCAATGGCAAC

FIGURE 5B

CAAGACCAAAGCCAGCTAGCCCTCAGGAAGGTGATGTCTGATGGACCAGTCAAGCCAGAAGGAGGTGAGCAGAAAGGCCCTGT
TCAAAGCACACAGCAAGAACATCCCCAAATTTAAAGCTCTCATCTTTAATTTTTAGAGATTGTCTGATAAAATATGTTTATCC
ACTTTTTAATGTGCTTTTGTGGGCATGGCATTTCAGGACTTCATCATCACCATGTAAGTCCCAAGATCAGTCCCGTAATATAT
TGACTACAGTGATTTGTATTTTTCTATGCACTGGGCATCTTTTGACTTTTGTTGGGAAATAGATTAACAATATTCATATTGCA
GAATGGAATGCATGCTACTAACCTAATCTGTTCAAGCATGACTATAAATATGTTTCATTGTGATAAAAGTTTAAATTGCTCAC
AGTTCAAGTTAGCCTACCAGTTGGAATGTGGATCAGTGTTTTTTGCCTATTATTTCAAGTGTAACTTTTAAAAATTTAGTGGA
TTTTGAAAATTCTTAGAGGAAAGTAAAGGAAAAATTGTTAATGCACTCATTTACCTTTACATGGTGAAAGTTCTCTCTTGATC
CTACAAACAGACATTTTCCACTCGTGTTTCCATAGTTGTTAAGTGTATCAGATGTGTTGGGCATGTGAATCTCCAAGTGCCTG
TGTAATAAATAAAGTATCTTTATTTCATTCAT

FIGURE 6A

>gi|4503776|ref|NM_003838.1| Homo sapiens fucose-1-phosphate guanylyltransferase (FPGT), mRNA

GCGTGCTGTGCGGCGCGGTCTCAGGGAAGGTGGGGCTATGGCAGCTGCTAGGGACCCTCCGGAAGTATCGCTGCGAGAAGCCACCC
AGCGAAAATTGCGGAGGTTTTCCGAGCTAAGAGGCAAACTTGTAGCACGTGGAGAATTCTGGGACATAGTTGCAATAACAGCGGCT
GATGAAAAACAGGAACTTGCTTACAACCAACAGCTGTCAGAAAAGCTGAAAAGAAAGGAGTTACCCCTTGGAGTTCAATATCACGT
TTTTGTGGATCCTGCTGGAGCCAAAATTGGAAATGGAGGATCAACACTTTGTGCCCTTCAATGTTTGGAAAAGCTATATGGAGATA
AATGGAATTCTTTTACCATCTTATTAATTCACTCTGGTGGCTACAGTCAACGACTTCCAAATGCAAGTGCTCTGGGAAAAATTTTC
ACTGCTTTACCTCTTGGTAACCCCATTTATCAGATGCTAGAATTAAAGCTAGCCATGTACATTGATTTCCCCTTAAATATGAATCC
TGGAATTCTGGTTACCTGTGCAGATGATATTGAACTTTATAGTATTGGAGAATTTGAGTTTATTAGGTTTGACAAACCTGGCTTTA
CTGCTTTAGCTCATCCTTCTAGTTTGACGATAGGTACCACACATGGAGTATTTGTCTTAGATCCTTTTGATGATTTAAAACATAGA
GACCTTGAATACAGGTCTTGCCATCGTTTCCTTCATAAGCCCAGCATAGAAAAGATGTATCAGTTTAATGCTGTGTGTAGACCTGG
AAATTTTTGTCAACAGGACTTTGCTGGGGGTGACATTGCCGATCTTAAATTAGACTCTGACTATGTCTACACAGATAGCCTATTTT
ATATGGATCATAAATCAGCAAAAATGTTACTTGCTTTTTATGAAAAAATAGGCACACTGAGCTGTGAAATAGATGCCTATGGTGAC
TTTCTGCAGGCTTTGGGACCTGGAGCAACTGTGGAGTACACCAGAAACACATCACATGTCATTAAAGAAGAGTCAGAGTTGGTAGA
AATGAGGCAGAGAATATTTCATCTTCTTAAAGGAACATCACTAAATGTTGTTGTTCTTAATAACTCCAAATTTTATCACATTGGAA
CAACCGAAGAATATTTGTTTTACTTTACCTCAGATAACAGTTTAAAGTCAGAGCTCGGCTTACAGTCCATAACTTTTAGTATCTTT
CCAGATATACCAGAATGCTCTGGCAAAACATCCTGTATCATTCAAAGCATACTGGATTCAAGATGTTCTGTGGCACCTGGCTCAGT
TGTGGAGTATTCCAGATTGGGGCCTGATGTTTCAGTTGGGGAAAACTGCATTATTAGTGGTTCTTACATCCTAACAAAAGCTGCCC
TCCCCGCACATTCTTTTGTATGTTCCTTAAGCTTAAAGATGAATAGATGCTTAAAGTATGCAACTATGGCATTTGGAGTGCAAGAC
AACTTGAAAAAGAGTGTGAAAACATTGTCAGATATAAAGTTACTTCAATTCTTTGGAGTCTGTTTCCTGTCATGCTTAGATGTTTG
GAATCTTAAAGTTACAGAGGAACTGTTCTCTGGTAACAAGACATGTCTGAGTTTGTGGACTGCACGCATTTTCCCAGTTTGTTCTT
CTTTGAGTGACTCAGTTATAACATCCCTAAAGATGTTAAATGCTGTTAAGAACAAGTCAGCATTCAGCCTGAATAGCTATAAGTTG
CTGTCCATTGAAGAAATGCTTATCTACAAAGATGTAGAAGATATGATAACTTACAGGGAACAAATTTTTCTAGAAATCAGTTTAAA
AAGCAGTTTGATGTAGAGATATTTTAAATATTGTACACTTTGCCTTTTTGAGTAACATTCCAGAGATAGGTATTTTTGGTAGGCTG
TTTCACTGAACTCAGTTAATGAAAACTGTATTAACATAATTGTTGTAGCATAATATTAATAGTGCAAAAGTACATATAAGTCATTT
TGATGAAAAATATTCCAAGACTAAGTTGAGAAAAGAGATACTATTTTGGATGTGTATCAGTATTTTTGTTTTTAATAATGATTGAT
TTGTGGAGCATTGTTTTTTCACATAATTAGTTTTAAAGGTAATTTTCTAAGCATACCTTTGGAATTTTTCCATCTTTTTTGAGGCT
TTTGGTCCAGTGAAGTTCTAAGTATTCACTGGCACTTCTCTCCTCAACTGTAATTCTATTTTTAATAATAAAAATGGCATACTGTA
GGGTCTTCAGAGTAGTGTAGGAATACTGTAGAAATACTTTTTCAGAAACGAATCCATAGCTGACAAATTCACTCAGTGCCCAATAT
ATTGTGATTATTTTCGTTGATAAAGAACTAGATACAAAGACCTCTGAAATTGATGATAAAATTTGTATCTCATTAATTTTATCAAA
ATGAAACTAAAAGTACATATGTATTATACACTTGAACATGTGTTTGTATATCTTTAAAATTTTCCTTTATGTCCATTCCATAGGAA
GACACACATATGCACACAAAACTCAGTTATCTGTGGGGGAAGTGGTAGTAATAATTGAGATTCATCAATAATCATATAATTTCACT
ATAGACATTACTTGCATTATCTCCTATCAGTCCTTCTCACAAAACTTCAATTACCAGATGAACTGACTTTAGTTTTCATCTTATTT
TTTGTCCACATGCTGGTGATGCTGAGAAACAATAATTGGCCCAAATGCAGACATCAAGAAGCAGGCAGGAAAATGGAAAAACTGAG
ATAATACACAGGTGATAAACAGTTTCGAGAAAATAAAAATTGGCTAGAATCTCAAGTTATGTGTTTCTATATTGGTATAAGCATAT
AAGTGAAAAGTCTTATAAGTGTAATAGAGAAAAGATTTGTCAGTGTGTTTTTTTAAATGAAATAACTAGTCTGTGCTACTTTATGT
CAATATAAAAATTGGTAAACTAGAAGTAACTTGTCCACAACCCTCAGTTATGATACTTATGTGCGTGTTTTTTTTTCCAAAGTTTT
TCCCAAGGAGAAGATACAAATATATGGTAGCTATTGTTTAAAAATGATTGATTTACTTGCAGATTTTTCAGAGGATGTTATGTCTT
TGTCATTCATTAAATGTTCAAAATTGTAGTTTTAAAAAAAAAAAAAA

FIGURE 6B

>gi|7705747|ref|NM_015978.1| Homo sapiens cardiac ankyrin repeat kinase (CARK), mRNA

AATCTTATAACTTGAAGAACTGCCCTGGAGAAAGGAAGAAACTTATAATAAATGGGAAATTATAAATCTAGACCAACCCAAACTTG
TACTGATGAATGGAAGAAAAAAGTCAGTGAATCATATGTTATCACAATAGAAAGATTAGAAGATGACCTGCAGATCAAGGAAAAAG
AACTGACAGAACTAAGGAATATATTTGGCTCTGATGAAGCCTTCAGTAAAGTCAATTTAAATTACCGCACTGAAAATGGGCTGTCT
CTACTTCATTTATGTTGCATTTGTGGAGGCAAGAAATCACATATTCGAACTCTTATGTTGAAAGGGCTCCGCCCATCTCGACTGAC
AAGAAATGGATTTACAGCCTTGCATTTAGCAGTTTACAAGGATAATGCAGAATTGATCACTTCTCTGCTTCACAGTGGAGCTGATA
TACAGCAGGTTGGATACGGTGGCCTCACTGCCCTCCATATTGCTACAATAGCTGGCCACCTAGAGGCTGCTGATGTGCTGTTGCAA
CATGGAGCTAATGTCAATATTCAAGATGCAGTTTTTTTCACTCCATTGCATATTGCAGCGTACTATGGACATGAACAGGTAACTCG
CCTTCTTTTGAAATTTGGTGCTGATGTAAATGTAAGTGGTGAAGTTGGAGATAGACCCCTCCACCTAGCATCTGCAAAAGGATTCT
TGAATATTGCAAAACTCTTGATGGAAGAAGGCAGCAAAGCAGATGTGAATGCTCAAGATAATGAAGACCATGTCCCACTCCATTTC
TGTTCTCGATTTGGACACCATGATATAGTTAAGTATCTGCTGCAAAGTGATTTGGAAGTTCAACCTCATGTTGTTAATATCTATGG
AGATACCCCCTTACACCTGGCATGCTACAATGGCAAATTTGAAGTTGCCAAGGAAATCATCCAAATATCAGGAACAGAAAGTCTGA
CTAAGGAAAACATCTTCAGTGAAACAGCTTTTCATAGTGCTTGTACCTATGGCAAGAGCATTGACCTAGTCAAATTTCTTCTTGAT
CAGAATGTCATAAACATCAACCACCAAGGAAGGGATGGGCACACTGGATTACACTCTGCTTGCTACCACGGTCACATTCGCCTGGT
TCAGTTCTTACTGGATAATGGAGCTGATATGAATCTAGTGGCTTGTGATCCCAGCAGGTCTAGTGGTGAAAAAGATGAGCAGACAT
GTTTGATGTGGGCTTATGAAAAAGGGCATGATGCCATTGTCACACTCCTGAAGCATTATAAGAGACCACAAGATGAATTGCCCTGT
AATGAATATTCTCAGCCTGGAGGAGATGGCTCCTATGTGTCTGTTCCATCACCCTTGGGGAAGATTAAAAGCATGACAAAAGAGAA
GGCAGATATTCTCCTCCTAAGAGCTGGATTGCCTTCACATTTCCATCTTCAGCTCTCAGAAATTGAGTTCCATGAGATTATTGGCT
CAGGTTCTTTTGGGAAAGTATATAAAGGACGATGCAGAAATAAAATAGTGGCTATAAAACGTTATCGAGCCAATACCTACTGCTCC
AAGTCAGATGTGGATATGTTTTGCCGAGAGGTGTCCATTCTCTGCCAGCTCAATCATCCCTGCGTAATTCAGTTTGTGGGTGCTTG
CTTGAATGATCCCAGCCAGTTTGCCATTGTCACTCAATACATATCAGGGGGTTCTCTGTTCTCCCTCCTTCATGAGCAGAAGAGGA
TTCTTGATTTGCAGTCTAAATTAATTATTGCAGTAGATGTTGCCAAAGGCATGGAGTACCTTCACAACCTGACACAGCCAATTATA
CATCGTGACTTGAACAGTCACAATATTCTTCTCTATGAGGATGGGCATGCTGTGGTGGCAGATTTTGGAGAATCAAGATTTCTACA
GTCTCTGGATGAAGACAACATGACAAAACAACCTGGGAACCTCCGTTGGATGGCTCCTGAGGTGTTCACGCAGTGCACTCGGTACA
CCATCAAAGCAGATGTCTTCAGCTATGCTCTGTGTCTGTGGGAAATTCTCACTGGCGAAATTCCATTCGCTCATCTCAAGCCAGCG
GCTGCGGCAGCAGACATGGCTTACCACCACATCAGACCTCCCATTGGCTATTCCATTCCCAAGCCCATATCATCTCTGCTGATACG
AGGGTGGAACGCATGTCCTGAAGGAAGACCCGAATTTTCTGAAGTTGTCATGAAGTTAGAAGAGTGTCTCTGCAACATTGAGCTGA
TGTCTCCTGCATCAAGTAACAGCAGTGGGTCTCTCTCACCTTCTTCTTCTTCTGATTGCCTGGTGAACCGGGGAGGACCTGGCCGG
AGTCATGTGGCAGCATTAAGAAGTCGTTTCGAATTGGAATATGCTCTAAATGCAAGGTCCTATGCTGCTTTGTCCCAAAGTGCTGG
ACAATATTCCTCTCAAGGTCTGTCTTTGGAGGAGATGAAAAGAAGTCTTCAATACACACCCATTGACAAATATGGCTATGTATCCG
ATCCCATGAGCTCAATGCATTTTCATTCTTGCCGAAATAGTAGCAGCTTTGAGGACAGCAGCTGACAGCATTCGGCGTATACCTAA
GGAGAGTTTTTTCCCCGAACTGACAGCAACGATTCCAACCACGGCAAGCTGGCTTCCAACTATAACATTTTACTCTCAAAGGTCTC
CTTAAATTGGGCTTGTTTTTACTTGTCCTATTTAATTCCCCACTATTAGCAGGCTTTGGATTTGTGCCTAAGGAATAATATGCAAA
AGAACCAAGACAGAATGTATATGAAGAATTGTTTTTAATTTTGTAAATTAAAAAAAAATTTAGATCGTTACTTGGAAATGGAGCCT
AAGTCTGTGGTGGACAGATAATAATTATGTTTTCCTGGGCTGAATTATGTAGACTTGTGTTTGACAGCTATGGGTTTATTTCTTAG
AACATTGTTCATTTTCTTTTCTCATTATGTTACTTCTAGTGTTCACCTCTGTGATTAAAGATTCTTTGGTGAAATAG

FIGURE 7

>gi|4758943|ref|NM_004726.1| Homo sapiens RALBP1 associated Eps domain containing 2 (REPS2), Mrna

CCGGGAGGAAGCGGCCGCGCGGCAGCTGCGGGGCGTGGGGGTGGTGGTGGCGGCGGCGGTGGTGGCGGCGGCGGCGGCGGCGG
CAGCTGAGGCCGAGGAGGCGGTGGCTGTGGCGGACGCAGCAGCACCCCAGCTAGGGATAGGGCTCCGCCGCGCCCCCTTGCTG
GCCCCATGGAGGCGGCAGCGGCGGCGGCGGCGGCGGCAGCGGCAGCGGCAGCGGCGGGCGGGGGCTGTGGCTCCGGGCCGCCG
CCGCTGCTGCTGAGCGAGGGCGAGCAGCAGTGCTACTCCGAGCTCTTCGCGCGCTGTGCCGGCGCCGCGGGCGGGGGCCCCGG
GTCTGGGCCCCCCGAGGCCGCCAGAGTCGCCCCCGGCACGGCCACTGCGGCCGCCGGCCCCGTGGCTGACCTGTTTCGGGCAT
CGCAGCTGCCCGCCGAGACGCTGCACCAGATCACAGAACTGTGTGGTGCAAAGCGGGTTGGTTATTTTGGTCCAACACAGTTT
TACATTGCCCTGAAATTAATTGCTGCAGCACAATCTGGCCTCCCGGTACGGATAGAGAGTATTAAATGTGAATTGCCTCTGCC
TCGCTTTATGATGTCAAAGAATGATGGTGAGATACGATTTGGGAACCCAGCTGAGCTGCATGGAACTAAGGTTCAGATTCCAT
ATTTAACTACAGAAAAAAATTCCTTCAAAAGAATGGACGATGAGGATAAACAGCAGGAAACACAGTCTCCCACGATGTCACCC
CTCGCCTCCCCTCCTTCTTCCCCGCCTCATTACCAGAGGGTGCCCTTGAGCCATGGCTACAGCAAACTGCGGAGCAGCGCAGA
ACAGATGCATCCAGCACCTTATGAAGCTAGGCAGCCCCTTGTCCAGCCCGAGGGATCCTCATCAGGGGGCCCAGGAACCAAGC
CCCTTCGGCATCAGGCTTCCCTTATCCGGTCCTTTTCAGTGGAGAGGGAACTACAGGATAACAGCAGTTACCCCGACGAACCC
TGGAGGATAACAGAAGAACAGCGCGAGTACTATGTCAATCAGTTCCGATCCCTTCAGCCAGACCCAAGCTCTTTCATTTCAGG
TTCTGTGGCCAAGAACTTCTTCACCAAATCAAAGCTTTCCATTCCAGAACTCTCCTATATATGGGAGCTTAGTGATGCTGACT
GTGATGGAGCCCTGACCCTGCCTGAGTTCTGTGCTGCGTTTCATCTCATTGTGGCTCGGAAGAACGGCTACCCATTGCCTGAG
GGCCTCCCTCCAACTCTGCAGCCAGAATACCTGCAGGCAGCTTTTCCTAAGCCCAAATGGGACTGTCAATTATTTGATTCTTA
TTCTGAGTCACTGCCGGCAAATCAACAACCTCGTGACTTGAATCGGATGGAGAAGACATCTGTTAAAGACATGGCTGACCTTC
CTGTCCCTAACCAGGATGTAACTAGTGATGACAAACAAGCTTTGAAAAGTACTATCAATGAAGCCTTACCAAAGGACGTGTCT
GAGGATCCAGCAACTCCCAAGGATTCCAACAGTCTCAAAGCAAGACCAAGATCCAGATCTTACTCTAGCACCTCCATAGAAGA
GGCCATGAAAAGGGGCGAGGACCCTCCCACCCCGCCACCTCGGCCACAGAAAACCCATTCCAGAGCCTCCTCCTTGGATCTGA
ATAAAGTCTTCCAGCCCAGTGTGCCAGCTACCAAGTCAGGATTGTTACCCCCACCACCTGCGCTCCCTCCAAGACCTTGTCCA
TCACAGTCTGAACAAGTGTCGGAGGCCGAGTTACTCCCACAGCTGAGCAGAGCCCCATCCCAGGCTGCAGAAAGTAGTCCAGC
AAAGAAGGATGTACTGTATTCTCAGCCACCATCAAAGCCCATTCGTAGGAAATTCAGACCAGAAAACCAAGCTACAGAAAACC
AAGAGCCTTCCACTGCTGCAAGTGGGCCAGCTTCTGCGGCAACCATGAAACCGCATCCAACAGTCCAAAAGCAGTCTTCCAAA
CAGAAGAAGGCCATTCAAACTGCTATCCGCAAAAATAAAGAGGCAAACGCAGTGCTGGCTCGGCTGAACAGTGAGCTCCAGCA
GCAGCTCAAGGAGGTTCATCAAGAACGAATTGCATTGGAAAACCAATTGGAACAACTTCGTCCGGTCACTGTGTTGTGACCCC
CCCATGGTTCAAGTGACAGTGGGTGACCTTGTCTGCCAAGATCTTTCTTTTGAATGTTTTGAACCCAACTACTTGTCATAGAT
GTTTGACTGTGTCAAAAGCTGTGAGCAGCAAAATATAATCCATA

FIGURE 8A

>gi|32528263|ref|NP_003665.2| cyclin-dependent kinase 10 isoform 1; serine/threonine protein kinase PISSLRE; CDC2-related protein kinase; cell division protein kinase 10; cyclin-dependent kinase related protein [Homo sapiens]

MGRCRSVKEFEKLNRIGEGTYGIVYRARDTQTDEIVALKKVRMDKEKDGIPISSLREI
TLLLRLRHPNIVELKEVVVGNHLESIFLVMGYCEQDLASLLENMPTPFSEAQVKCIVL
QVLRGLQYLHRNFIIHRDLKVSNLLMTDKGCVKTADFGLARAYGVPVKPMTPKVVT
LWYRAPELLLGTTTQTTSIDMWAVGCILAELLAHRPLLPGTSEIHQIDLIVQLLGTPSE
NIWPGFSKLPLVGQYSLRKQPYNNLKHKFPWLSEAGLRLLHFLFMYDPKKRATAGD
CLESSYFKEKPLPCEPELMPTFPHHRNKRAAPATSEGQSKRCKP

FIGURE 8B

>gi|16950647|ref|NP_443713.1| cyclin-dependent kinase 10 isoform 2; serine/threonine protein kinase PISSLRE; CDC2-related protein kinase; cell division protein kinase 10; cyclin-dependent kinase related protein [Homo sapiens]

MGRCRSVKEFEKLNRIGEGTYGIVYRARDTQTDEIVALKKVRMDKEKDGIPISSLREI
TLLLRLRHPNIVELKEVVVGNHLESIFLVMGYCEQDLASLLENMPTPFSEAQVKCIVL
QVLRGLQYLHRNFIIHRDLKVSNLLMTDKGCVKTADFGLARAYGVPVKPMTPKVVT
LWYRAPELLLGTTTQTTSIDMWAVGCILAELLAHRPLLPGTSEIHQIDLIVQLLGTPSE
NIWPGFSKLPLVGQYSLRKQPYNNLKHKFPWLSEAGLRLLHFLFMYDPKKRATAGD
CLESSYFKEKPLRLPISGVCEGCREPG

FIGURE 8C

>gi|32528266|ref|NP_443714.2| cyclin-dependent kinase 10 isoform 3; serine/threonine protein kinase PISSLRE; CDC2-related protein kinase; cell division protein kinase 10; cyclin-dependent kinase related protein [Homo sapiens]

MDKEKDGIPISSLREITLLLRLRHPNIVELKEVVVGNHLESIFLVMGYCEQDLASLLEN
MPTPFSEAQVKCIVLQVLRGLQYLHRNFIIHRDLKVSNLLMTDKGCVKTGGCNLGQ
ALSLDGTW

FIGURE 9

>gi|37538612|ref|XP_168530.2| similar to KIAA0559 protein [Homo sapiens]

MTSSGAQKKVKRTLPNPPPEEISTGTQSTFSTMGTVSRRRICRTNTMARAKILQDIDR
ELDLVERESAKLRKKQAELDEEEKEIDAKLRYLEMGINRRKEALLKEREKRERAYLQ
GVAEDRDYMSDSEVSSTRPTRIESQHGIERPRTAPQTEFSQFIPPQTQTESQLVPPTSPY
TQYQYSSPALPTQAPTSYTQQSHFEQQTLYHQQVSPYQTQPTFQAVATMSFTPQVQP
TPTPQPSYQLPSQMMVIQQKPRQTTLYLEPKITSNYEVIRNQPLMIAPVSTDNTFAVS
HLGSKYNSLDLRIGLEERSSMASSPISSISADSFYADIDHHTPRNYVLIDDIGEITKGTA
ALSTAFSLHEKDLSKTDRLLRTTETRRSQEVTDFLAPLQSSSRLHSYVKAEEDPMEDP
YELKLLKHQIKQEFRRGTESLDHLAGLSHYYHADTSYRHFPKSEKYSISRLTLEKQAA
KQLPAAILYQKQSKHKKSLIDPKMSKFSPIQESRDLEPDYSSYMTSSTSSIGGISSRARL
LQDDITFGLRKNITDQQKFMGSSLGTGLGTLGNTIRSALQDEADKPYSSGSRSRPSSR
PSSVYGLDLSIKRDSSSSSLRLKAQEAEALDVSFSHASSSARTKPTSLPISQSRGRIPIVA
QNSEEESPLSPVGQPMGMARAAAGPLPPISADTRDQFGSSHSLPEVQQHMREESRTR
GYDRDIAFIMDDFQHAMSDSEAYHLRREETDWFDKPRESRLENGHGLDRKLPERLV
HSRPLSQHQEQIIQMNGKTMHYIFPHARIKITRDSKDHTVSGNGLGIRIVGGKEIPGHS
GEIGAYIAKILPGGSAEQTGKLMEGMQVLEWNGIPLTSKTYEEVQSIISQQSGEAEICV
RLDLNMLSDSENSQHLELHEPPKAVDKAKSPGVDPKQLAAELQKVSLQQSPLVLSSV
VEKGSHVHSGPTSAGSSSVPSPGQPGSPSVSKKKHGSSKPTDGTKVVSHPITGEIQLQI
NYDLGNLIIHILQARNLVPRDNNGYSDPFVKVYLLPGRGQVMVVQNASAEYKRRTK
HVQKSLNPEWNQTVIYKSISMEQLKKKTLEVTVWDYDRFSSNDFLGEVLIDLSSTSH
LDNTPRWYPLKEQTESIDHGKSHSSQSSQQSPKPSVIKSRSHGIFPDPSKDMQVPTIEK
SHSSPGSSKSSSEGHLRSHGPSRSQSKTSVTQTHLEDAGAAIAAAEAAVQQLRIQPSK
RRK

FIGURE 10A

>gi|4503777|ref|NP_003829.1| fucose-1-phosphate guanyltransferase; GDP-beta-L-fucose pyrophosphorylase [Homo sapiens]

MAAARDPPEVSLREATQRKLRRFSELRGKLVARGEFWDIVAITAADEKQELAYNQQ
LSEKLKRKELPLGVQYHVFVDPAGAKIGNGGSTLCALQCLEKLYGDKWNSFTILLIH
SGGYSQRLPNASALGKIFTALPLGNPIYQMLELKLAMYIDFPLNMNPGILVTCADDIE
LYSIGEFEFIRFDKPGFTALAHPSSLTIGTTHGVFVLDPFDDLKHRDLEYRSCHRFLHK
PSIEKMYQFNAVCRPGNFCQQDFAGGDIADLKLDSDYVYTDSLFYMDHKSAKMLLA
FYEKIGTLSCEIDAYGDFLQALGPGATVEYTRNTSHVIKEESELVEMRQRIFHLLKGT
SLNVVVLNNSKFYHIGTTEEYLFYFTSDNSLKSELGLQSITFSIFPDIPECSGKTSCIIQSI
LDSRCSVAPGSVVEYSRLGPDVSVGENCIISGSYILTKAALPAHSFVCSLSLKMNRCL
KYATMAFGVQDNLKKSVKTLSDIKLLQFFGVCFLSCLDVWNLKVTEELFSGNKTCL
SLWTARIFPVCSSLSDSVITSLKMLNAVKNKSAFSLNSYKLLSIEEMLIYKDVEDMITY
REQIFLEISLKSSLM

FIGURE 10B

>gi|7705748|ref|NP_057062.1| cardiac ankyrin repeat kinase [Homo sapiens]

MGNYKSRPTQTCTDEWKKKVSESYVITIERLEDDLQIKEKELTELRNIFGSDEAFSKV
NLNYRTENGLSLLHLCCICGGKKSHIRTLMLKGLRPSRLTRNGFTALHLAVYKDNAE
LITSLLHSGADIQQVGYGGLTALHIATIAGHLEAADVLLQHGANVNIQDAVFFTPLHI
AAYYGHEQVTRLLLKFGADVNVSGEVGDRPLHLASAKGFLNIAKLLMEEGSKADV
NAQDNEDHVPLHFCSRFGHHDIVKYLLQSDLEVQPHVVNIYGDTPLHLACYNGKFE
VAKEIIQISGTESLTKENIFSETAFHSACTYGKSIDLVKFLLDQNVININHQGRDGHTGL
HSACYHGHIRLVQFLLDNGADMNLVACDPSRSSGEKDEQTCLMWAYEKGHDAIVT
LLKHYKRPQDELPCNEYSQPGGDGSYVSVPSPLGKIKSMTKEKADILLLRAGLPSHFH
LQLSEIEFHEIIGSGSFGKVYKGRCRNKIVAIKRYRANTYCSKSDVDMFCREVSILCQL
NHPCVIQFVGACLNDPSQFAIVTQYISGGSLFSLLHEQKRILDLQSKLIIAVDVAKGME
YLHNLTQPIIHRDLNSHNILLYEDGHAVVADFGESRFLQSLDEDNMTKQPGNLRWM
APEVFTQCTRYTIKADVFSYALCLWEILTGEIPFAHLKPAAAAADMAYHHIRPPIGYSI
PKPISSLLIRGWNACPEGRPEFSEVVMKLEECLCNIELMSPASSNSSGSLSPSSSSDCLV
NRGGPGRSHVAALRSRFELEYALNARSYAALSQSAGQYSSQGLSLEEMKRSLQYTPI
DKYGYVSDPMSSMHFHSCRNSSSFEDSS

FIGURE 11

>gi|4758944|ref|NP_004717.1| RALBP1 associated Eps domain containing 2; partner of Ral-binding protein 1 [Homo sapiens]

MMSKNDGEIRFGNPAELHGTKVQIPYLTTEKNSFKRMDDEDKQQETQSPTMSPLASP
PSSPPHYQRVPLSHGYSKLRSSAEQMHPAPYEARQPLVQPEGSSSGGPGTKPLRHQA
SLIRSFSVERELQDNSSYPDEPWRITEEQREYYVNQFRSLQPDPSSFISGSVAKNFFTKS
KLSIPELSYIWELSDADCDGALTLPEFCAAFHLIVARKNGYPLPEGLPPTLQPEYLQAA
FPKPKWDCQLFDSYSESLPANQQPRDLNRMEKTSVKDMADLPVPNQDVTSDDKQA
LKSTINEALPKDVSEDPATPKDSNSLKARPRSRSYSSTSIEEAMKRGEDPPTPPPRPQK
THSRASSLDLNKVFQPSVPATKSGLLPPPPALPPRPCPSQSEQVSEAELLPQLSRAPSQ
AAESSPAKKDVLYSQPPSKPIRRKFRPENQATENQEPSTAASGPASAATMKPHPTVQ
KQSSKQKKAIQTAIRKNKEANAVLARLNSELQQQLKEVHQERIALENQLEQLRPVTV
L

FIGURE 12

CDK10 – Combined M & F

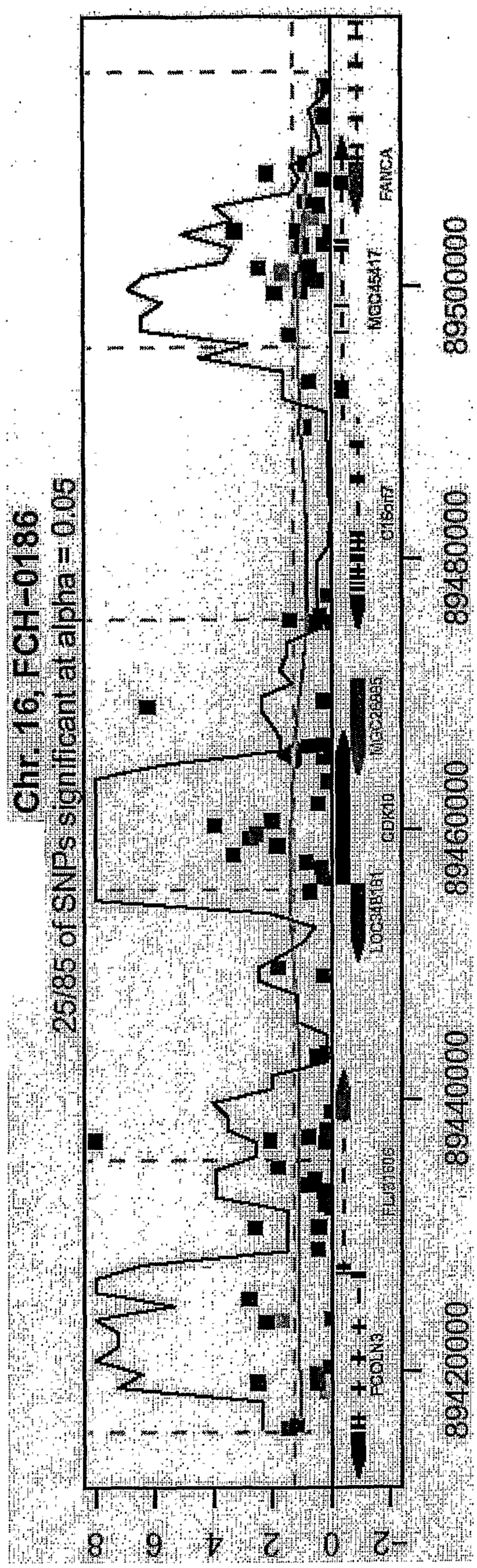


FIGURE 13

CDK10 – Females

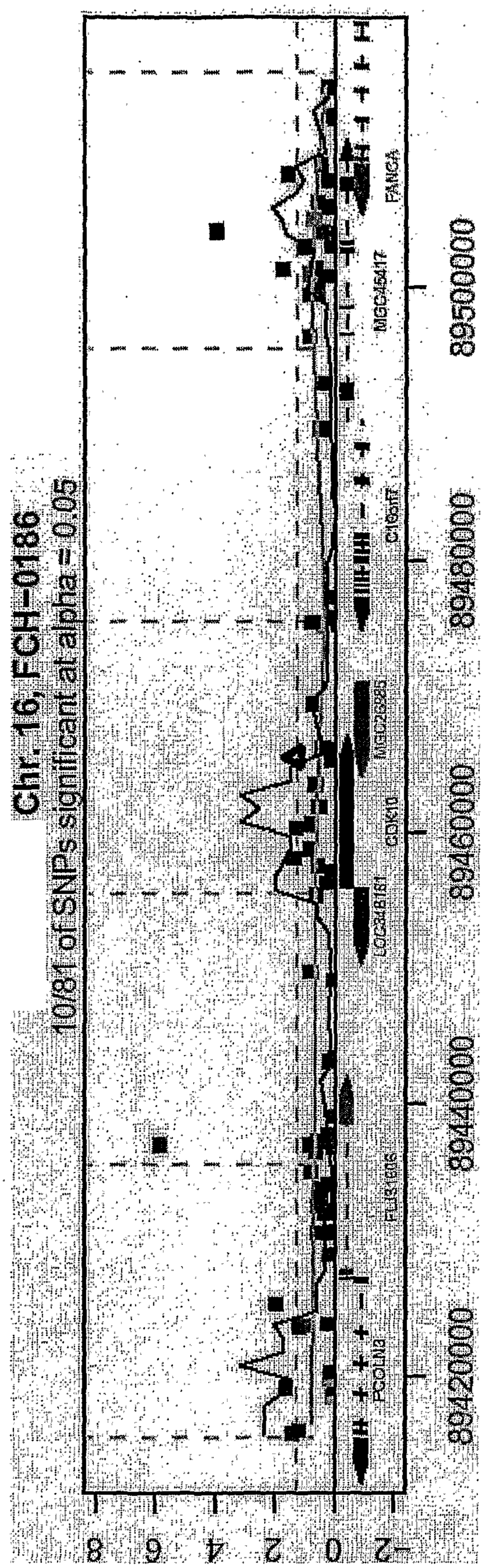
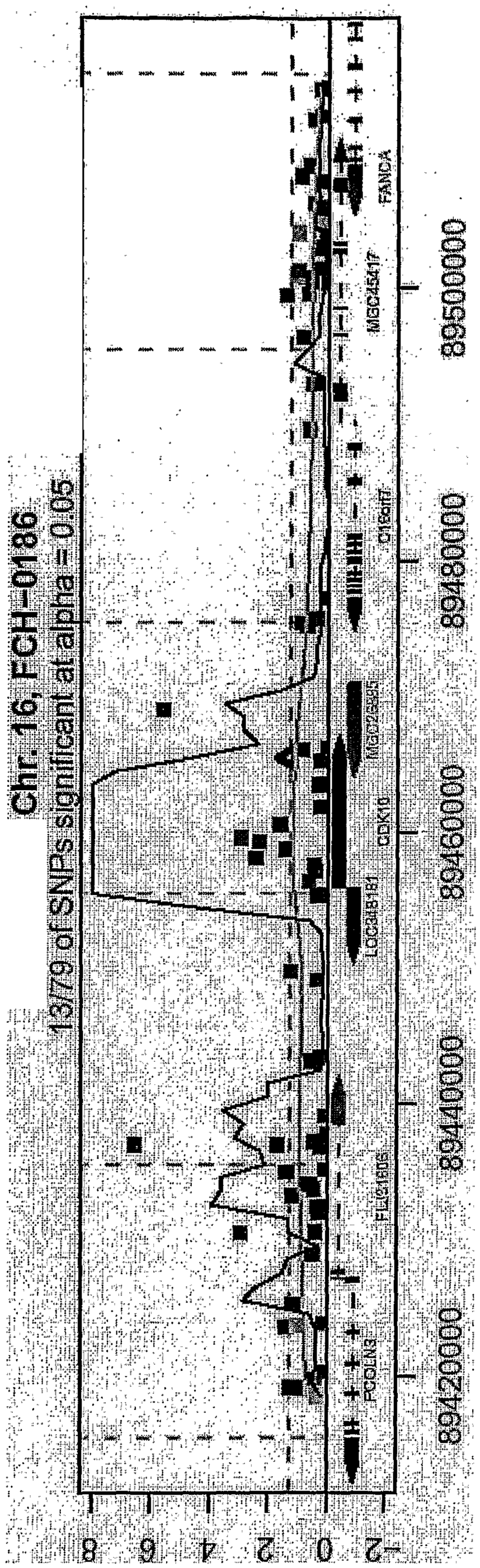


FIGURE 14

CDK10 – Males



Chromosome position

FIGURE 15

PCLO – Combined Females & Males

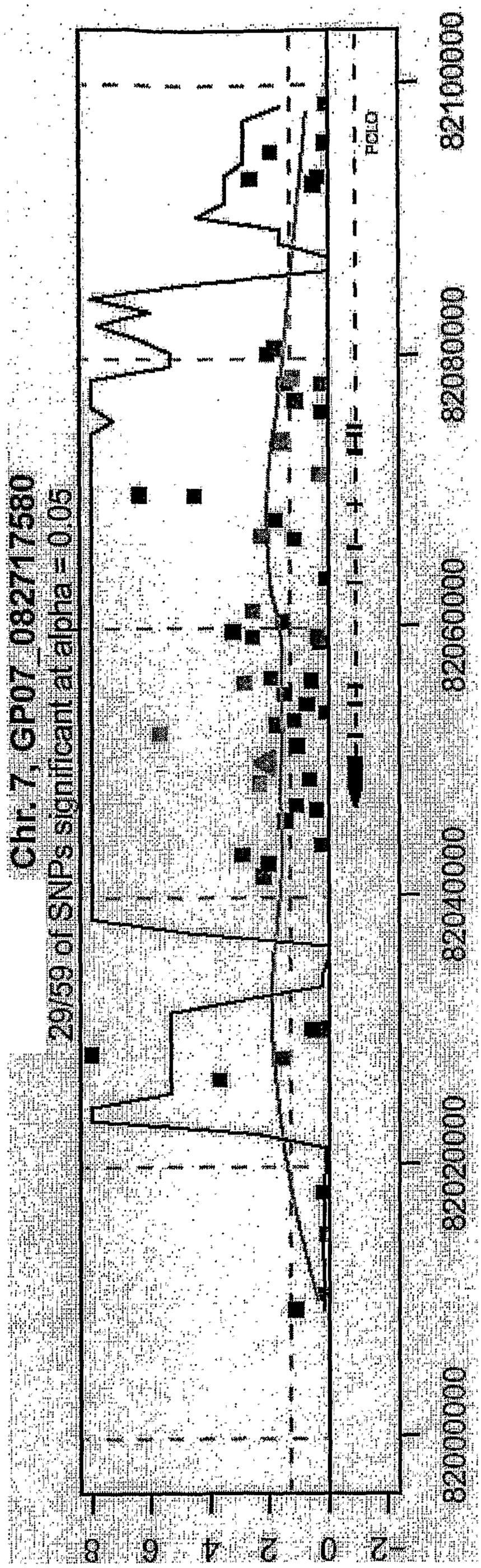


FIGURE 16

PCLO – Females

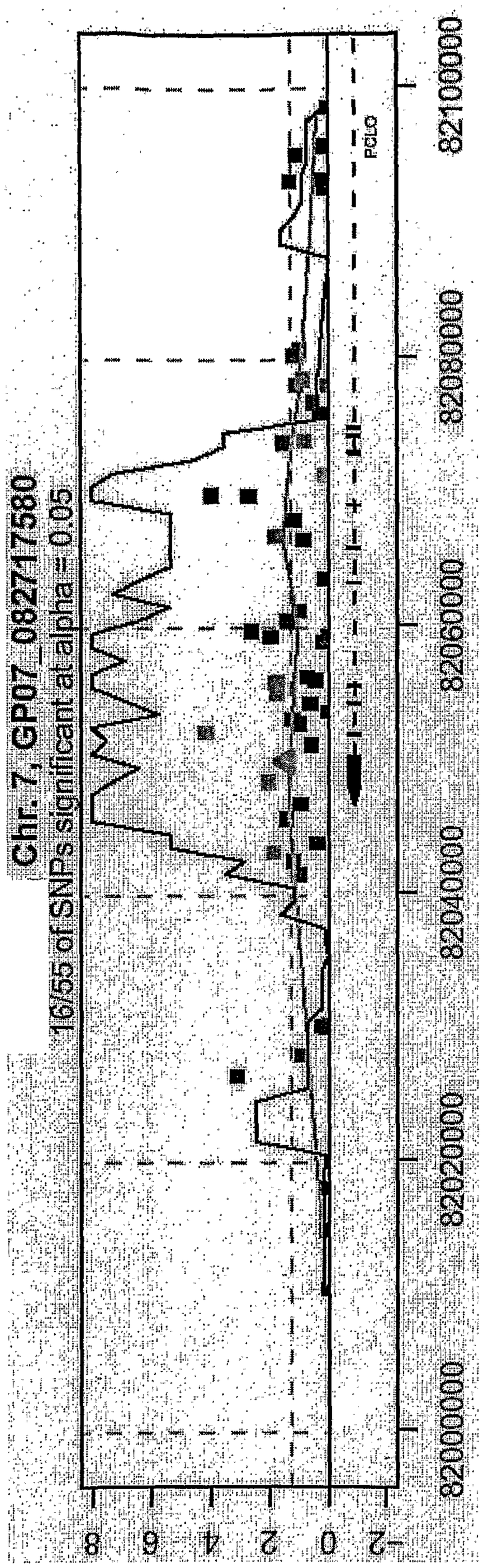


FIGURE 17

PCLO –Males

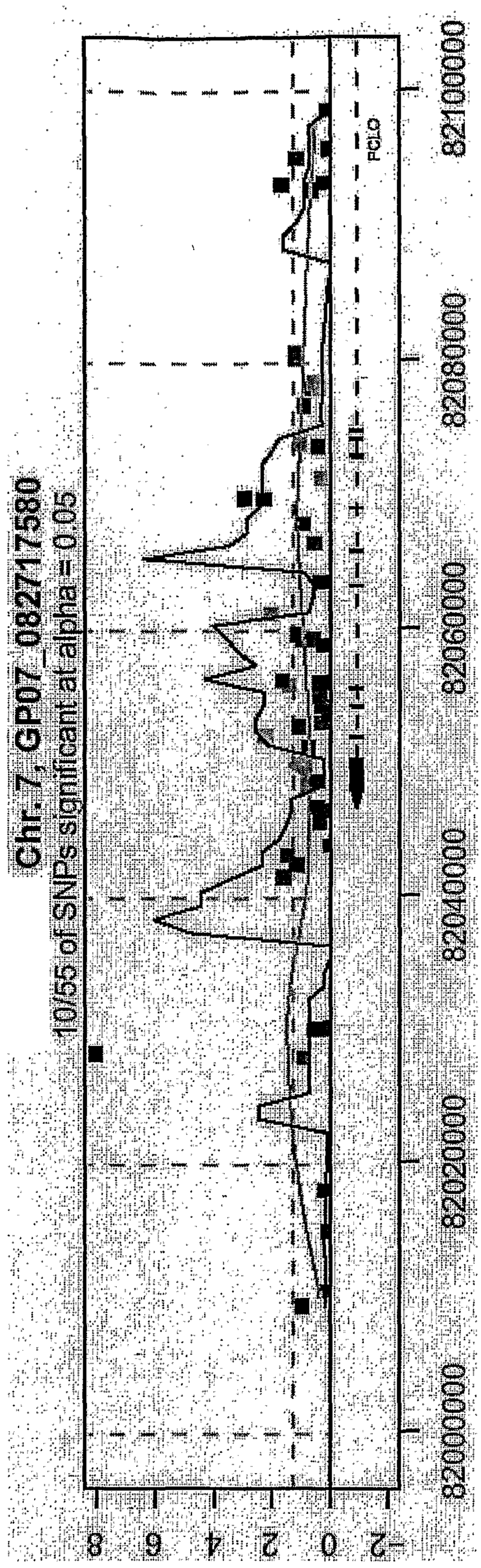


FIGURE 18

FPGT/CARK – Combined Males & Females

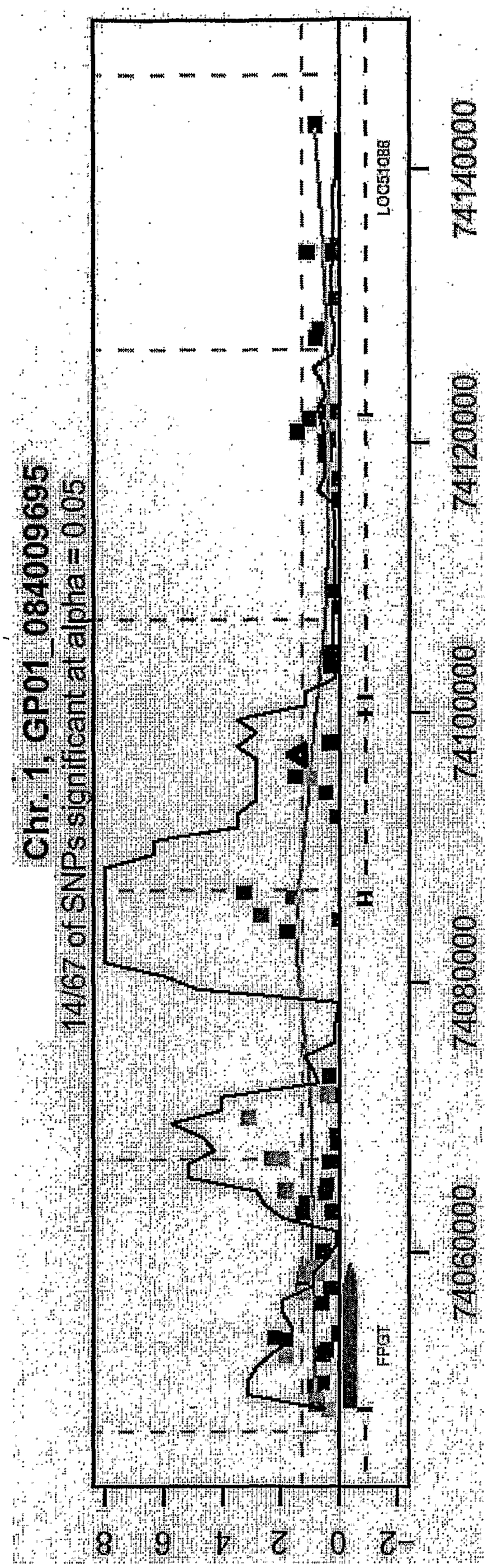


FIGURE 19

FPGT/CARK – Females

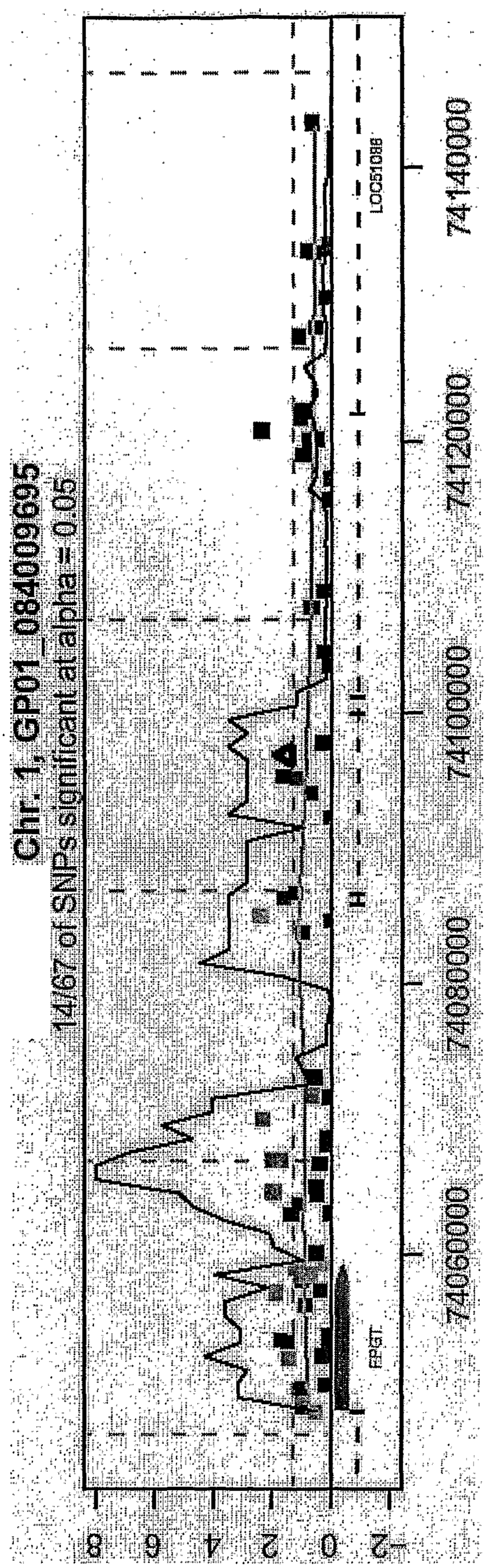
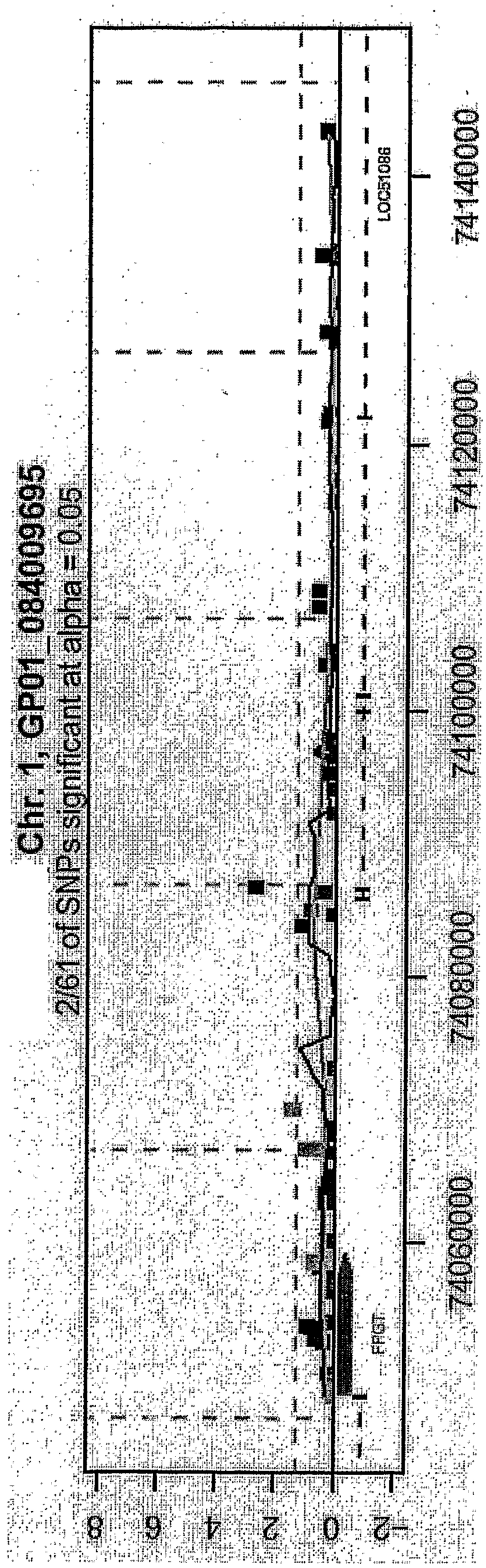


FIGURE 20

FPGT/CARK – Males



Chromosome position

FIGURE 21

WST-1 proliferation assay
CDK10 siRNA cocktail
(melanoma A375 cell line)

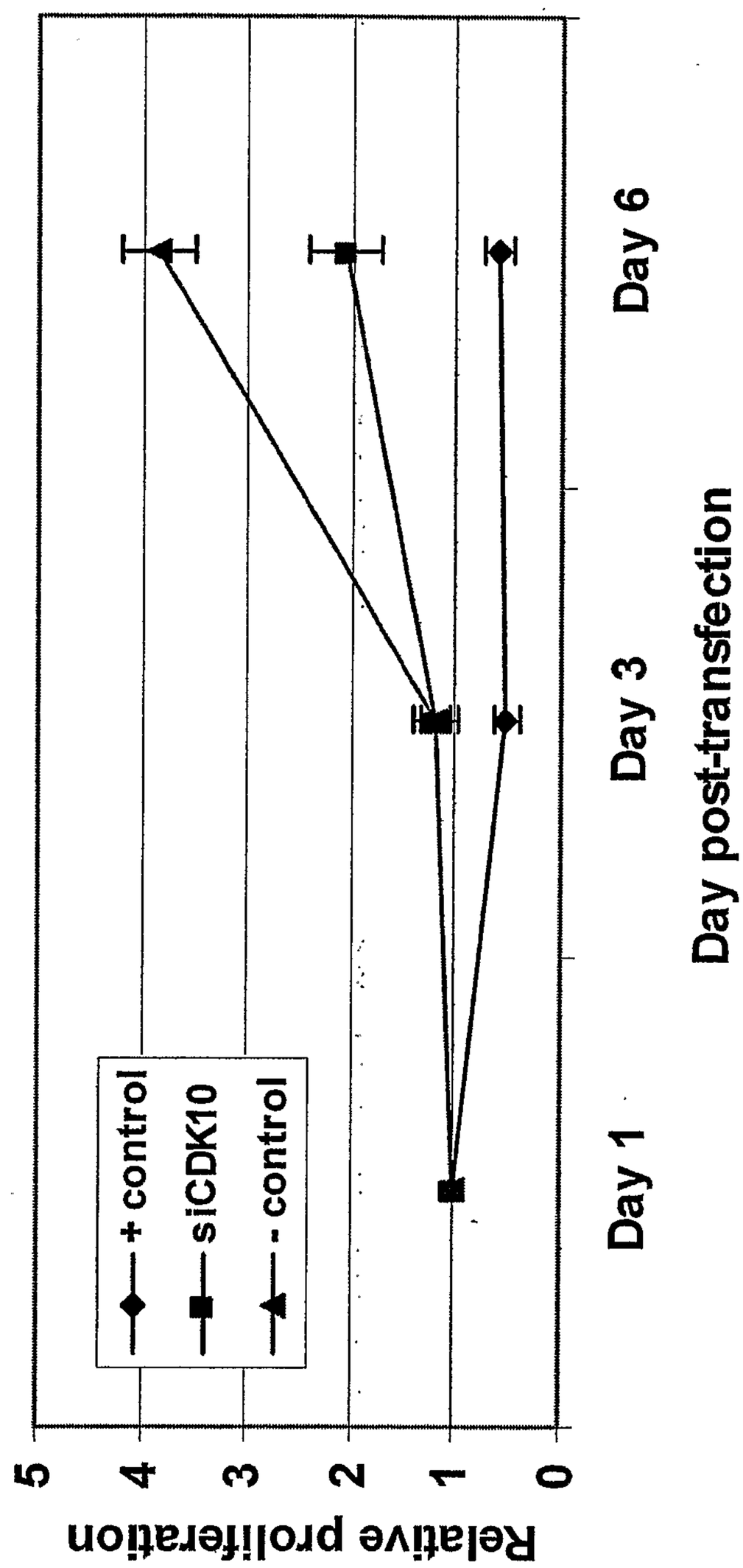


FIGURE 22-A

>X:16326411-16527030
rs1904528:38753

```
atggaggcgg cagcggcggc ggcggcggcg gcagcggcag cggcagcggc gggcgggggc      60
tgtggctccg ggccgccgcc gctgctgctg agcgagggcg agcagcagtg ctactccgag     120
ctcttcgcgc gctgtgccgg cgccgcgggc gggggccccg ggtctgggcc ccccgaggcc     180
gccagagtcg cccccggcac ggccactgcg gccgccggcc ccgtggctga cctgtttcgg     240
gcatcgcagc tgcccgccga gacgctgcac caggtgggtc cctccgcctc ctgtccctgc     300
gggtctgtgg ggcagtgtgt gcgggggcgg aggttgcgag tggggcgaca gggctgcccc     360
cagggacccg gaggcctcgg ccagttctga gagagaggac tctgcagccg gggatggcgg     420
cgacgccctt gtccccgggg gacaccagcc tccttcgcag ctcagctcct cgcccagtgc     480
tgggtgcgct ctccccatct tccttccctg agacagtctg acactctctc ccctcccccg     540
gccatttctg gggttctgca gccgcccaga cccaaagttt gtcctgttct ggaagtggtg     600
tttgttttgg ctgctgcctg gtttaacctc tgctcgctgc tcctgcccct ccctctcctg     660
agtgggttct cagggtgcct tgctgggatt tcaacttgaa gggtgtgtgt gtccgtaggg     720
ttcgaggccc agggctgaat gttgtcctct ctatgtagtt gtaatatata agtatctact     780
atatgtaatt gcccataaca tatttctaaa tattaatatt aaatcgaaaa ccttaatgac     840
aagttgcaga acagggacac gggactgcaa gaggacgttt gtcaagtcaa aaccaaattt     900
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```

FIGURE 22-B

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FIGURE 22-C

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FIGURE 22-D

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FIGURE 22-E

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FIGURE 22-F

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FIGURE 22-G

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FIGURE 22-H

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```

FIGURE 22-I

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FIGURE 22-J

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actcaactcc actcttaata gtgccaaaat ggctatagac aatatggaaa tgattgtgtg    40860
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agaaatcaaa gtctaaatag atggggaaca taccatgttc caggattgga agactcaaca    42000
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tctttgacaa aattgcaaca gcaattgaac ggagaaggaa agatagcctt tttgacaaat    42360
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ctagggaaat gtaaattcag accaaagtga gctatcacta catacctata agaatggcta    42900
aaattaaaaa tagtgacagc atcaaatgat ggcaaggctg tagagaaatg gaatcattca    42960
tactttgctg atgggatgta aaatgataca gcccctctga aaaacagttt ggcagtttct    43020
```

FIGURE 22-K

```
taaagacact aaacatgcaa ctaccatatg acccagcaat tgcactcctg ggcatttatc    43080
ccagagaagt gaagatttat gttcatataa atgccagtat gtgaatgttt tataggagtt    43140
ttattcataa tagcccataa ctggaaacaa tacagatgtt ctttagtgga tgaatggtta    43200
gacaaactgg tatatccata gcatggaata ctacccagca gtaaaaagga gtgaagtact    43260
gatacatgca atgatctgga tggatctcca gagaattatg ccgagtgaga aaagccaatc    43320
ctgagtggtt taaataccat atgattccat ttatgtaaca ttcttgaagt gacaaaatta    43380
tggagatgga gaacagatta gtccatgcca ggggttgagg gggcaagggt tgggagtaaa    43440
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cactttaaga ggccgaggcg ggtgaattgc ttgaggtcag gagtttgaga tcagcctgac    43560
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aagggtacat aggatctctg ggtatcattt cttacctctg catataaaac tacagttgtc    43980
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tctggctcag ttttgttatg aaatggagcc acgtgggtcc atgtgagtga gtccctgtgc    44160
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agagatccaa ggggcctgac ctttacaaac tgtttacagg ctatggagtt tgctggctca    46260
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ggtatggggc tgctcctgga actggatgtt gttcctgtca ctagaaaaca atcatctact    47280
gttcttgctg tttcacagca ctcattactg attcagatgc ccgtgtgcca cgtgtttata    47340
```

FIGURE 22-L

```
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tatgtgtgta tgtatatgtg tgtatatata cacacacgta catatatata catatatata     47520
cacacacgta catatatata cacacacgta catatatatg cacacacaca tatatataca     47580
cacacgtaac atttataata cgccatggaa tactactcag ccataaaaag gaatgaaata     47640
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gaatggaaaa ccgaacgttg tattttctca cttataagtg ggagctaagc tatgaggatg     47760
caaaggcata agaatgaaac agtggacttt ggggcctcag agggaagggt gggaggtgag     47820
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ctcagaaatc agcactgaag aacttaactc atgtaaccaa ataccatctg ttcccccaaa     47940
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cttatgaaaa tataagtaaa tgcatctata ttcaacccca ttttagaaga aatgatacct     51600
actatatcag ctgctttctg tgcaccttgc tttttttctt tttcacactt tagcatgatg     51660
```

FIGURE 22-M

```
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FIGURE 22-N

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FIGURE 22-O

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FIGURE 22-P

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FIGURE 22-Q

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FIGURE 22-R

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FIGURE 22-S

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FIGURE 22-T

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FIGURE 22-U

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FIGURE 22-V

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FIGURE 22-W

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FIGURE 22-X

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FIGURE 22-Y

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FIGURE 22-Z

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FIGURE 22-AA

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FIGURE 22-BB

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FIGURE 22-CC

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FIGURE 22-DD

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FIGURE 22-EE

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FIGURE 22-FF

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FIGURE 22-GG

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FIGURE 22-HH

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FIGURE 22-II

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FIGURE 22-JJ

```
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FIGURE 22-KK

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FIGURE 22-LL

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FIGURE 22-MM

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FIGURE 22-NN

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FIGURE 22-OO

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FIGURE 22-PP

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FIGURE 22-QQ

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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

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NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

4A

>gi|32528262|ref|NM_003674.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 1, mRNA

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4B

>gi|32528264|ref|NM_052987.2| Homo sapiens cyclin-dependent kinase (CDC2-like) 10 (CDK10), transcript variant 2, mRNA

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