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(54) Title: GENETIC ALTERATIONS IN ISOCITRATE DEHYDROGENASE AND OTHER GENES IN MALIGNANT GLIOMA

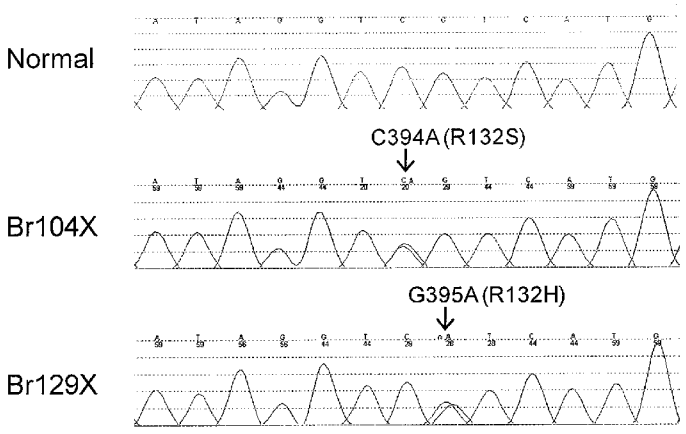

Fig. 1.

(57) Abstract: We found mutations of the R132 residue of isocitrate dehydrogenase 1 (IDH1) in the majority of grade II and III astrocytomas and oligodendrogliomas as well as in glioblastomas that develop from these lower grade lesions. Those tumors without mutations in IDH1 often had mutations at the analogous R172 residue of the closely related IDH2 gene. These findings have important implications for the pathogenesis and diagnosis of malignant gliomas.

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GENETIC ALTERATIONS IN ISOCITRATE DEHYDROGENASE AND OTHER GENES IN MALIGNANT GLIOMA

[01] This application was made using funds from the United States government. Therefore the U.S. government retains certain rights in the invention under the terms of NIH grants CA 43460, CA 57345, CA 62924, R01CA118822, NS20023-21, R37CA11898-34, and CA 121113.

TECHNICAL FIELD OF THE INVENTION

[02] This invention is related to the area of cancer diagnostics, prognostics, drug screening, and therapeutics. In particular, it relates to brain tumors in general, and glioblastoma multiforme, in particular.

BACKGROUND OF THE INVENTION

[03] Gliomas, the most common type of primary brain tumors, are classified as Grade I to Grade IV using histopathological and clinical criteria established by the World Health Organization (WHO) [1]. This group of tumors includes a number of specific histologies, the most common of which are astrocytomas, oligodendrogliomas, and ependymomas. Grade I gliomas, often considered to be benign lesions, are generally curable with complete surgical resection and rarely, if ever, evolve into higher-grade lesions[2]. However, tumors of Grades II and III are malignant tumors that grow invasively, progress to higher-grade lesions, and carry a correspondingly poor prognosis. Grade IV tumors (glioblastoma multiforme, GBM) are the most invasive form and have a

dismal prognosis[3, 4]. Using histopathologic criteria, it is impossible to distinguish a secondary GBM, defined as one which occurs in a patient previously diagnosed with a lower grade glioma, from a primary GBM which has no known antecedent tumor [5, 6].

[04] A number of genes are known to be genetically altered in gliomas, including TP53, PTEN, CDKN2A, and EGFR [7-12]. These alterations tend to occur in a defined order in the progression to high grade tumors. TP53 mutation appears to be a relatively early event during astrocytoma development, while loss or mutation of PTEN and amplification of EGFR are characteristic of higher-grade tumors[6,13,14]. In oligodendrogliomas, allelic losses of 1p and 19q occur in many Grade II tumors while losses of 9p21 are largely confined to Grade III tumors[15].

[05] There is a continuing need in the art to identify the causes, identifiers, and remedies for glioblastomas and other brain tumors.

SUMMARY OF THE INVENTION

[06] According to one aspect of the invention a method is provided of characterizing a glioblastoma multiforme (GBM) tumor in a human subject. A GBM tumor is analyzed to identify the presence or absence of a somatic mutation at codon 132 in isocitrate dehydrogenase 1 (*IDH1*) or at codon 172 in isocitrate dehydrogenase 2 (*IDH2*) in a GBM tumor of a human subject.

[07] Also provided as another aspect of the invention is an isolated antibody which specifically binds R132H IDH1, or R132C IDH1, or R132S IDH1, or R132L IDH1, or R132G IDH1, but not R132 IDH1; or R172M IDH2, R172G IDH2, or R172K IDH2, but not R172; *i.e.,* mutant forms of IDH1 or IDH2 which are found in GBM. Also provided is an isolated antibody which specifically binds R132 IDH1 or R172 IDH2, *i.e.,* wild-type active sites of IDH1 or IDH2.

[08] Another aspect of the invention is a method of immunizing a mammal. An IDH1 mutant polypolypeptide comprising at least 8 contiguous amino acid residues of a human IDH1 protein or an IDH2 mutant polypolypeptide comprising at least 8 contiguous amino acid residues of a human IDH2 protein found in a human tumor is administered to a mammal. The at least 8 contiguous amino acid residues comprise residue 132 or IDH1 or residue 172 of IDH2. Residue 132 or residue 172 is not arginine. Antibodies and/ or T cells which are immunoreactive with epitopes found on the IDH1 or IDH2 mutant polypeptide but not found on normal IDH1 or IDH2 are produced.

[09] Also provided as another aspect of the invention is an IDH1 or IDH2 mutant polypeptide comprising at least 8 but less than 200 contiguous amino acid residues of a human IDH1 or IDH2 protein found in a human tumor. The at least 8 contiguous amino acid residues comprise residue 132 of IDH1 or residue 172 of IDH2. Residues 132 or 172 are not R.

[10] An additional aspect of the invention is an isolated polynucleotide comprising at least 18 but less than 600 contiguous nucleotide residues of a coding sequence of a human IDH1 or human IDH2 protein found in

a human tumor. The at least 18 contiguous amino acid residues comprise nucleotides 394 and/or 395 of IDH1 or nucleotide 515 or IDH2. Nucleotides 394 and/or 395 of *IDH1* are not C and/or G, respectively. Residue 515 of *IDH2* is not G.

[11] Another aspect of the invention is a method of immunizing a mammal. An IDH1 polypeptide comprising at least 8 contiguous amino acid residues of a human IDH1 protein or an IDH2 polypeptide comprising at least 8 contiguous amino acid residues of a human IDH2 protein is administered to a mammal. The at least 8 contiguous amino acid residues comprise residue 132 of IDH1 or residue 172 of IDH2. Residue 132 or residue 172 is arginine. Antibodies and/ or T cells which are immunoreactive with epitopes found on the IDH1 or IDH2 polypeptide are produced.

[12] Also provided as another aspect of the invention is an IDH1 or IDH2 polypeptide comprising at least 8 but less than 200 contiguous amino acid residues of a human IDH1 or IDH2 protein. The at least 8 contiguous amino acid residues comprise residue 132 of IDH1 or residue 172 of IDH2. Residues 132 or 172 are R.

[13] Still another aspect of the invention is a method of detecting or diagnosing glioblastoma multiforme (GBM) or minimal residual disease of GBM or molecular relapse of GBM in a human. A somatic mutation in a gene or its encoded mRNA or protein is determined in a test sample relative to a normal sample of the human. The gene is selected from the group consisting of those listed in **Figure 10, Table S7.** The human is identified as likely to have glioblastoma multiforme, minimal residual

disease, or molecular relapse of GBM when the somatic mutation is determined.

[14] Yet another aspect of the invention is a method of characterizing a glioblastoma multiforme in a human. A CAN-gene mutational signature for a glioblastoma multiforme is determined by determining in a test sample relative to a normal sample of the human, a somatic mutation in at least one gene or its encoded cDNA or protein. The gene is selected from the group consisting of those listed in **Figure 10, Table S7.** The glioblastoma multiforme is assigned to a first group of glioblastoma multiforme tumors that have the CAN-gene mutational signature.

[15] Another method provided by the invention is for characterizing a glioblastoma multiforme tumor in a human. A mutated pathway selected from the group consisting of TP53, RB1, and PI3K/PTEN is identified in a glioblastoma multiforme tumor by determining at least one somatic mutation in a test sample relative to a normal sample of the human. The at least one somatic mutation is in one or more genes selected from the group consisting of TP53, MDM2, MDM4, RB1, CDK4, CDKN2A, PTEN, PIK3CA, PIK3R1, and IRS1. The glioblastoma multiforme is assigned to a first group of glioblastoma multiforme tumors that have a mutation in one of said pathways. The first group is heterogeneous with respect to the genes in the pathway that have a somatic mutation and homogeneous with respect to the pathway that has a somatic mutation.

[16] Also provided is a method to detect or diagnose glioblastoma multiforme, or minimal residual disease of GBM or molecular relapse of GBM in a human. Expression is determined in a clinical sample of one or more genes listed in **Figure 10, Table S5 or S9** (brain overexpressed genes from SAGE). The expression of the one or more genes in the clinical sample is compared to expression of the one or more genes in a corresponding sample of a control human or control group of humans. A clinical sample with elevated expression relative to a control is identified as likely to have glioblastoma multiforme, or minimal residual disease of GBM or molecular relapse of GBM in a human.

[17] Another aspect of the invention is a method to monitor glioblastoma multiforme burden. Expression in a clinical sample is determined of one or more genes listed in **Figure 10, Table S5 or S9** (brain overexpressed genes from SAGE). The step of determining is repeated one or more times. An increase, decrease or stable level of expression over time is identified.

[18] Yet another aspect of the invention is a method to monitor glioblastoma multiforme burden. A somatic mutation is determined in a clinical sample of one or more genes listed in **Figure 10, Table S7.** The step of determining is repeated one or more times. An increase, decrease or stable level of said somatic mutation over time is identified.

[19] Still another aspect of the invention relates to a method to detect or diagnose gliobastoma multiforme. Expression in a clinical sample of one or more genes listed in **Figure 10, Table S6** (homozygous

deletions) is determined. Expression of the one or more genes in the clinical sample is compared to expression of the one or more genes in a corresponding sample of a control human or control group of humans. A clinical sample with reduced expression relative to a control is identified as likely to have gliobastoma multiforme.

[20] A further aspect of the invention is a method to monitor gliobastoma multiforme burden. Expression in a clinical sample of one or more genes listed in **Figure 10, Table S6** (homozygous deletions) is determined. The step of determining is repeated one or more times. An increase, decrease or stable level of expression over time is identified.

[21] These and other embodiments which will be apparent to those of skill in the art upon reading the specification provide the art with new tools for analyzing, detecting, stratifying and treating GBM.

BRIEF DESCRIPTION OF THE DRAWINGS

[22] **Fig. 1. Sequence alterations in IDH1.** Representative examples of somatic mutations at codon 132 of the IDH1 gene. The top sequence chromatogram was obtained from analysis of DNA from normal tissue while the lower chromatograms were obtained from the indicated GBM samples. Arrows indicate the location of the recurrent heterozygous missense mutations C394A (in tumor Br104X) and G395A (in tumor Br129X) resulting in the indicated amino acid changes.

[23] **Fig. 2. Structure of the active site of IDH1.** The crystal structure of the human cytosolic NADP(+) -dependent IDH is shown in ribbon

format (PDBID: 1T0L) (*42*). The active cleft of IDH1 consists of a NADP-binding site and the isocitrate-metal ion-binding site. The alpha-carboxylate oxygen and the hydroxyl group of isocitrate chelate the Ca2+ ion. NADP is colored in orange, isocitrate in purple and Ca2+ in blue. The Arg132 residue, displayed in yellow, forms hydrophilic interactions, shown in red, with the alpha-carboxylate of isocitrate.

[24] **Fig. 3.** Overall survival among patients < 45 years old according to IDH1 mutation status. The hazard ratio for death among patients with mutated IDH1, as compared to those with wildtype IDH1, was 0.19 (95 percent confidence interval, 0.08 to 0.49; P< 0.001). The median survival was 3.8 years for patients with mutated IDH1, as compared to 1.5 years for patients with wildtype IDH1.

[25] **Fig. 4A-4B. *IDH1* and *IDH2* mutations in human gliomas. Fig. 4**A. Schematic diagram of mutations at codon R132 in IDH1 (bottom) and R172 in IDH2 (top) identified in human gliomas. Codons 130 to 134 of IDH1 and 170 to 174 of IDH2 are shown. The number of patients with each mutation (n) is listed at the right of the figure. **Fig. 4**B. Number and frequency of *IDH1* and *IDH2* mutations in human gliomas and other tumor types. The non-CNS cancers included 35 lung cancers, 57 gastric cancers, 27 ovarian cancers, 96 breast cancers, 114 colorectal cancers, 95 pancreatic cancers, seven prostate cancers, and peripheral blood specimens from 4 chronic myelogenous leukemias, 7 chronic lymphocytic leukemias, seven acute lymphoblastic leukemias, and 45 acute myelogenous leukemias.

[26] **Fig. 5A-5B.** Survival for patients with malignant gliomas according to IDH1 and IDH2 mutation status. For patients with anaplastic astrocytomas (Fig. 5A), the median survival was 65 months for patients with mutated IDH1 or IDH2, as compared to 19 months for patients with wildtype IDH1 and IDH2.

For patients with GBM (Fig. 5B), the median survival was 39 months for patients with mutated IDH1 or IDH2, as compared to 13.5 months for patients with wildtype IDH1 and IDH2.

[27] **Fig. 6. Model of malignant glioma development.** For each tumor type common genetic alterations (*IDH1/IDH2* mutation, *TP53* mutation, 1p 19q loss, and *CDKN2A* loss) are indicated. Detailed frequencies of genetic alterations are contained in Table 1 and 2 or **reference**[1]. In general, tumors on the right acquire *IDH* alterations, while those on the left do not.

[28] **Fig. 7. Sequence alterations in *IDH1* and *IDH2*.** Representative examples of somatic mutations at codon 132 of the *IDH1* gene (top) and codon 172 of the *IDH2* gene (bottom). In each case, the top sequence chromatogram was obtained from analysis of DNA from normal tissue while the lower chromatograms were obtained from the indicated tumor samples. Arrows indicate the location of the missense mutations and resulting amino acid changes in *IDH1* in tumor TB2604 (anaplastic astrocytoma), 640 (anaplastic astrocytoma), and 1088 (anaplastic oligodendroglioma), and in I*DH2* in tumor H883 (anaplastic astrocytoma) and H476 (anaplastic oligodendroglioma).

[29] **Fig. 8. Sequence alterations in *IDH1* in progressive gliomas.** Representative examples of somatic mutations at codon 132 of the *IDH1* are indicated in three representative cases. The top sequence chromatogram was obtained from analysis of DNA from normal tissue while the lower chromatograms were obtained from the indicated brain

tumor samples. Arrows indicate the location of the mutations and the resulting amino acid changes in *IDH1*. In all cases, the identical *IDH1* mutations were found in the lower- and higher-grade tumors from each patient.

[30] **Fig. 9A-9B. Age distribution of glioma patients with mutated and wild-type *IDH*.** Age distribution of oligodendroglioma (O), anaplastica oligodendroglioma (AO), diffuse astrocytoma (DA), anaplastic astrocytoma (AA), and glioblastoma multiforme (GBM) in patients with wild-type *IDH* genes (**Fig. 9**A) or mutated IDH genes (**Fig. 9** B).

[31] **Fig. 10. Compendium of Tables S3-S10.** Table S3 (somatic mutations identified in GBM discovery screen). Tables S4 (somatic mutations in prevalence screen), Table S5 (amplified genes), Table S6 (homozygously deleted genes), Table S7 (top CAN-candidate genes), Table S8 (candidate gene sets enriched for genetic alterations in GBM), Table S9 (overexpressed genes in SAGE), and Table S10 (extracellular subset of overexpressed genes in SAGE).

[32] **Fig. 11. Summary of genetic and clinical characteristics of brain tumors.**

[33] **Fig. 12. Evaluation of frequency of common genetic alterations in IDH1/IDH2 mutated and wildtype gliomas.**

[34] **A sequence listing** is part of this application.

DETAILED DESCRIPTION OF THE INVENTION

[35] In a genome-wide analysis of GBMs, we identified somatic mutations of codon 132 of the isocitrate dehydrogenase 1 gene (IDH1) in ~12% of GBMs analyzed [16]. These mutations were found at higher frequency in secondary GBMs (5 of 6 patients evaluated). One interpretation of these data is that IDH1 mutations occur in a subset of lower-grade gliomas, driving them to progress to GBMs. To evaluate this possibility, we have analyzed a large number of gliomas of various types. Remarkably, we found IDH1 mutations in the majority of early malignant gliomas. Furthermore, many of the gliomas without IDH1 mutations had analogous mutations in the closely related IDH2 gene. These results suggest that IDH mutations play an early and essential role in malignant glioma development.

[36] Somatic mutations are mutations which occur in a particular clone of somatic cells during the lifetime of the individual organism. The mutation is thus not inherited or passed on. The mutation will appear as a difference relative to other cells, tissues, organs. When testing for a somatic mutation in a brain tissue suspected of being cancerous, a comparison can be made to normal brain tissue that appears to be non-neoplastic, or to a non-brain sample, such as blood cells, or to a sample from an unaffected individual.

[37] The common amino acid at codon 132 of IDH1 and codon 172 of IDH2 in healthy tissues is arginine (R). Mutant codons have been found with substitutions of histidine (H), serine (S), and cysteine (C), leucine (L), and glycine (G) of IDH1 codon 132 and of methionine (M), lysine (K), and glycine (G) of codon 172 of IDH2. The mutations at codon

132 and codon 172 can be detected using any means known in the art, including at the DNA, mRNA, or protein levels. Antibodies which specifically bind to the arginine-132 form of the enzyme, the histidine-132 form of the enzyme, the serine-132 form of the enzyme, leucine-132 form of the enzyme, glycine-132 form of the enzyme, or the cysteine-132 form of the enzyme can be used in assays for mutation detection. Likewise antibodies which specifically bind to the arginine-172, methionine-172, lysine-172, or glycine-172 forms of IDH2 can be used in assays for mutation detection. Similarly, probes which contain codons for these amino acid residues in the context of the coding sequence of IDH1 or IDH2 can be used for detecting the gene or mRNA of the different forms. Primers which contain all or part of these codons can also be used for allele-specific amplification or extension. Primers hybridizing to regions surrounding these codons can be used to amplify the codons, followed by subsequent analysis of the amplified region containing codon 132 of IDH1 or codon 172 of IDH2.

[38] Interestingly, the codon 132 mutations of IDH1 and codon 172 mutations of IDH2 have been found to be strongly associated with secondary GBM and with a favorable prognosis. Drugs can be tested against groups of glioblastoma patients that are stratified with regard to the 132nd amino acid residue of IDH1 and/or the 172nd amino acid residue of IDH2. The groups may comprise wild-type (arginine) and variants (combined) or variants (each separately). Drug sensitivity can be determined for each group to identify drugs which will or will not be efficacious relative to a particular mutation or wild-type (arginine). Both sensitivity and resistance information are useful to guide treatment decisions.

[39] Once a codon 132 or 172 mutation is identified in a tumor, inhibitors of IDH1 or IDH2 may be used therapeutically. Such inhibitors may be specific for a mutation in the tumor or may simply be an inhibitor of IDH1 or IDH2. Small molecule inhibitors as well as antibodies and antibody-derivatives can be used. Such antibodies include monoclonal and polyclonal antibodies, ScFv antibodies, and other constructs which comprise one or more antibody Fv moieties. Antibodies can be humanized, human, or chimeric, for example. Antibodies may be armed or unarmed. Armed antibodies may be conjugated to toxins or radioactive moieties, for example. Unarmed antibodies may function to bind to tumor cells and participate in host immunological processes, such as antibody-dependent cell-medicated cytotoxicity. Antibodies may preferentially bind to mutant versus wild-type IDH1 or IDH2, specifically bind to mutant versus wild-type IDH1 or IDH2, or bind equally to both mutant and wild-type IDH1 or IDH2. Preferably the antibodies will bind to an epitope in the active site which may include codon 132 or codon 172. Epitopes may be continuous or discontinuous along the primary sequence of the protein. Inhibitors may include alpha-methyl isocitrate, aluminum ions, or oxalomalate. Other inhibitors may be used and optionally identified using enzyme assays known in the art, including spectrophotometric assays (Kornberg, A., 1955) and bioluminescent assays (Raunio, R. et al., 1985). Inhibitors may be alternatively identified by binding tests, for example by *in vitro* or *in vivo* binding assays. Peptides and proteins which bind to IDH1 or IDH2 may also be used as inhibitors.

[40] Inhibitory RNA molecules may be used to inhibit expression. These may be, for example, siRNA, microRNA or antisense oligonucleotides

or constructs. These can be used to inhibit the expression of IDH1 or IDH2 as appropriate in a human.

[41] Potential therapeutic efficacy can be tested for an antibody, polynucleotide, protein, small molecule, or antibody by contacting with cells, tissues, whole animals, or proteins. Indications of efficacy include modulation of enzyme activity, inhibition of cancer cell growth, prolongation of life expectancy, inhibition of cancer cell proliferation, stimulation of cancer cell apoptosis, and inhibition or retardation of tumor growth. Any assays known in the art can be used, without limitation. Combinations of candidates and combinations of candidates with known agents can be assessed as well. Known agents may include, for example, chemotherapeutic anti-cancer agents, biological anti-cancer agents, such as antibodies and hormones, radiation.

[42] In order to raise or increase an immune response to a glioblastoma in a person or mammal with a tumor, in a person with a likelihood of developing a tumor, or in an apparently healthy individual, a polypeptide can be administered to the person or mammal. The polypeptide will typically comprise at least 6, at least 8, at least 10, at least 12, or at least 14 contiguous amino acid residues of human IDH1 protein including residue 132 or IDH2 including residue 172. Typically but not always, the polypeptide will contain a residue other than arginine at residue 132 of IDH1 or residue 172 or IDH2. In the situation where the person or mammal already has a tumor, the amino acid at residue 132 can be matched to the residue in the tumor. The polypeptide may comprise the whole of IDH1, but can comprise less than 200, less than 150, less than 100, less than 50, less than 30 amino acid residues. Although applicants do not wish to be bound by any

mechanism of action, the polypeptide immunization may act though an antibody and/or T cell response. Polypeptides can be administered with immune adjuvants or conjugated to moieties which stimulate an immune response. These are well known in the art, and can be used as appropriate.

[43] Antibodies which specifically bind to an epitope on IDH1 or IDH2 do so with a higher avidity or a higher association rate than they bind to other proteins. Preferably the higher avidity or rate of association is at least about 2-fold, 5-fold, 7-fold, or 10-fold relative to other proteins that do not contain the epitope.

[44] An isolated polynucleotide can be used to encode and deliver the polypeptide for immunization. The polynucleotide can be used to manufacture the polypeptide in a host cell in culture, or may be used in a gene therapy context to raise an immune response *in vivo* upon expression in the vaccine recipient. Polynucleotides can also be used as primers or probes, which may or may not be labeled with a detectable label. Primers can be used for primer extension, for example, using a primer that is complementary to nucleotides adjacent to but not including either nt 394 or nt 395 of IDH1 or nucleotide 515 of IDH2. Products can be detected and distinguished using labeled nucleotides as reagents. Different labels may be used on different nucleotides so that the identity of the analyte can be readily determined. Typically the polynucleotide for use as a primer or probe will comprise at least 10, at least 12, at least 14, at least 16, at least 18, at least 20 contiguous nucleotides of IDH1 or IDH2 coding sequence. Typically the polynucleotide will comprise less than 600, less than 500, less than 400,

less than 300, less than 200, less than 100 nucleotides of IDH1 or IDH2 coding sequence.

[45] Our data identified IDH1 as a major target of genetic alteration in patients with GBM. All mutations in this gene resulted in amino acid substitutions at position 132, an evolutionarily conserved residue located within the isocitrate binding site (42). In addition, the only previously-reported mutation of IDH1 was another missense mutation affecting this same residue in a colorectal cancer patient (10). The functional effect of these IDH1 mutations is unclear. The recurrent nature of the mutations is reminiscent of activating alterations in other oncogenes such as BRAF, KRAS, and PIK3CA. The prediction that this mutation would be activating is strengthened by the lack of observed inactivating changes (i.e. frameshift or stop mutations, splice site alterations), the lack of alterations in other key residues of the active site, and by the fact that all mutations observed to date were heterozygous (without any evidence of loss of the second allele through LOH). Interestingly, enzymatic studies have shown that substitution of arginine at residue 132 with glutamate results in a catalytically inactive enzyme suggesting that this residue plays a critical role in IDH1 activity(46). However, the nature of the substitutions observed in GBMs is qualitatively different, with arginine changed to histidine or serine. Histidine forms hydrogen bonding interactions with carboxylate as part of the catalytic activity of many enzymes (47), and could serve an analogous function to the known interaction of Arg132 and the α-carboxylate of isocitrate. It is conceivable that R132H alterations may lead to higher overall catalytic activity. Increased activity of IDH1 would be expected to result in higher levels of NADPH, providing additional cellular defenses against reactive oxygen species, preventing

apoptosis and increasing cellular survival and tumor growth. Further biochemical and molecular analyses will be needed to determine the effect of alterations of IDH1 on enzymatic activity and cellular phenotypes.

[46] Regardless of the specific molecular consequences of IDH1 and IDH2 alterations, it is clear that detection of mutations in IDH1 and IDH2 will be clinically useful. Although significant effort has focused on the identification of characteristic genetic lesions in primary and secondary GBMs, the altered genes identified to date are far from perfect for this purpose. For example, in comparing primary versus secondary GBMs, TP53 is mutated in ~30% vs. 65%, respectively, EFGR amplification is present in ~35% vs. 5-10%, and PTEN mutation is present in ~25% vs. ~5% (5). Our study revealed IDH1 mutation to be a novel and significantly more specific marker for secondary GBM, with 5 of the 6 (83%) secondary GBM samples analyzed having a mutation in this gene, while only 7 of 99 (7%) primary GBM patients had such alterations ($P<0.001$, binomial test). The sole secondary GBM patient sample that did not have an IDH1 mutation was both genetically and clinically unusual, harboring mutations of PTEN but not TP53, and occurring in an older patient (age 56 years) with a prior diagnosis of ganglioglioma (which is rarely known to undergo malignant transformation) (48). It is possible that this patient had two distinct CNS tumors which were completely unrelated, and that the GBM in this case was actually a primary tumor.

[47] One intriguing hypothesis is that IDH1 alterations identify a biologically-specific subgroup of GBM patients, including both patients who would be classified as having secondary GBMs as well as a

subpopulation of primary GBM patients with a similar tumor biology and more protracted clinical course (Table 4). Interestingly, patients with IDH1 mutations had a very high frequency of TP53 mutation and a very low frequency of mutations in other commonly-altered GBM genes. For example, such patients had TP53 mutation without any detected mutation of EGFR, PTEN, RB1, or NF1 in 83% of cases (10 of 12 patients); in contrast, only 12% of patients with wildtype IDH1 (11 of 93) had the same mutation pattern (Fig. 12)($P<0.001$, binomial test). In addition to this relative genetic uniformity, the patients with mutated IDH1 had distinct clinical characteristics, including younger age and a significantly improved clinical prognosis (Table 4) even after adjustment for age and TP53 mutation status (both of which are associated with improved survival). Perhaps most surprisingly, they all shared mutation of a single amino acid residue of IDH1, a protein that previously had no genetic link to GBMs or other cancers. This unforeseen result clearly validates the utility of genome-wide screening for genetic alterations in the study of human cancers.

[48] Mutations that have been found in GBM tumors are shown in Figure 10, Table S7. These mutations can be detected in test samples, such as suspected tumor tissue samples, blood, CSF, urine, saliva, lymph etc. A somatic mutation is typically determined by comparing a sequence in the test sample to a sequence in a normal control sample, such as from healthy brain tissue. One or more mutations can be used for this purpose. If the patient has undergone surgery, detection of the mutation in tumor margin or remaining tissue can be used to detect minimal residual disease or molecular relapse. If GBM has been previously undiagnosed, the mutation may serve to help diagnose, for example in conjunction with

other physical findings or laboratory results, including but not limited to biochemical markers and radiological findings.

[49] CAN-gene signatures can be determined in order to characterize a GBM. A signature is a set of one or more somatic mutations in a CAN gene. The CAN genes for GBM are listed in Fig. 10, Table S7. Once such a signature has been determined, a GBM can be assigned to a group of GBMs sharing the signature. The group can be used to assign a prognosis, to assign to a clinical trial group, to assign to a treatment regimen, and/or to assign for further characterization and studies. In a clinical trial group, drugs can be assessed for the ability to differentially affect GBMs with and without the signature. Once a differential effect is determined, the signature can be used to assign patients to drug regimens, or to avoid unnecessarily treating patients in whom the drug will not have a beneficial effect. The drug in a clinical trial can be one which is previously known for another purpose, previously known for treating GBM, or previously unknown as a therapeutic. A CAN-gene signature may comprise at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9. at least 10 genes. The number of genes or mutations in a particular signature may vary depending on the identity of the CAN genes in the signature. Standard statistical analyses can be used to achieve desired sensitivity and specificity of a CAN gene signature.

[50] Analysis of the mutated genes in the analyzed GBM tumors has revealed interesting involvement of pathways. Certain pathways frequently carry mutations in GBMs. A single gene mutation appears to exclude the presence of a mutation in another gene in that pathway in a particular tumor. Frequently mutated pathways in GBMs are the TP53,

RB1, PI3K/PTEN pathways. Pathways can be defined using any of the standard reference databases, such as MetaCore Gene Ontology (GO) database, MetaCore canonical gene pathway maps (MA) database, MetaCore GeneGo (GG) database, Panther, TRMP, KEGG, and SPAD databases. Groups can be formed based on the presence or absence of a mutation in a certain pathway. Such groups will be heterogeneous with respect to mutated gene but homogeneous with respect to mutated pathway. As with CAN gene signatures, these groups can be used to characterize a GBM. Once a mutation in a pathway has been determined, a GBM can be assigned to a group of GBMs sharing the mutated pathway. The group can be used to assign a prognosis, to assign to a clinical trial group, to assign to a treatment regimen, and/or to assign for further characterization and studies. In a clinical trial group, drugs can be assessed for the ability to differentially affect GBMs with and without the mutated pathway. Once a differential effect is determined, the pathway can be used to assign patients to drug regimens, or to avoid unnecessarily treating patients in whom the drug will not have a beneficial effect. The drug in a clinical trial can be one which is previously known for another purpose, previously known for treating GBM, or previously unknown as a therapeutic. Among the genes in the pathways which may be found mutant are: TP53, MDM2, MDM4, RB1, CDK4, CDKN2A, PTEN, PIK3CA, PIK3RI, and IRS 1. This list is not necessarily exhaustive.

[51] Expression levels can be determined and overexpression may be indicative of a new GBM tumor, molecular relapse, or minimal residual disease of GBM. Highly increased expression found in GBM tumors are shown in Fig. 10, Table S5 and Fig. 10, Table S9. These overexpressed genes can be detected in test samples, such as suspected tumor tissue

samples, blood, CSF, urine, saliva, lymph etc. Elevated expression is typically determined by comparing expression of a gene in the test sample to expression of a gene in a normal control sample, such as from healthy brain tissue. Elevated expression of one or more genes can be used for this purpose. If the patient has undergone surgery, detection of the elevated expression in tumor margin or remaining tissue can be used to detect minimal residual disease or molecular relapse. If GBM has been previously undiagnosed, the elevated expression may serve to help diagnose, for example in conjunction with other physical findings or laboratory results, including but not limited to biochemical markers and radiological findings. For these purposes, any means known in the art for quantitating expression can be used, including SAGE or microarrays for detecting elevated mRNA, and antibodies used in various assay formats for detecting elevated protein expression. For detecting protein expression, the genes listed in Fig. 10, Table S10 are particularly useful.

[52] Tumor burden can be monitored using the mutations listed in Fig. 10, Table S7. This may be used in a watchful waiting mode, or during therapy to monitor efficacy, for example. Using a somatic mutation as a marker and assaying for level of detectable DNA, mRNA, or protein over time, can indicate tumor burden. The level of the mutation in a sample may increase, decrease or remain stable over the time of analysis. Therapeutic treatments and timing may be guided by such monitoring.

[53] Analysis of the GBMs revealed certain genes which are homozygously deleted. These are listed in Fig. 10, Table S6. Determining loss of expression of one or more of these genes can be used as a marker of GBM. This may be done in a sample of blood or lymph node or in a brain tissue sample. Expression of one or more of these genes may be tested.

Techniques such as ELISA or IHC may be used to detect diminution or loss of protein expression in a sample. Similarly the homozygously deleted genes listed in Fig. 10, Table S6 may be used to monitor tumor burden over time. Expression can be repeatedly monitored so that in increase, decrease, or stable level of expression can be ascertained.

[54] The data resulting from this integrated analysis of mutations and copy number alterations have provided a novel view of the genetic landscape of glioblastomas. The combination of different types of genetic data, including point mutations, amplifications, and deletions allows for identification of individual CAN-genes as well as groups of genes that may be preferentially affected in complex cellular pathways and processes in GBMs. Identification of virtually all genes previously shown to be affected in GBMs by mutation, amplification, or deletion validates the comprehensive genomic approach we have employed.

[55] It should be noted, however, that our approach, like all genome-wide studies, has limitations. First we did not assess chromosomal translocations, which is one type of genetic alteration that could play an important role in tumorigenesis. However, observations of recurrent chromosomal translocations have only rarely been reported in cyotogenetic studies of GBM. We also did not assess epigenetic alterations, though our large scale expression studies should have identified any genes that were differentially expressed through this mechanism (Fig. 10, Table S9). Additionally, for copy number changes we focused on regions that were truly amplified or homozygously deleted as these have historically been most useful in identifying cancer genes. The SNP array data we have generated for these samples, however, contains information that can be analyzed to determine loss of heterozygosity (LOH) or small copy number

gains due to duplications rather than true amplification events. Analysis of such data for known cancer genes, such as CDKN2A or NF1, identified additional tumors that had LOH in these regions, but given the substantial fraction of the genome that undergoes LOH in GBMs, such observations are in general not likely to be helpful in pinpointing new candidate cancer genes. Finally, the primary tumors used in our analysis contained small amounts of contaminating normal tissue, as is the rule for this sample type, which limited our ability to detect homozygous deletions and to a lesser extent, somatic mutations, in those specific tumors. This was true even though we carefully selected these tumors to contain a minimal stromal component by histological and molecular biologic criteria. This observation serves as an important reminder of the value of early passage xenografts and cell lines for such large scale genomic studies.

[56] Despite these limitations, our studies provide a number of important genetic and clinical insights into GBMs. The first of these is that the pathways known to be altered in GBMs affect a larger fraction of gene members and patients than previously anticipated. A majority of the tumors analyzed had alterations in members of each of the TP53, RB1, and PI3K pathways. The fact that all but one of the cancers with mutations in members of a pathway did not have alterations in other members of the same pathway is significant and suggests that such alterations are functionally equivalent in tumorigenesis. These observations also point to distinct opportunities for potential therapeutic intervention in these pathways in GBMs. The second observation is that a variety of new genes and pathways not previously implicated in GBMs were identified. Among the new pathways detected, a number of these appear to be involved in brain specific ion transport and

signaling processes and represent interesting and potentially useful aspects of GBM biology.

[57] These data immediately raise questions with important implications for the treatment and counseling of patients with GBMs as well as those with lower-grade gliomas. For example, are mutations in IDH also present in a subset of patients diagnosed with lower-grade gliomas (WHO grades I-III)? If IDH1 mutations are indeed found to be a relatively early genetic event in glioma progression, are these patients at increased risk of progression to GBM? Given the significant clinical difficulty of deciding which low grade glioma patients will receive adjuvant radiation therapy or chemotherapy (and how aggressive treatment should be), the knowledge that a patient is at increased risk for malignant progression would significantly alter the risk-benefit analysis of such treatment decisions. For pediatric patients, in whom radiation therapy can have particularly devastating effects on neurocognitive development and function, these decisions are particularly difficult and any additional risk-classification would be especially useful. IDH mutations may also provide one biological explanation for the occasional long-term GBM survivor, and could help to identify patients that would receive particular benefit from specific currently-available therapies. The utility of IDH as a clinical marker is likely to be enhanced by the fact that only a single codon of the gene needs to be examined to determine mutation status. Finally, it is conceivable that new treatments may be designed to take advantage of these IDH alterations, either as monotherapy or in combination with other agents. Along these lines, inhibition of mitochondrial IDH2 has recently been shown to result in increased sensitivity of tumor cells to a variety of chemotherapeutic agents (49). In summary, this finding of

IDH mutations in a subset of GBM patients and in at least one other cancer type opens a new avenue of research that could illuminate a previously unappreciated aspect of human tumorigenesis.

[58] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE 1

Materials and Methods

[59] DNA was extracted from primary tumor and xenograft samples and patient-matched normal blood lymphocytes obtained from the Tissue Bank at the Preston Robert Tisch Brain Tumor Center at Duke and collaborating centers, as previously described [17]. All brain tumors analyzed were subjected to consensus review by two neuropathologists. The panel of brain tumors consisted of 21 pilocytic astrocytomas and 2 subependymal giant cell gliomas (WHO Grade I); 31 diffuse astrocytomas, 51 oligodendrogliomas, three oligoastrocytomas, 30 ependymomas, and seven pleomorphic xanthoastrocytomas (WHO Grade II); 43 anaplastic astrocytomas, 36 anaplastic oligodendrogliomas, and seven anaplastic oligoastrocytomas (WHO Grade III); 178 GBMs and 55 medulloblastomas (WHO Grade IV). The GBM samples included 165 primary and 13 secondary cases. Fifteen of the GBMs were from patients <20 years old). Secondary GBMs were

defined as those that were resected >1 year after a prior diagnosis of a lower grade glioma (WHO Grades I-III). Sixty-six of the 178 GBMs, but none of the lower grade tumors, had been analyzed in our prior genome-wide mutation analysis of GBMs[16]. In addition to the brain tumors, 494 non-CNS cancers were examined: 35 lung cancers, 57 gastric cancers, 27 ovarian cancers, 96 breast cancers, 114 colorectal cancers, 95 pancreatic cancers, seven prostate cancers, 4 chronic myelogenous leukemias, 7 chronic lymphocytic leukemias, 7 acute lymphoblastic leukemias, and 45 acute myelogenous leukemias. All samples were obtained in accordance with the Health Insurance Portability and Accountability Act. Acquisition of tissue specimens was approved by the Duke University Health System Institutional Review Board and the corresponding IRBs at collaborating institutions.

[60] Exon 4 of the *IDH1* gene was PCR-amplified and sequenced in the matched tumor and normal DNAs for each patient as previously described [16]. In selected patients without an R132 *IDH1* mutation (those with Grade II or III lesions or secondary GBM), the remaining seven exons of *IDH1* and all 11 exons of *IDH2* were sequenced and analyzed for mutations. All coding exons of *TP53* and *PTEN* were also sequenced in the panel of oligodendrogliomas, anaplastic oligodendrogliomas, anaplastic astrocytomas, and GBMs. *EGFR* amplification and *CDKN2A/CDKN2B* deletion were analyzed by quantitative real-time PCR in the same tumors[18]. Oligodendroglioma and anaplastic oligodendroglioma samples were evaluated for loss of heterozygosity (LOH) at 1p and 19q as previously described [15, 19].

[61] Clinical information included date of birth, date the study sample was obtained, date of pathologic diagnosis, date and pathology of any preceding diagnosis of a lower grade glioma, administration of radiation therapy and/or chemotherapy prior to the date that the study sample was obtained, date of last patient contact, and patient status at last contact. Clinical information for survival analysis was available for all 482 primary brain tumor patients. Kaplan-Meier survival curves were plotted and the survival distributions were compared by the Mantel Cox log-rank test and the Wilcoxon test. Overall survival was calculated by using date of GBM diagnosis and date of death or last patient contact. The correlations between the occurrence of *IDH1/IDH2* mutations and other genetic alterations were examined using Fisher's exact test.

EXAMPLE 2

High frequency alterations of IDH1 in young GBM patients

[62] The top CAN-gene list included a number of individual genes which had not previously been linked to GBMs. The most frequently mutated of these genes, IDH1, encodes isocitrate dehydrogenase 1, which catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate, resulting in the production of NADPH. Five isocitrate dehydrogenase genes are encoded in the human genome, with the products of three (IDH3 alpha, IDH3 beta, IDH3 gamma) forming a heterotetramer ($\alpha_2\beta\gamma$ in the mitochondria and utilizing NAD(+) as an electron acceptor to catalyze the rate-limiting step of the tricarboxylic acid cycle. The fourth isocitrate dehydrogenase (IDH2) is also localized to the mitochondria, but like IDH1, uses NADP(+) as an electron acceptor. The IDH1 product, unlike the rest of the IDH proteins, is contained within the cytoplasm and peroxisomes (41). The protein forms an asymmetric

homodimer (42), and is thought to function to regenerate NADPH and α-ketoglutarate for intraperoxisomal and cytoplasmic biosynthetic processes. The production of cytoplasmic NADPH by IDH1 appears to play a significant role in cellular control of oxidative damage (43) (44). None of the other IDH genes, other genes involved in the tricarboxylic acid cycle, or other peroxisomal proteins were found to be genetically altered in our analysis.

[63] IDH1 was found to be somatically mutated in five GBM tumors in the Discovery Screen. Suprisingly, all five had the same heterozygous point mutation, a change of a guanine to an adenine at position 395 of the IDH1 transcript (G395A), leading to a replacement of an arginine with a histidine at amino acid residue 132 of the protein (R132H). In our prior study of colorectal cancers, this same codon had been found to be mutated in a single case through alteration of the adjacent nucleotide, resulting in a R132C amino acid change (10). Five additional GBMs evaluated in our Prevalence Screen were found to have heterozygous R132H mutations, and an additional two tumors had a third distinct mutation affecting the same amino acid residue, R132S (Fig. 1; Table 4). The R132 residue is conserved in all known species and is localized to the substrate binding site, forming hydrophilic interaction with the alpha-carboxylate of isocitrate (Fig. 2) (42, 45).

[64] Several important observations were made about IDH1 mutations and their potential clinical significance. First, mutations in IDH1 preferentially occurred in younger GBM patients, with a mean age of 33 years for IDH1-mutated patients, as opposed to 53 years for patients with wildtype IDH1 ($P<0.001$, t-test, Table 4. In patients under 35

years of age, nearly 50% (9 of 19) had mutations in IDH1. Second, mutations in IDH1 were found in nearly all of the patients with secondary GBMs (mutations in 5 of 6 secondary GBM patients, as compared to 7 of 99 patients with primary GBMs, $P<0.001$, binomial test), including all five secondary GBM patients under 35 years of age. Third, patients with IDH1 mutations had a significantly improved prognosis, with a median overall survival of 3.8 years as compared to 1.1 years for patients with wildtype IDH1 ($P<0.001$, log-rank test). Although younger age and mutated TP53 are known to be positive prognostic factors for GBM patients, this association between IDH1 mutation and improved survival was noted even in patients < 45 years old (Fig. 3, $P<0.001$, log-rank test), as well as in the subgroup of young patients with TP53 mutations ($P<0.02$, log-rank test).

EXAMPLE 3

Glioblastoma multiforme (GBM) DNA Samples

[65] Tumor DNA was obtained from GBM xenografts and primary tumors, with matched normal DNA for each case obtained from peripheral blood samples, as previously described (1). All samples were given the histologic diagnosis of glioblastoma multiforme (GBM; World Health Organization Grade IV), except for two Discovery Screen samples who were recorded as "high grade glioma, not otherwise specified". Samples were classified as recurrent for patients in whom a GBM had been diagnosed at least 3 months prior to the surgery when the study GBM sample was obtained. There were 3 recurrent GBMs in the Discovery Screen, and 15 in the Prevalence Screen. Samples were classified as secondary for patients in whom a lower grade glioma

(WHO grade I-III) had been histologically confirmed at least 1 year prior to the surgery when the study GBM sample was obtained. One Discovery Screen sample and 5 Prevalence Screen samples were classified as secondary.

[66] Pertinent clinical information, including date of birth, date study GBM sample obtained, date of original GBM diagnosis (if different than the date that the GBM sample was obtained, as in the case of recurrent GBMs), date and pathology of preceding diagnosis of lower grade glioma (in cases of secondary GBMs), the administration of radiation therapy and/or chemotherapy prior to the date that the GBM sample was obtained, date of last patient contact, and patient status at last contact. All samples were obtained in accordance with the Health Insurance Portability and Accountability Act (HIPAA). All samples were obtained in accordance with the Health Insurance Portability and Accountability Act (HIPAA). As previously described, tumor-normal pair matching was confirmed by typing nine STR loci using the PowerPlex 2.1 System (Promega, Madison, WI) and sample identities checked throughout the Discovery and Prevalence screens by sequencing exon 3 of the HLA-A gene. PCR and sequencing was carried out as described in (1).

EXAMPLE 4

Statistical analysis of clinical data

[67] Paired normal and malignant tissue from 105 GBM patients were used for genetic analysis. Complete clinical information (i.e. all pertinent

clinical information such as date of initial GBM diagnosis, date of death or last contact) was available for 91 of the 105 patients. Of these 91 patients, five (all IDH1-wildtype) died within the first month after surgery and were excluded from analysis (Br308T, Br246T, Br23X, Br301T, Br139X), as was a single patient (Br119X) with a presumed surgical cure (also IDH1-wildtype) who was alive at last contact ~ 10 years after diagnosis. Kaplan Meier survival curves were compared using the Mantel Cox log-rank test. Hazard ratios were computed using the Mantel-Haenszel method. The following definitions were used in the GBM patient grouping and survival analysis computations: 1) Patient age refered to the age at which the patient GBM sample was obtained. 2) Recurrent GBM designates a GBM which was resected >3 months after a prior diagnosis of GBM. 3) Secondary GBM designates a GBM which was resected > 1 year after a prior diagnosis of a lower grade glioma (WHO I-III). 4) Overall survival was calculated using date of GBM diagnosis and date of death or last patient contact. All confidence intervals were calculated at the 95% level.

EXAMPLE 5

IDH1 and IDH2 Mutations

[68] Sequence analysis of IDH1 in 976 tumor samples revealed a total of 167 somatic mutations at residue R132, including R132H (148 tumors), R132C (8 tumors), R132S (2 tumors), R132L (8 tumors) and R132G (1 tumor) (Fig. 4A, Fig. 7). Tumors with somatic R132 mutations included 25 of 31 (81%) diffuse astrocytomas (WHO Grade II), 41 of 51 (80%) oligodendrogliomas (WHO Grade II), 3 of 3 (100%) oligoastrocytomas (WHO Grade II), one of 7 (14%) pleomorphic xanthoastrocytomas (WHO Grade II), 41 of 61 (67%) anaplastic

astrocytomas (WHO Grade III), 31 of 36 (86%) anaplastic oligodendrogliomas (WHO Grade III), 7 of 7 (100%) anaplastic oligoastrocytomas (WHO grade III), 11 of 13 (85%) secondary GBMs, and 7 of 165 (4%) primary GBMs (Figure 1B, Figure 11). In contrast, no R132 mutations were observed in 21 pilocytic astrocytomas (WHO Grade I), two subependymal giant cell astrocytomas (WHO Grade I), 30 ependymomas (WHO Grade II), 55 medulloblastomas, or in any of the 494 non-CNS tumor samples. Sequence analysis of the remaining IDH1 exons revealed no other somatic mutations of IDH1 in the R132-negative tumors.

[69] If IDH1 were critical to the development or progression of oligodendrogliomas and astrocytomas, we reasoned that alterations in other genes with similar functions to IDH1 might be found in those in those tumors without IDH1 mutations. We therefore analyzed the IDH2 gene, which encodes the only human protein homologous to IDH1 that utilizes NADP+ as an electron acceptor. Sequence evaluation of all IDH2 exons in these samples, revealed eight somatic mutations, all at residue R172: R172M in three tumors, R172K in three tumors, and R172G in two tumors (Fig. 1A, Fig. 7). The R172 residue in IDH2 is the exact analogue of the R132 residue of IDH1, which is located in the active site of the enzyme and forms hydrogen bonds with the isocitrate substrate.

[70] To further evaluate the timing of IDH alterations in glioma progression, we assessed IDH1 mutations in seven patients with progressive gliomas in which both low- and high-grade tumor samples were available. Sequence analysis identified IDH1 mutations in both the low and high-grade tumors in all seven cases (Fig. 8, Table 4). These results

unambiguously demonstrate that IDH1 alterations occur in low-grade tumors and that subsequent cancers in such patients are directly derived from these early lesions.

[71] We also examined the oligodendrogliomas, anaplastic oligodendrogliomas, anaplastic astrocytomas, and a subset of GBMs for mutations of TP53 and PTEN, amplification of EGFR, deletion of CDKN2A/CDKN2B , and LOH of 1p/19q (Fig. 12). TP53 mutations were much more common in anaplastic astrocytomas (63%) and secondary GBMs (60%) than in oligodendrogliomas (16%) or anaplastic oligodendrogliomas (10%) ($p<0.001$, Fisher's exact test). Conversely, deletions of 1p and 19q were found more often in oligodendrocytic than astrocytic tumors, as expected 15.

[72] Comparison of these alterations with those in IDH1 and IDH2 revealed several striking correlations. Nearly all of the anaplastic astrocytomas and GBMs with mutated IDH1/IDH2 also had mutation of TP53 (82%), but only 5% had any alteration of PTEN, EGFR, or CDKN2A/CDKN2B (Fig. 12). Conversely, anaplastic astrocytomas and GBMs with wild-type IDH1 had few TP53 mutations (21%) and more frequent alterations of PTEN, EGFR, or CDKN2A/CDKN2B (40%) ($p<0.001$, Fisher's exact test). Loss of 1p/19q was observed in 85% (45/53) of the oligodendrocytic tumors with mutated IDH1 or IDH2 but in none (0/9) of the patients with wild-type IDH genes ($p<0.001$, Fisher's exact test).

[73] Patients with anaplastic astrocytomas and GBMs with IDH1 or IDH2 mutations were significantly younger than those with wild-type IDH1 and IDH2 genes (median age of 34 years vs. 58 years, $p<0.001$,

Student's t-test). Interestingly, despite the lower median age of patients with IDH1 or IDH2 mutations, no mutations were identified in GBM from patients who were less than 20 years old (0 of 18 patients, Fig. 9). In patients with oligodendrogliomas and anaplastic oligodendrogliomas, the median age of the patients with IDH1 or IDH2 mutation was 39 years, with IDH1 mutations identified in two teenagers (14 and 16 yrs), but not in younger patients (0 of 4).

[74] Our prior observation of improved prognosis for GBM patients with mutated IDH1 16 was confirmed in this larger data set and extended to include patients with mutations in IDH2. Patients with IDH1 or IDH2 mutations had a median overall survival of 39 months, significantly longer than the 13.5 month survival in patients with wild-type IDH1 (Fig. 5, $p<0.001$, log-rank test). Mutations of IDH genes were also associated with improved prognosis in patients with anaplastic astrocytomas (WHO Grade III), with median overall survival of 65 months for patients with mutations and 19 months for those without ($p<0.001$, log-rank test). Differential survival analyses could not be performed in patients with diffuse astrocytomas, oligodendrogliomas, or anaplastic oligodendrogliomas because there were so few tumors of these types without IDH gene mutations.

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[75] The disclosure of each reference cited is expressly incorporated herein. The references in the following list are cited in the text with superscript reference numerals.

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EXAMPLE 6

Sequencing Strategy

[76] We extended our previously-developed sequencing strategy for identification of somatic mutations to include 23,219 transcripts from 20,583 genes. These included 2783 additional genes from the Ensembl databases that were not present in the CCDS or RefSeq databases analyzed in previous studies (10, 11). In addition, we redesigned PCR primers for regions of the genome that (i) were difficult to PCR amplify and had been sub-optimally analyzed in prior studies; or (ii) were found to share significant identity with other human or mouse sequences. The combination of these new, redesigned, and existing primers sequences resulted in a total of 208,311 primer pairs (table S1; available on-line at *Science* 26 September 2008: Vol. 321. no. 5897, pp. 1807 - 1812) that were successfully used for sequence analysis of the coding exons of these genes.

[77] Twenty-two GBM samples (Fig. 10, Table S2) were selected for PCR sequence analysis, consisting of 7 samples extracted directly from patient tumors and 15 tumor samples passaged in nude mice as xenografts. One tumor (Br27P) was a secondary GBM obtained from a patient who had previously been treated with both radiation therapy and chemotherapy, including temozolomide. All other tumors were categorized as primary GBMs and had not received tumor-directed treatment prior to the acquisition of the studied tumor sample.

[78] In the first stage of this analysis, called the Discovery Screen, the primer pairs were used to amplify and sequence 175,471 coding exons and adjacent

intronic splice donor and acceptor sequences in the 22 GBM samples and in one matched normal sample. The data were assembled for each amplified region and evaluated using stringent quality criteria, resulting in successful amplification and sequencing of 95.0% of targeted amplicons and 93.0% of targeted bases in the 22 tumors. A total of 689 Mb of sequence data were generated through this approach. The amplicon traces were analyzed using automated approaches to identify changes in the tumor sequences that were not present in the reference sequences of each gene, then alterations present in the normal control sample and in single nucleotide polymorphism (SNP) databases were removed from further analyses. The remaining sequence traces of potential alterations were visually inspected to remove false-positive mutation calls generated through our automated software. All exons containing putative mutations were then re-amplified and sequenced in the affected tumor and matched normal DNA samples. This process allowed confirmation of the mutation in the tumor sample and determined whether the alteration was somatic (i.e. tumor-specific) or was present in the germline. All putative somatic mutations were examined computationally and experimentally to confirm that the alterations did not arise through the aberrant co- amplification of related gene sequences (12).

Table 1. Summary of genomic analyses of GBM

Sequencing analysis	
Number of genes analyzed	20,583
Number of transcripts analyzed	23,781
Number of exons analyzed	184,292
Primer pairs designed for amplification	219,229
Fraction of passing amplicons*	95.0%
Total number of nucleotides sequenced	689,071,123
Fraction of passing amplicon sequences successfully analyzed#	98.4%
Fraction of targeted bases sucessfully analyzed#	93.0%
Number of somatic mutations identified (n=22 samples)	2,328
Number of somatic mutations (excluding Br27P)	996
Missense	870
Nonsense	43
Insertion	3
Deletion	46
Duplication	7
Splice site or UTR	27
Average number of sequence alterations per sample	47.4
Copy number analysis	
Total number of SNP loci assessed for copy number changes	1,069,688
Number of copy number alterations identified (n=22 samples)	281
Amplifications	147
Homozygous deletions	134
Average number of amplifications per sample	6.7
Average number of homozygous deletions per sample	6.1

*Passing amplicons were defined as having PHRED20 scores or better over 90% of the target sequence in 75% of samples analyzed. #Fraction of nucleotides having PHRED20 scores or better (see Supporting Online Materials for additional information).

EXAMPLE 7

Analysis of sequence alterations

[79] We found that 2043 genes (10% of the 20,661 genes analyzed) contained at least one somatic mutation that would be expected to alter the protein sequence. The vast majority of these alterations were single-base substitutions (94%), while the others were small insertions, deletions, or duplications. The tumor sample Br27P obtained from the patient previously treated with radiation therapy and chemotherapy (including temozolomide), had 1332 total somatic mutations, 17-fold higher than any of the other 21 patients (Fig. 10, Table S3). The mutation spectrum of this sample, comprising an excess of C>T transitions in the 5' cytosine of CpC dinucleotides, was dramatically different from those of the other GBM patients, but was consistent with previous observations of a hypermutation phenotype in glioma samples of patients treated with temozolomide (13, 14). In the previously-reported patients, the hypermutability was thought to occur due to prolonged exposure of an akylating agent in the presence of MSH6 mismatch repair deficiency; however, in BR27P, no somatic alterations were observed in MSH6 or in any of the other mismatch repair genes (MSH2, MLH1, MLH3, PMS 1, PMS2). In contrast to BR27P, none of the other 21 tumor samples analyzed in the Discovery Screen were known to have received prior radiation or chemotherapeutic treatment, and none had the characteristic CpC mutation spectrum that has been found in such pre-treated tumors.

[80] After removing Br27P from consideration, the remaining 993 mutations were observed to be distributed relatively evenly among the 21 remaining tumors (Fig. 10, Table S3). The number of somatic mutations identified in each tumor ranged between 17 and 79 with a mean of 47 mutations per tumor, or 1.51 mutations per Mb of GBM tumor genome sequenced. Six DNA samples extracted from primary tumors had somewhat smaller numbers of mutations than those obtained from xenografts, likely because of the masking effect of non-neoplastic cells in the former. It has previously been shown that cell lines and xenografts provide the optimal template DNA for cancer genome sequencing analyses (15) and that they faithfully represent the alterations present in primary tumors (16).

[81] Both the total number and frequency of sequence alterations in GBMs were substantially smaller than the number and frequency of such alterations observed in cancers of the colon or breast, and slightly less than in pancreas (10, 11, 17). The most likely explanation for this difference is the reduced number of cell generations in glial cells prior to the onset of neoplasia. It has been suggested that up to half of the somatic mutations observed in colorectal cancers occur in epithelial stem cells during the normal cell renewal processes (16). As normal glial stem cells turn over much less frequently than mammary or colon epithelial cells, they would be expected to contain many fewer mutations when the tumor-initiating mutation occurred (18).

[82] We further evaluated a set of 20 mutated genes identified in the Discovery Screen in a second screen, called a Prevalence Screen, comprising an additional 83 GBMs with well-documented clinical histories (table S2, available on line at *Science* 26 September 2008: Vol. 321. no. 5897, pp. 1807 - 1812). These genes were mutated in at least two tumors and had mutation frequencies >10 mutations per Mb of tumor DNA sequenced. Nonsilent somatic mutations were identified in 15 of these 20 genes in the additional tumor samples (Fig. 10, Table S4). The mutation frequency of all analyzed genes in the Prevalence Screen was 24 mutations per Mb of tumor DNA, markedly increased from the overall mutation frequency in the Discovery Screen of 1.5 mutations per Mb ($p<0.001$, binomial test). Additionally, the observed ratio of nonsilent to silent mutations (NS:S) among mutations in the Prevalence Screen was 14.8:1, substantially higher than the 3.1:1 ratio that was observed in the Discovery Screen ($P<0.001$, binomial test). The increased mutation frequency and higher number of nonsilent mutations suggested that genes mutated in the Prevalence Screens were enriched for genes that actively contributed to tumorigenesis.

[83] In addition to the frequency of mutations in a gene, the type of mutation can provide information useful for evaluating its potential role in disease (19). Nonsense mutations, out-of-frame insertions or deletions, and splice site changes generally lead to inactivation of the protein products. The likely effect of missense mutations can be assessed through evaluation of the mutated residue by evolutionary or structural means. To evaluate missense

mutations, we developed a new algorithm that employs machine learning of 56 predictive features based on the physical-chemical properties of amino acids involved in the substation and their evolutionary conservation at equivalent positions of conserved proteins (12). Approximately 15% of the missense mutations identified in this study were predicted to have a statistically significant effect on protein function when assessed by this method (Fig. 10, Table S3). We were also able to make structural models of 244 of the 870 missense mutations identified in this study (20). In each case, the model was based on x- ray crystallography or nuclear magnetic resonance spectroscopy of the normal protein or a closely related homolog. This analysis showed that 35 of the missense mutations were located close to a domain interface or substrate-binding site and were likely to impact function (links to structural models available in (12)).

EXAMPLE 8

Analysis of copy number changes

[84] The same tumors were then evaluated for copy number alterations through genomic hybridization of DNA samples to Illumina high density oligonucleotide arrays containing ~1 million SNP loci probes (21). We have recently developed a sensitive and specific approach for the identification of focal amplifications resulting in 12 or more copies per nucleus (6-fold or greater amplification compared to the diploid genome) as well as deletions of both copies of a gene (homozygous deletions) using such arrays (22). Such focused alterations can be used to identify underlying candidate genes in these regions. It is impossible to reliably identify such candidate genes in regions with larger chromosomal aberrations, such as those involving gains or losses of entire chromosomal arms, which occur frequently in tumors and are of unknown significance.

[85] We identified a total of 147 amplifications (Fig. 10, Table S5) and 134 homozygous deletions (Fig. 10, Table S6) in the 22 samples used in the Discovery Screen, with 0 to 34 amplifications and 0 to 14 deletions found per tumor sample. Although the number of amplifications was similar between primary samples and those tumors that had been passaged as xenografts, the latter samples allowed detection of a larger number of

homozygous deletions (average of 8.0 deletions per xenograft versus 2.2 per primary sample). These observations are consistent with previous reports documenting the difficulty of identifying homozygous deletions in samples containing contaminating normal DNA (23) and highlight the importance of using purified human tumor cells, such as those present in xenografts or cell lines, for genomic analyses.

EXAMPLE 9

Integration of sequencing, copy number and expression analyses

[86] Mutations that arise during tumorigenesis may provide a selective advantage to the tumor cell (driver mutations) or have no net effect on tumor growth (passenger mutations). The mutational data obtained from sequencing and analysis of copy number alterations were integrated in order to identify GBM candidate cancer genes (CAN-genes) that would be most likely to be drivers and therefore worthy of further investigation. The bioinformatic approach employed to determine if a gene was likely to harbor driver mutations involved comparison of the number and type of mutations observed in each gene to the number that would be expected due to the passenger mutation rates. For sequence alterations, we calculated upper and lower bounds of passenger rates. The upper bound was conservatively calculated as the total number of observed alterations minus those mutations occurring in known cancer genes divided by the amount of tumor DNA sequenced, while the lower bound was determined on the basis of the observed silent mutations and estimates of expected NS:S ratios (12). For copy number changes, we made the very conservative assumption that all amplifications and deletions were passengers when determining the background rate. For analysis of each gene, all types of alterations (sequence changes, amplifications and homozygous deletions), were then combined to estimate the passenger probability for that gene (see (12) for a more detailed description of the statistical methods).

[87] The top-ranked CAN-genes, together with their passenger probabilities, are listed in Fig. 10, Table S7. The CAN-genes included a number of genes that had been well established with respect to their involvement in gliomas, including TP53, PTEN, CDKN2A, RB1, EGFR, NF1, PIK3CA and PIK3R1 (24-34). The most frequently altered of these genes in our analyses included CDKN2A (altered in 50% of GBMs), TP53, EGFR, and PTEN (altered in 30-40%), NF1, CDK4 and RB1 (altered in 12-15%), and PIK3CA and PIK3R1 (altered in 8-10%). Overall, these frequencies, which are similar to or in some cases higher than those previously reported, validate the sensitivity of our approach for detection of somatic alterations.

Table 2. Most frequently altered GBM *CAN*-genes

Gene	Point mutations^		Amplifications[&]		Homozygous deletions[&]		Fraction of tumors with any alteration	Passenger Probability[·]
	Number of tumors	Fraction of tumors	Number of tumors	Fraction of tumors	Number of tumors	Fraction of tumors		
CDKN2A	0/22	0%	0/22	0%	11/22	50%	50%	0.00
TP53	37/105	35%	0/22	0%	1/22	5%	40%	0.00
EGFR	15/105	14%	5/22	23%	0/22	0%	37%	0.00
PTEN	27/105	26%	0/22	0%	1/22	5%	30%	0.00
NF1	16/105	15%	0/22	0%	0/22	0%	15%	0.04
CDK4	0/22	0%	3/22	14%	0/22	0%	14%	0.00
RB1	8/105	8%	0/22	0%	1/22	5%	12%	0.01
IDH1	12/105	11%	0/22	0%	0/22	0%	11%	0.00
PIK3CA	10/105	10%	0/22	0%	0/22	0%	10%	0.10
PIK3R1	8/105	8%	0/22	0%	0/22	0%	8%	0.14

The most frequently-altered *CAN*-genes are listed; all *CAN*-genes are listed in Table S7. ^Fraction of tumors with point mutations indicates the fraction of mutated GBMs out of the 105 samples in the Discovery and Prevalence Screens. CDKN2A and CDK4 were not analyzed for point mutations in the Prevalence Screen because no sequence alterations were detected in these genes in the Discovery Screen. [&]Fraction of tumors with amplifications and deletions indicates the number of tumors with these types of alterations in the 22 Discovery Screen samples. [·]Passenger probability indicates the Passenger probability - Mid (*12*).

[88] Analysis of additional gene members within pathways affected by these genes identified alterations of critical genes in the TP53 pathway (TP53, MDM2, MDM4), the RB1 pathway (RB1, CDK4, CDKN2A), and the PI3K/PTEN pathway (PIK3CA, PIK3R1, PTEN, IRS1). These alterations resulted in aberrant pathways in a majority of tumors (64%, 68%, and 50%, respectively) and in all cases but one, mutations within each tumor affected only a single member of each pathway in a mutually exclusive manner ($P<0.05$) (Table 3).

Systematic analyses of functional gene groups and pathways contained within the well-annotated MetaCore database (35) identified enrichment of mutated genes in additional members of the TP53 and PI3K/PTEN pathways as well as in a variety of other cellular processes, including those regulating cell adhesion as well as brain specific cellular pathways such those involving synaptic transmission, transmission of nerve impulses, and channels involved in transport of sodium, potassium and calcium ions (Fig. 10, Table S8). Interestingly, none of these latter pathways were observed as being enriched in large-scale studies on pancreatic cancers (17) and may represent a subversion of normal glial cell processes to promote dysregulated growth and invasion. Many members of the detected pathways had not been appreciated to have any role in GBMs or any other human cancer, and substantial effort will be required to determine their role in tumorigenesis.

Table 3. Mutations of the TP53, PI3K, and RB1 pathways in GBM

	TP53				PI3K Pathway					RB1			
Tumor sample	TP53	MDM2	MDM4	All genes	PTEN	PIK3CA	PIK3R1	IRS1	All genes	RB1	CDK4	CDKN2A	All genes
Br02	Del			Alt				Mu	Alt			Del	Alt
Br03	Mu			Alt	Mu				Alt				
Br04	Mu			Alt	Mu				Alt	Mu			Alt
Br05			Amp	Alt		Mu			Alt			Del	Alt
Br06												Del	Alt
Br07	Mu			Alt	Mu				Alt	Del			Alt
Br08												Del	Alt
Br09P	Mu			Alt							Amp		Alt
Br10P	Mu			Alt									
Br11P	Mu			Alt									
Br12P	Mu			Alt			Mu		Alt				
Br13	Mu			Alt								Del	Alt
Br14							Mu		Alt			Del	Alt
Br15										Mu		Del	Alt
Br16		Amp		Alt							Amp		Alt
Br17					Mu				Alt			Del	Alt
Br20P													
Br23	Mu			Alt	Del				Alt				
Br25					Mu				Alt			Del	Alt
Br26						Mu			Alt			Del	Alt
Br27P	Mu			Alt							Amp		Alt
Br29P	Mu			Alt									
Fraction of tumors with altered gene/pathway[#]	0.55	0.05	0.05	0.64	0.27	0.09	0.09	0.05	0.50	0.14	0.14	0.45	0.68

* Mut, mutated; Amp, amplified; Del, deleted; Alt, altered [#]Fraction of affected tumors in 22 Discovery Screen samples

[89] Gene expression patterns can inform the analysis of pathways because they can reflect epigenetic alterations not detectable by sequencing or copy number analyses. They can also point to downstream effects on gene expression resulting from the altered pathways described above. To analyze the transcriptome of GBMs, we performed SAGE (serial analysis of gene expression) (36) on all GBM samples used for mutation analysis for which RNA was available (total of 18 samples) as well as two independent normal brain RNA controls. When combined with massively parallel sequencing-by-synthesis methods (37-40), SAGE provides a highly quantitative and sensitive measure of gene expression.

[90] The transcript analysis was first used to help identify target genes from the amplified and deleted regions that were identified in this study. Though some of these regions contained a known tumor suppressor gene or oncogene, many contained several genes that had not previously been implicated in cancer. In tables S5 and S6, a candidate target gene could be identified within several of these regions through the use of the mutational as well as transcriptional data.

[91] Second, we attempted to identify genes that were differentially expressed in GBMs compared to normal brain. There was a high number (143) of genes that were expressed at an average 10-fold higher level in 18 GBMs analyzed (compared to normal brain samples). Among the 143 over-expressed genes, there were 16 that were secreted or expressed on the cell surface. Many of these were over expressed in the xenografts as well as in the primary brain tumors, suggesting new opportunities for diagnostic and therapeutic applications.

EXAMPLE 10

High frequency alterations of IDH 1 in young GBM patients

[92] The top CAN-gene list (Fig. 10, Table S7) included a number of individual genes which had not previously been linked to GBMs. The most frequently mutated of these genes,

IDH1, encodes isocitrate dehydrogenase 1, which catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate, resulting in the production of NADPH. Five isocitrate dehydrogenase genes are encoded in the human genome, with the products of three (IDH3 alpha, IDH3 beta, IDH3 gamma) forming a heterotetramer (2 in the mitochondria and utilizing NAD(+) as an electron acceptor to catalyze the rate-limiting step of the tricarboxylic acid cycle. The fourth isocitrate dehydrogenase (IDH2) is also localized to the mitochondria, but like IDH1, uses NADP(+) as an electron acceptor. The IDH1 product, unlike the rest of the IDH proteins, is contained within the cytoplasm and peroxisomes (41). The protein forms an asymmetric homodimer (42), and is thought to function to regenerate NADPH and -ketoglutarate for intraperoxisomal and cytoplasmic biosynthetic processes. The production of cytoplasmic NADPH by IDH1 appears to play a significant role in cellular control of oxidative damage (43) (44). None of the other IDH genes, other genes involved in the tricarboxylic acid cycle, or other peroxisomal proteins were found to be genetically altered in our analysis.

[93] IDH1 was found to be somatically mutated in five GBM tumors in the Discovery Screen. Suprisingly, all five had the same heterozygous point mutation, a change of a guanine to an adenine at position 395 of the IDH1 transcript (G395A), leading to a replacement of an arginine with a histidine at amino acid residue 132 of the protein (R132H). In our prior study of colorectal cancers, this same codon had been found to be mutated in a single case through alteration of the adjacent nucleotide, resulting in a R132C amino acid change (10). Five additional GBMs evaluated in our Prevalence Screen were found to have heterozygous R132H mutations, and an additional two tumors had a third distinct mutation affecting the same amino acid residue, R132S (Fig. 1; Table 4). The R132 residue is conserved in all known species and is localized to the substrate binding site, forming hydrophilic interaction with the alpha-carboxylate of isocitrate (Fig. 2) (42, 45).

Table 4. Characteristics of GBM patients with IDH1 mutations

Patient ID	Patient age (years)*	Sex	Recurrent GBM#	Secondary GBM^	Overall survival (years)&	IDH1 Mutation		Mutation of TP53	Mutation of PTEN, RB1, EGFR, or NF1
						Nucleotide	Amino acid		
Br10P	30	F	No	No	2.2	G395A	R132H	Yes	No
Br11P	32	M	No	No	4.1	G395A	R132H	Yes	No
Br12P	31	M	No	No	1.6	G395A	R132H	Yes	No
Br104X	29	F	No	No	4.0	C394A	R132S	Yes	No
Br106X	36	M	No	No	3.8	G395A	R132H	Yes	No
Br122X	53	M	No	No	7.8	G395A	R132H	No	No
Br123X	34	M	No	Yes	4.9	G395A	R132H	Yes	No
Br237T	26	M	No	Yes	2.6	G395A	R132H	Yes	No
Br211T	28	F	No	Yes	0.3	G395A	R132H	Yes	No
Br27P	32	M	Yes	Yes	1.2	G395A	R132H	Yes	No
Br129X	25	M	Yes	Yes	3.2	C394A	R132S	No	No
Br29P	42	F	Yes	Unknown	Unknown	G395A	R132H	Yes	No
IDH1 mutant patients (n=12)	33.2	67% M	25%	42%	3.8	100%	100%	83%	0%
IDH1 wildtype patients (n=93)	53.3	65% M	16%	1%	1.5	0%	0%	27%	60%

*Patient age refers to age at which patient GBM sample was obtained. #Recurrent GBM designates a GBM which was resected >3 months after a prior diagnosis of GBM. ^Secondary GBM designates a GBM which was resected > 1 year after a prior diagnosis of a lower grade glioma (WHO I-III). &Overall survival was calculated using date of GBM diagnosis and date of death or last patient contact: patients Br10P and Br11P were alive at last contact. Median survival for IDH1 mutant patients and IDH1 wildtype patients was calculated using logrank test. Previous pathologic diagnoses in secondary GBM patients were oligodendroglioma (WHO grade II) in Br123X, low grade glioma (WHO grade I-II) in Br237T and Br211T, anaplastic astrocytoma (WHO grade III) in Br27P, and anaplastic oligodendroglioma (WHO grade III) in Br129X. Abbreviations: GBM (glioblastoma multiforme, WHO grade IV), WHO (World Health Organization), M (male), F (female), mut (mutant). Mean age and median survival are listed for the groups of IDH1-mutated and IDH1-wildtype patients.

[94] Several important observations were made about IDH1 mutations and their potential clinical significance. First, mutations in IDH1 preferentially occurred in younger GBM patients, with a mean age of 33 years for IDH1-mutated patients, as opposed to 53 years for patients with wildtype IDH1 ($P<0.001$, t-test, Table 4). In patients under 35 years of age, nearly 50% (9 of 19) had mutations in IDH1. Second, mutations in IDH1 were found in nearly all of the patients with secondary GBMs (mutations in 5 of 6 secondary GBM patients, as compared to 7 of 99 patients with primary GBMs, $P<0.001$, binomial test), including all five secondary GBM patients under 35 years of age. Third, patients with IDH1 mutations had a significantly improved prognosis, with a median overall survival of 3.8 years as compared to 1.1 years for patients with wildtype IDH1 ($P<0.001$, log-rank test). Although younger age and mutated TP53 are known to be positive prognostic factors for GBM patients, this association between IDH1 mutation and improved survival was noted even in patients < 45 years old (Fig. 3, $P<0.001$, log-rank test), as well as in the subgroup of young patients with TP53 mutations ($P<0.02$, log-rank test).

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The disclosure of each reference cited is expressly incorporated herein.

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EXAMPLE 11

Materials and Methods

Gene Selection

[95] The protein coding exons from 23,781 transcripts representing 20,735 unique genes were targeted for sequencing. This set comprised 14,554 transcripts from the highly curated Consensus Coding Sequence (CCDS) database (http://www.ncbi.nlm.nih.gov/CCDS/), a further 6,019 transcripts from the Reference Sequence (RefSeq) database (http://www.ncbi.nlm.nih.gov/projects/RefSeq/) and an additional 3,208 transcripts with intact open reading frames from the Ensembl database (http://www.ensembl.org/). We excluded transcripts from genes that were located on the Y chromosome or were precisely duplicated within the genome. As detailed below, 23,219 transcripts representing 20,661 genes were successfully sequenced.

Bioinformatic Resources

[96] Consensus Coding Sequence (Release 1), RefSeq (release 16, March 2006) and Ensembl (release 31) gene coordinates and sequences were acquired from the UCSC Santa Cruz Genome Bioinformatics Site (http://genome.ucsc.edu). The positions listed in the Supplementary Tables correspond to UCSC Santa Cruz hg17, build 35.1. The single nucleotide polymorphisms used to filter-out known SNPs were those present in dbSNP (release 125) that had been validated by the HapMap project. BLAT and In Silico PCR (http://genome.ucsc.edu/cgi-bin/hgPcr) were used to perform homology searches in the human and mouse genomes.

Primer Design

[97] Primer 3 software (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi) was used to generate primers no closer than 50 bp to the target boundaries, producing products of 300 to 600 bp . Exons exceeding 350 bp were divided into several overlapping amplicons. In silico PCR and BLAT were used to select primer pairs yielding a single PCR product from a unique genomic position. Primer pairs for duplicated regions giving multiple in silico PCR or BLAT hits were redesigned at positions that were maximally different between the target and duplicated sequences. A universal primer (M13F, 5'- GTAAAACGACGGCCAGT-3'; SEQ ID NO: 136) was added to the 5' end of the primer with the smallest number of mono-

or dinucleotide repeats between itself and the target region. The primer sequences used in this study are listed in table S1 available on line at *Science* 26 September 2008: Vol. 321. no. 5897, pp. 1807 - 1812.

Glioblastoma multiforme (GBM) DNA Samples

[98] Tumor DNA was obtained from GBM xenografts and primary tumors, with matched normal DNA for each case obtained from peripheral blood samples, as previously described (1). The Discovery Screen consisted of 22 tumor samples (15 xenografts and 7 primary tumors), with the Prevalence screen including another 83 samples (53 xenografts and 30 primary tumors). Additional clinical information regarding Discovery and Prevalence Screen samples is available in table S2, available on line at *Science* 26 September 2008: Vol. 321. no. 5897, pp. 1807 - 1812. All samples were given the histologic diagnosis of glioblastoma multiforme (GBM; World Health Organization Grade IV), except for two Discovery Screen samples who were recorded as "high grade glioma, not otherwise specified". Samples were classified as recurrent for patients in whom a GBM had been diagnosed at least 3 months prior to the surgery when the study GBM sample was obtained. There were 3 recurrent GBMs in the Discovery Screen, and 15 in the Prevalence Screen. Samples were classified as secondary for patients in whom a lower grade glioma (WHO grade I-III) had been histologically confirmed at least 1 year prior to the surgery when the study GBM sample was obtained. One Discovery Screen sample and 5 Prevalence Screen samples were classified as secondary.

Table 5. Overview of GBM samples used in the Prevalence and Discovery Screens:

	Discovery	Validation	Total
Number of samples	22	83	105
Patient age			
Mean age (years)	48.6	51.7	51.0
Median age (years)	45	53	52
Patient sex			
Male	14	55	69
Female	8	28	36
Sample source			
Xenograft	15	53	68
Primary tumor	7	30	37
GBM subclasses			
Recurrent	3	15	18
Recurrent with prior chemotherapy	1	10	11
Secondary	1	5	6

[99] Pertinent clinical information, including date of birth, date study GBM sample obtained, date of original GBM diagnosis (if different than the date that the GBM sample was obtained, as in the case of recurrent GBMs), date and pathology of preceding diagnosis of lower grade glioma (in cases of secondary GBMs), the administration of radiation therapy and/or chemotherapy prior to the date that the GBM sample was obtained, date of last patient contact, and patient status at last contact. All samples were obtained in accordance with the Health Insurance Portability and Accountability Act (HIPAA). All samples were obtained in accordance with the Health Insurance Portability and Accountability Act (HIPAA). As previously described, tumor-normal pair matching was confirmed by typing nine STR loci using the PowerPlex 2.1 System (Promega, Madison, WI) and sample identities checked throughout the Discovery and Prevalence screens by sequencing exon 3 of the HLA-A gene. PCR and sequencing was carried out as described in (1).

Statistical analysis of clinical data

[100] Paired normal and malignant tissue from 105 GBM patients were used for genetic analysis. Complete clinical information (i.e. all pertinent clinical information such as date of initial GBM diagnosis, date of death or last contact) was available for 91 of the 105 patients. Of these 91 patients, five (all IDH1-wildtype) died within the first month after surgery and were excluded from analysis (Br308T, Br246T, Br23X, Br301T, Br139X), as was a single patient (Br119X) with a presumed surgical cure (also IDH1- wildtype) who was alive at last contact ~ 10 years after diagnosis. Kaplan Meier survival curves were compared using the Mantel Cox log-rank test. Hazard ratios were computed using the Mantel-Haenszel method. The following definitions were used in the GBM patient grouping and survival analysis computations: 1) Patient age refered to the age at which the patient GBM sample was obtained. 2) Recurrent GBM designates a GBM which was resected >3 months after a prior diagnosis of GBM. 3) Secondary GBM designates a GBM which was resected > 1 year after a prior diagnosis of a lower grade glioma (WHO I-III). 4) Overall survival was calculated using date of GBM diagnosis and date of death or last patient contact. All confidence intervals were calculated at the 95% level.

Mutation Discovery Screen

[101] CCDS, RefSeq and Ensembl genes were amplified in 22 GBM samples and one control samples from normal tissues of one of the GBM patients. All coding sequences and the flanking 4 bp were analyzed using Mutations Surveyor (Softgenetics, State College, PA) coupled to a relational database (Microsoft SQL Server). For an amplicon to be further analyzed, at least three quarters of the tumors were required to have 90% or more of bases in the region of interest with a Phred quality score of 20. In the amplicons that passed this quality control, mutations identical to those observed in the normal sample as well as known single nucleotide polymorphisms were removed. The sequencing chromatogram of each detected mutation was then visually inspected to remove false positive calls by the software. Every putative mutation was re-amplified and sequenced in tumor DNA to eliminate artifacts. DNA from normal tissues of the same patient in which the mutation was identified was amplified and sequenced to determine whether the mutations were somatic.

When a mutation was found, BLAT was used to search the human and mouse genomes for related exons to ensure that putative mutations were the result of amplification of homologous sequences. When there was a similar sequence with 90% identity over 90% of the target region, additional steps were performed. Mutations potentially arising from human duplications were re-amplified using primers designed to distinguish between the two sequences. Mutations not observed using the new primer pair were excluded. The remainder were included as long as the mutant base was not present in the homologous sequence identified by BLAT. Mutations originally observed in mouse xenografts were re-amplified in DNA from primary tumors and included either if the mutation was present in the primary tumors or if the mutant was not identified in the homologous mouse sequence identified by BLAT.

Mutation prevalence screen

[102] We further evaluated a set of 20 mutated genes that had been identified in the Discover Screen in a second (Prevalence) screen, which included an additional 83 GBMs (tabl S2). The genes selected were mutated in at least two tumors and had mutatio frequencies >10 mutations per Mb of tumor DNA sequenced. The primers used (table S1, available on line at *Science* 26 September 2008: Vol. 321. no. 5897, pp. 1807 - 1812) and methods of analysis and duration of potential mutations were the same as in the Discovery screen. All somatic mutations observed in the Prevalence screen are reported in Fig. 10, Table S4.

Copy Number Analysis

[103] The Illumina Infinium II Whole Genome Genotyping Assay employing the BeadChip platform was used to analyze tumor samples at 1,072,820 (1M) SNP loci. All SNP positions were based on the hg18 (NCBI Build 36, March 2006) version of the human genome reference sequence. The genotyping assay begins with hybridization to a 50 nucleotide oligo, followed by a two-color fluorescent single base extension. Fluorescence intensity image files were processed using Illumina BeadStation software to provide normalized intensity values (R) for each SNP position. For each SNP, the normalized experimental

intensity value (R) was compared to the intensity values for that SNP from a training set of normal samples and represented as a ratio (called the "Log R Ratio") of log2(Rexperimental/Rtraining set).

[104] The SNP array data were analyzed using modifications of a previously described method (2). Homozygous deletions (HDs) were defined as three or more consecutive SNPs with a Log R Ratio value of -2. The first and last SNPs of the HD region were considered to be the boundaries of the alteration for subsequent analyses. To eliminate chip artifacts and potential copy number polymorphisms, we removed all HDs that were included in copy number polymorphism databases. Adjacent homozygous deletions separated by three or fewer SNPs were considered to be part of the same deletion, as were HDs within 100,000 bp of each other. To identify the target genes affected by HDs, we compared the location of coding exons in the RefSeq, CCDS and Ensembl databases with the genomic coordinates of the observed HDs. Any gene with a portion of its coding region contained within a homozygous deletion was considered to be affected by the deletion.

[105] As outlined in (2), amplifications were defined by regions containing three SNPs with an average LogR ratio 0.9, with at least one SNP having a LogR ratio 1.4. As with HDs, we excluded all putative amplifications that had identical boundaries in multiple samples. As focal amplifications are more likely to be useful in identifying specific target genes, a second set of criteria were used to remove complex amplifications, large chromosomal regions or entire chromosomes that showed copy number gains. Amplifications > 3Mb in size and groups of nearby amplifications (within 1 Mb) that were also > 3Mb in size were considered complex. Amplifications or groups of amplifications that occurred at a frequency of 4 distinct amplifications in a 10 Mb region or 5 amplifications per chromosome were deemed to be complex. The amplifications remaining after these filtering steps were considered to be focal amplifications and were the only ones included in subsequent statistical analyses. To identify protein coding genes affected by amplifications, we compared the location of the start and stop positions of each gene within the RefSeq, CCDS and Ensmbl databases with the genomic coordinates of the observed amplifications. As amplifications containing only a fraction of a gene are less likely to have a functional

consequence, we only considered genes whose entire coding regions were included in the observed amplifications.

Estimation of passenger mutation rates

[106] From the synonymous mutations observed in the Discovery Screen, we estimated a lower bound of the passenger rate. The lower bound was defined as the product of the synonymous mutation rate and the NS:S ratio (1.02) observed in the HapMap database of human polymorphisms. The calculated rate of 0.38 mutations/Mb successfully sequenced is likely an underestimate because selection against nonsynonymous mutations may be more stringent in the germline than in somatic cells. An upper bound was calculated from the total observed number of non-synonymous mutations/Mb after excluding the most highly mutated genes known to be drivers from previous studies (*TP53*, *PTEN*, and *RB1*). The resultant passenger mutation rate of 1.02 non-synonymous mutations/Mb represents an over-estimate of the background rate as some of the mutations in genes other than *TP53*, *PTEN*, and *RB1* were likely to be drivers. A 'Mid" measure of 0.70 mutations/Mb was obtained from the average of the lower and upper bound rates. For comparisons of the number and type of somatic mutations identified in the Discovery and Prevalence Screens, two sample t-tests between percents were used.

Expression analysis

[107] SAGE tags were generated using a Digital Gene Expression-Tag Profiling preparation kit (Illumina, San Diego, CA) as recommended by the manufacturer. In brief, RNA was purified using guianidine isothiocyanate and reverse transcription with oligo-dT magnetic beads was performed on ~1 ug of total RNA from each sample. Second strand synthesis was accomplished through RNAse H nicking and DNA polymerase I extension. The double-stranded cDNA was digested with the restriction enonuclease Nla III and ligated to an adapter containing a Mme I restriction site. After Mme I digestion, a second adapter was ligated, and the adapter-ligated cDNA construct was enriched by 18 cycles of PCR and fragments of 85 bp were purified from a polyacrylamide gel. The library size was estimated

using real-time PCR and the tags sequenced on a Genome Analyzer System (Illumina, San Diego, CA).

Statistical Analysis

Overview of Statistical Analysis

[108] The statistical analyses focused on quantifying the evidence that the mutations in a gene or a biologically defined set of genes reflect an underlying mutation rate that is higher than the passenger rate. In both cases, the analysis integrates data on point mutations with data on copy number alterations (CNA). The methodology for the analysis of point mutations is based on that described in (3) while the methodology for integration across point mutations and CNA's is based on (2). We provide a self-contained summary herein, as several modifications to the previously described methods were required.

Statistical Analyses of CAN-genes

[109] The mutation profile of a gene refers to the number of each of the twenty-five context-specific types of mutations defined earlier (3). The evidence on mutation profiles is evaluated using an Empirical Bayes analysis (4) comparing the experimental results to a reference distribution representing a genome composed only of passenger genes. This is obtained by simulating mutations at the passenger rate in a way that precisely replicates the experimental plan. Specifically, we consider each gene in turn and simulate the number of mutations of each type from a binomial distribution with success probability equal to the context-specific passenger rate. The number of available nucleotides in each context is the number of successfully sequenced nucleotides for that particular context and gene in the samples studied. When considering nonsynonymous mutations other than indels, we focus on nucleotides at risk, as defined previously (3).

[110] Using these simulated datasets, we evaluated the passenger probabilities for each of the genes that were analyzed in this study. These passenger probabilities represent statements

about specific genes rather than about groups of genes. Each passenger probability is obtained via a logic related to that of likelihood ratios: the likelihood of observing a particular score in a gene if that gene is a passenger is compared to the likelihood of observing it in the real data. The gene-specific score used in our analysis is based on the Likelihood Ratio Test (LRT) for the null hypothesis that, for the gene under consideration, the mutation rate is the same as the passenger mutation rate. To obtain a score, we simply transform the LRT to s = log(LRT). Higher scores indicate evidence of mutation rates above the passenger rates. This general approach for evaluating passenger probabilities follows that described by Efron and Tibshirani (4). Specifically, for any given score s, F(s) represents the proportion of simulated genes with scores higher than s in the experimental data, F0 is the corresponding proportion in the simulated data, and p0 is the estimated overall proportion of passenger genes (discussed below). The variation across simulations is small but nonetheless we generated and collated 100 datasets to estimate F0. We then numerically estimated the density functions f and f0 corresponding to F and F0 and calculated, for each score s, the ratio p0•f0(s)/f(s), also known as "local false discovery rate" (4). Density estimation was performed using the function "density" in the R statistical programming language with default settings. The passenger probability calculations depend on an estimate of p0, the proportion of true passengers. Our implementation seeks to give an upper bound to p0 and thus provide conservatively high estimates of the passenger probability. To this end we set p0=1. We also constrained the passenger probability to change monotonically with the score by starting with the lowest values and recursively setting values that decrease in the next value to their right. We similarly constrain passenger probabilities to change monotonically with the passenger rate.

[111] An open source package for performing these calculations in the R statistical environment, named CancerMutationAnalysis, is available at http://astor.som.jhmi.edu/~gp/software/CancerMutationAnalysis/cma.htm. A detailed mathematical account of our specific implementation is provided in (5) and general analytic issues are discussed in (6).

[112] Statistical Analysis of CNA. For each of the genes involved in amplifications or deletions, we further quantified the strength of the evidence that they drive tumorigenesis through estimations of their passenger probabilities. In each case, we obtain the passenger probability as an a posteriori probability that integrates information from the somatic mutation analysis of (3) with the data presented in this article. The passenger probabilities derived from the point mutation analysis serve as a priori probabilities. These are available for three different scenarios of passenger mutation rates and results are presented separately for each in Fig. 10, Table S3. Then, a likelihood ratio for "driver" versus "passenger" was evaluated using as evidence the number of samples in which a gene was found to be amplified (or deleted). The passenger term is the probability that the gene in question is amplified (or deleted) at the frequency observed. For each sample, we begin by computing the probability that the observed amplifications (and deletions) will include the gene in question by chance. Inclusion of all available SNPs is required for amplification, while any overlap of SNPs is sufficient for deletions. Specifically, if in a specific sample N SNPs are typed, and K amplifications are found, whose sizes, in terms of SNPs involved, are A1 ... AK, a gene with G SNPs will be included at random with probability (A 1-G+1)/N + ... + (AK-G+1)/N for amplifications and (A 1+G-1)/N + ... + (AK+G-1)/N for deletions. We then compute the probability of the observed number of amplifications (or deletions) assuming that the samples are independent but not identically distributed Bernoulli random variables, using the Thomas and Traub algorithm (7). Our approach to evaluating the likelihood under the null hypothesis is highly conservative, as it assumes that all the deletions and amplifications observed only include passengers. The driver term of the likelihood ratio was approximated as for the passenger term, after multiplying the sample-specific passenger rates above by a gene- specific factor reflecting the increase (alternative hypothesis) of interest. This increase is estimated by the ratio between the empirical deletion rate of the gene and the overall deletion rate.

[113] This combination approach makes an approximating assumption of independence of amplifications and deletions. In reality, amplified genes cannot be deleted, so independence is technically violated. However, because of the relatively small number of amplification

and deletion events, this assumption is tenable for the purposes of our analysis. Inspection of the likelihood, in a logarithmic scale, suggests that it is roughly linear in the overall number of events, supporting the validity of this approximation as a scoring system.

Analysis of mutated gene pathways and groups

[114] Four types of data were obtained from the MetaCore database (GeneGo, Inc., St. Joseph, MI): pathway maps, Gene Ontology (GO) processes, GeneGo process networks, and protein-protein interactions. The memberships of each of the 23,781 transcripts in these categories were retrieved from the databases using RefSeq identifiers. In GeneGo pathway maps, 22,622 relations were identified, involving 4,175 transcripts and 509 pathways. For Gene Ontology processes, a total of 66,397 pairwise relations were identified, involving 12,373 transcripts and 4,426 GO groups. For GeneGo process networks, a total of 23,356 pairwise relationships, involving 6,158 transcripts and 127 processes, were identified. The predicted protein products of each mutated gene were also evaluated with respect to their physical interactions with proteins encoded by other mutated genes as inferred from the MetaCore database.

[115] For each of the gene sets considered, we quantified the strength of the evidence that they included a higher-than-average proportion of drivers of carcinogenesis after consideration of set size. For this purpose, we sorted the genes by a score based on the combined passenger probability described above (taking into account mutations, homozygous deletions, and amplifications). We compared the ranking of the genes contained in the set with the ranking of those outside, using the Wilcoxon test, as implemented by the Limma package in Bioconductor (8), then corrected for multiplicity by the q-value method with an alpha of 0.2 (9).

Bioinformatic Analysis

Overview of Bioinformatic Analysis

[116] We have developed a novel bioinformatics software pipeline (depicted below) to compute: (1) a score for ranking somatic missense mutations by the likelihood that they are passengers (LSMUT). The scores are based on properties derived from protein sequences, amino acid residue changes and positions within the proteins; and (2) qualitative annotations of each mutation, based on protein structure homology models.

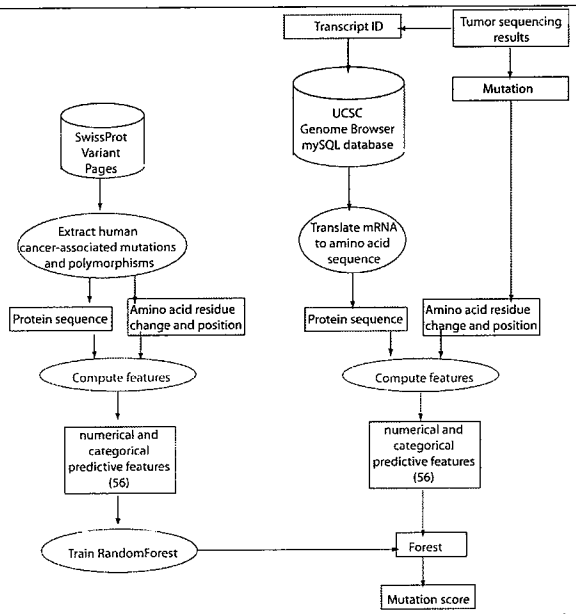
Mutation Scores

[117] We tested several supervised machine learning algorithms to identify one that would reliably distinguish between presumably neutral polymorphisms and cancer-associated mutations. The best algorithm was a Random Forest (12), which we trained on 2,840 cancer-associated mutations and 19,503 polymorphisms from the SwissProt Variant Pages (13) using parallel Random Forest software (PARF) [http://www.irb.hrien/cir/projects/info/parf]. Cancer- associated mutations were identified by parsing for the keywords "cancer", "carcinoma", "sarcoma", "blastoma", "melanoma", "lymphoma", "adenoma" and "glioma". For each mutation or polymorphism, we computed 58 numerical and categorical features (see table below). Two mutations present in the GBM tumor samples were found in the SwissProt Variant Pages and removed from the training data. Because the training set contained ~7 times as many polymorphisms as cancer- associated mutations, we used class weights to upweight the minority class (cancer-associated mutation weight was 5.0 and polymorphism weight was 1.0). The mtry parameter was set to 8 and the forest size to 500 trees. Missing feature values were filled in using the Random Forest proximity-based imputation algorithm (12) with six iterations. Full parameter settings and all data used to build the Random Forest are available upon request.

[118] We then applied the trained forest to 594 GBM missense mutations and to a control set of 142 randomly generated missense mutations in transcripts of 78 genes that were found to be non- mutated in 11 colorectal cancers (5). For each mutation, the 58 predictive features were computed as described above and the trained forest was used to compute a

predictive score for ranking the mutations. Specifically, the scores used are the fraction of trees that voted in favor of the "Polymorphic" class for each mutation.

[119] To test the hypothesis that the scores of missense mutations in top-ranked CAN-genes were distributed differently than random missense mutations, we applied a modified Kolmogorov-Smirnov (KS) test, in which ties are broken by adding a very small random number to each score. The scores of missense mutations in the top 13 CAN genes were found to be significantly different from the mutations in the control set ($P<0.001$).



Bioinformatics software pipeline to compute mutation scores. A supervised machine learning prediction algorithm (RandomForest) is trained on ~22,000 annotated variants (cancer-associated mutations and polymorphisms) from the SwissProt variant pages. A total of 56 numeric and categorical predictive features are calculated for each variant.

[120] We estimate that mutations with scores <0.7 (~15% of the missense mutations) are unlikely to be passengers. The threshold is based on the putative similarity of passengers to the neutral polymorphisms in the SwissProt Variant set, of which only ~2% have scores <0.7. Scores of SwissProt Variants were obtained by randomly partitioning them into two folds, training a Random Forest on each (as described above) and then scoring each fold with the Random Forest trained on the other one.

Homology Models

[121] The protein translations of mRNA transcripts found to have somatic missense mutations were input into ModPipe 1.0/MODELLER 9.1 homology model building software (14, 15). For each mutation, we identified all models that included the mutated position. If more than one model was produced for a mutation, we selected the model having the highest sequence identity with its template structure. The resulting model was used to compute the solvent accessibility of the wild type residue at the mutated position, using DSSP software (16). Accessibility values were normalized by dividing by the maximum residue solvent accessibility for each side chain type in a Gly-X-Gly tri-peptide (17). Solvent accessibilities greater than 36% were considered to be "exposed", those between 9% and 35% were considered "intermediate", and those < 9% were considered "buried". DSSP was also used to compute the secondary structure of the mutated position. We used the LigBase (18) and PiBase (19) databases to identify mutated residue positions in the homology models that were close to ligands or domain interfaces in the equivalent positions of their template structures. Finally, for each mutation, we generated an image of the mutation mapped onto its homology model with UCSF Chimera (20). The images and associated information for each mutation are available at http://karchinlab.org/Mutants/CAN-genes/pancreatic/Pancreatic_cancer.html). Model coordinates are available on request.

Table 6. The 58 numerical and categorical features used to train the Random Forest

#	Feature	Description
1	Net residue charge change	The change in formal charge resulting from the mutation.
2	Net residue volume change	The change in residue volume resulting from the mutation (*18*).
3	Net residue hydrophobicity change	The change in residue hydrophobicity resulting from the substitution (*19*).
4	Positional Hidden Markov model (HMM) conservation score	This feature is calculated based on the degree of conservation of the residue estimated from a multiple sequence alignment built with SAM-T2K software (*20*), using the protein in which the mutation occurred as the seed sequence (*21*). The SAM-T2K alignments are large, superfamily-level alignments that include distantly related homologs (as well as close homologs and orthologs) of the

		protein of interest.
5	Entropy of HMM alignment	The Shannon entropy calculated for the column of the SAM-T2K multiple sequence alignment, corresponding to the location of the mutation (*21*).
6	Relative entropy of HMM alignment	Difference in Shannon entropy calculated for the column of the SAM-T2K multiple sequence alignment (corresponding to the location of the mutation) and that of a background distribution of amino acid residues computed from a large sample of multiple sequence alignments (*21*).
7	Compatibility score for amino acid substitution in the column of a multiple sequence alignment of orthologs.	These multiple sequence alignments are calculated using groups of orthologous proteins from the OMA database (*22*), which are aligned with T-Coffee software (*23*). The compatibility score for the mutation in the column of interest is computed as: (P(most frequent residue in the column) – 2*P(wild type) + P(mutant) + P(Deletion) – 1) / (5 * number of unique amino acid residues in the column)
8	Grantham score	The Grantham substitution score for the wild type => mutant transition (*24*).
9-11	Predicted residue solvent accessibility	These features consist of the probability of the wild type residue being buried, intermediate or exposed as predicted by a neural network trained with Predict-2nd software (*20*) on a set of 1763 proteins with high resolution X-ray crystal structures sharing less than 30% homology (*25*).
12-14	Predicted contribution to protein stability	These features consist of the probability that the wild type residue contributes to overall protein stability in a manner that is highly stabilizing, average or destabilizing, as predicted by a neural network trained with Predict-2nd software (*20*) on a set of 1763 proteins with less than 30% homology. Stability estimates for the neural net training data were calculated using the FoldX force field (*26*).
15-17	Predicted flexibility (Bfactor)	These features consist of the probability that the wild type residue backbone is stiff, intermediate or flexible as predicted by a neural network trained with Predict-2nd software (*20*) on a set of 1763 proteins with less than 30% homology. Flexibilities for the neural net training data were estimated based on normalized temperature factors, computed using the method of (*27*) from the X-ray crystal structure files.
18-20	Predicted secondary structure	These features consist of the probability that the secondary structure of the region in which the wild type residue exists is helix, loop or strand as predicted by a neural net trained with Predict-2nd software (*20*) on a set of 1763 proteins with crystal structures and with less than 30% homology.
21	Change in hydrophobicity	Change in residue hydrophobicity due to the wild type → mutant transition.
22	Change in volume	Change in residue volume due to the wildtype → mutant transition.
23	Change in charge	Change in residue formal charge due to the wild type -> mutant transition.
24	Change in polarity	Change in residue polarity due to the wildtype → mutant transition.
25	EX substitution score	Amino acid substitution score from the EX matrix (*28*)
26	PAM250 substitution score	Amino acid substitution score from the PAM250 matrix (*29*)

27	BLOSUM 62 substitution score	Amino acid substitution score from the BLOSUM 62 matrix (*30*)
28	MJ substitution score	Amino acid substitution score from the Miyazawa-Jernigan contact energy matrix (*28, 31*)
29	HGMD2003 mutation count	Number of times that the wild type → mutant substitution occurs in the Human Gene Mutation Database, 2003 version (*28, 32*).
30	VB mutation count	Amino acid substitution score from the VB (Venkatarajan and Braun) matrix (*28, 33*)
31-34	Probability of seeing the wild type residue in the first, middle, or last position of an amino acid triple	Calculated by joint frequencies of amino acid triples in human proteins found in UniProtKB (*11*)
35-37	Probability of seeing the mutant residue in the first, middle, or last position of an amino acid triple	Calculated by joint frequencies of amino acid triples in human proteins found in UniProtKB (*11*)
38-40	Difference in probability of seeing the wildtype vs. the mutant residue in the first, middle, or last position of an amino acid triple	Calculated by joint frequencies of amino acid triples in human proteins found in UniProtKB (*11*)
41	Probability of seeing the wildtype at the center of a window of 5 amino acid residues	Calculated by a Markov chain of amino acid quintuples in human proteins found in UniProtKB (*11*)
42	Probability of seeing the mutant at the center of a window of 5 amino acid residues	Calculated by a Markov chain of amino acid quintuples in human proteins found in UniProtKB (*11*)
43-56	Binary categorical features from the UniProt KnowledgeBase feature table for the protein product of the transcript	These features give annotations, curated from the literature, of general binding sites, general active sites, lipid, metal, carbohydrate, DNA, phosphate and calcium binding sites, disulfides, seleno-cysteines, modified residues, propeptide residues, signal peptide residues, known mutagenic sites, transmembrane regions, compositionally biased regions, repeat regions, known motifs, and zinc fingers. The integer 1 indicates that a feature is present and the integer 0 indicates that it is absent at a mutated position.

References for Example 11

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CLAIMS

1. A method of characterizing a GBM tumor in a human subject, comprising:

analyzing a GBM tumor in a human subject to identify the presence or absence of a somatic mutation at

- codon 132 in isocitrate dehydrogenase 1 (*IDH1*); or
- codon 172 in isocitrate dehydrogenase 2 (*IDH2*).

2. The method of claim 1 wherein the somatic mutation is R132H in *IDH1*.
3. The method of claim 1 wherein the somatic mutation is R132S in *IDH1* .
4. The method of claim 1 wherein the somatic mutation is R132C in *IDH1*.
5. The method of claim 1 wherein the somatic mutation is R132L in *IDH1*
6. The method of claim 1 wherein the somatic mutation is R132G in *IDH1*.
7. The method of claim 1 wherein the somatic mutation is R172M in *IDH2*.
8. The method of claim 1 wherein the somatic mutation is R172K in *IDH2*.
9. The method of claim 1 wherein the somatic mutation is R172G in *IDH2*.
10. The method of claim 1 further comprising the step of:

identifying the tumor as likely to be a secondary GBM when the somatic mutation is present or a primary GBM when the somatic mutation is absent.

11. The method of claim 1 further comprising the step of:

assigning a more favorable prognosis (longer life expectancy) when the somatic mutation is present or a less favorable prognosis (shorter life expectancy) when the somatic mutation is absent.

12. The method of claim 1 further comprising the step of:

assigning the subject to a clinical trial group based on presence or absence of the somatic mutation.

13. The method of claim 1 further comprising the step of:

prescribing an IDH1 or an IDH2 inhibitor to treat the GBM tumor.

14. The method of claim 1 further comprising the step of:

administering an IDH1 or an IDH2 inhibitor to treat the GBM tumor.

15. The method of claim 13 wherein the inhibitor is an antibody which specifically binds IDH1, IDH2, or IDH1 and IDH2.
16. The method of claim 14 wherein the inhibitor is an antibody which specifically binds IDH1, IDH2, or IDH1 and IDH2.
17. The method of claim 13 wherein the inhibitor is an antibody which specifically binds codon 132 of IDH1, codon 172 of IDH2 or both of said codons.
18. The method of claim 14 wherein the inhibitor is an antibody which specifically binds codon 132 of IDH1, codon 172 of IDH2 or both of said codons.
19. The method of claim 13 further comprising: prescribing a chemotherapy agent in concert with the IDH1 inhibitor.
20. The method of claim 14 further comprising: administering a chemotherapy agent in concert with the IDH1 inhibitor.
21. The method of claim 1 comprising: amplifying at least a portion of:
    - the *IDH1* gene or cDNA of the *IDH1* mRNA, said portion comprising codon 132 or nucleotide 394 or 395 of *IDH1* transcript; or
    - the *IDH2* gene or cDNA of the *IDH2* mRNA, said portion comprising codon 172 or nucleotide 515 of *IDH2* transcript.
22. The method of claim 1 wherein the step of determining employs an antibody which specifically binds to isocitrate dehydrogenase 1 (IDH1), to isocitrate dehydrogenase 2 (IDH2), or to both IDH1 and IDH2.
23. The method of claim 1 wherein the step of determining employs an antibody which preferentially binds to one or more of R132H, R132C, R132S, R132L, and R132G, of isocitrate dehydrogenase 1 (IDH1) and R172M, R172G, and R172K of IDH2, relative to R132 IDH1 or R172 IDH2.
24. The method of claim 1 wherein the step of determining employs hybridization of an oligonucleotide probe comprising:
    - *IDH1* codon 132 or nucleotide 394 or 395 of *IDH1* transcript plus sufficient adjacent nucleotides of *IDH1* to achieve specific hybridization; or
    - *IDH2* codon 172 or nucleotide 515 of *IDH2* transcript plus sufficient adjacent nucleotides of *IDH2* to achieve specific hybridization.

25. The method of claim 1 wherein the step of determining comprises using primer extension to generate a reaction product comprising at least a portion of:
    - *IDH1* that includes codon 132 or nucleotide 394 or 395 of *IDH1* transcript; or
    - *IDH2* that includes codon 172 or nucleotide 515 of *IDH2* transcript.

26. An isolated antibody which specifically binds:
    - R132H IDH1, or R132C IDH1, or R132S IDH1, or R132L IDH1, or R132G IDH1, but not R132 IDH1;
    - R172M IDH2, R172G, or R172K of IDH2, but not R172 IDH2;
    - R132 IDH1; or
    - R172 IDH2.

27. The antibody of claim 26 which is a monoclonal antibody.

28. The antibody of claim 26 which is a single chain variable region molecule.

29. A method of immunizing a mammal, comprising the step of:

administering to a mammal a mutant polypeptide comprising at least 8 contiguous amino acid residues of:
    - a human IDH1 protein found in a human tumor, said at least 8 contiguous amino acid residues comprising residue 132, wherein residue 132 is not arginine; or
    - a human IDH2 protein found in a human tumor, said at least 8 contiguous amino acid residues comprising residue 172, wherein residue 172 is not arginine;

whereby antibodies and/ or T cells which are immunoreactive with epitopes found on the IDH1 mutant polypeptide but not found on normal IDH1 or found on the IDH2 mutant polypeptide but not found on normal IDH2 are produced.

30. The method of claim 29 wherein the mutant polypeptide comprises a R132H residue of IDH1.

31. The method of claim 29 wherein the mutant polypeptide comprises a R132S residue of IDH1.

32. The method of claim 29 wherein the mutant polypeptide comprises a R132C residue of IDH1.

33. The method of claim 29 wherein the mutant polypeptide comprises a R132G residue of IDH1.

34. The method of claim 29 wherein the mutant polypeptide comprises a R132L residue of IDH1.
35. The method of claim 29 wherein the mutant polypeptide comprises a R172M residue of IDH2.
36. The method of claim 29 wherein the mutant polypeptide comprises a R172K residue of IDH2.
37. The method of claim 29 wherein the mutant polypeptide comprises a R172G residue of IDH2.
38. A mutant polypeptide comprising at least 8 contiguous amino acid residues of:
    - a human IDH1 protein found in a human tumor, said at least 8 contiguous amino acid residues comprising residue 132, wherein residue 132 is not arginine; or
    - a human IDH2 protein found in a human tumor, said at least 8 contiguous amino acid residues comprising residue 172, wherein residue 172 is not arginine.

39. The mutant polypeptide of claim 38 wherein the polypeptide is an IDH1 polypeptide and residue 132 is selected from the group consisting of histidine, cysteine, leucine, serine, and glycine.
40. The mutant polypeptide of claim 38 wherein the polypeptide is a human IDH2 polypeptide and residue 172 is selected from the group consisting of glycine, lysine, and methione.
41. An isolated polynucleotide comprising at least 18 but less than 600 contiguous nucleotide residues of a coding sequence of a human IDH1 or IDH2 protein found in a human tumor, said at least 18 contiguous amino acid residues comprising:
    - nucleotides 394 and/or 395 of IDH1, wherein said nucleotides 394 and/or 395 are not C and/or G, respectively;
    - nucleotide 515 of IDH2, wherein said nucleotide 515 is not a G.

42. The isolated polynucleotide of claim 41 wherein the coding sequence is of a human IDH1 protein and the nucleotide 394 is selected from the group consisting of T, A, and G or nucleotide 395 is selected from the group consisting of A and T.

43. The isolated polynucleotide of claim 41 wherein the coding sequence is of a human IDH2 protein and the nucleotide 515 is selected from the group consisting of T and A or nucleotide 514 is a G.

44. A method of immunizing a mammal, comprising the step of:

administering to a mammal a polypeptide comprising at least 8 and less than 200 contiguous amino acid residues of:

- a human IDH1 protein, said at least 8 contiguous amino acid residues comprising residue 132, wherein residue 132 is arginine; or
- a human IDH2 protein, said at least 8 contiguous amino acid residues comprising residue 172, wherein residue 172 is arginine;

whereby antibodies and/ or T cells which are immunoreactive with epitopes found on the IDH1 polypeptide or found on the IDH2 mutant polypeptide are produced.

45. An isocitrate dehydrogenase polypeptide comprising at least 8 and less than 200 contiguous amino acid residues of:

- a human IDH1 protein, said at least 8 contiguous amino acid residues comprising residue 132, wherein residue 132 is arginine; or
- a human IDH2 protein, said at least 8 contiguous amino acid residues comprising residue 172, wherein residue 172 is arginine.

46. A method of screening a test substance for cancer treatment, comprising:

contacting a test substance with a human IDH1 or IDH2 protein;

assaying enzyme activity of the human IDH1 or IDH2 protein;

identifying a test substance which modulates enzyme activity as a candidate therapeutic agent;

testing the candidate therapeutic agent in a cell, tissue, or whole animal cancer model to determine cancer cell growth inhibition, prolongation of life expectancy, inhibition of cancer cell proliferation, stimulation of apoptosis, or inhibition of tumor growth.

47. The method of claim 46 wherein the protein is IDH1.
48. The method of claim 46 wherein the protein is IDH2.
49. The method of claim 46 wherein the modulator is an inhibitor.
50. The method of claim 46 wherein the modulator is an enhancer.
51. The method of claim 46 wherein the step of testing is done in the presence of a chemotherapeutic anti-cancer drug.
52. The method of claim 46 wherein the step of testing is done in the absence of a chemotherapeutic anti-cancer drug.
53. The method of claim 47 wherein the protein has a non-arginine amino acid at residue 132.
54. The method of claim 48 wherein the protein has a non-arginine amino acid at residue 172.
55. The method of claim 46 wherein the enzyme is assayed using a spectrophotometric assay.
56. The method of claim 46 wherein the enzyme is assayed using a bioluminescent assay.
57. The method of claim 46 wherein the cell, tissue, or whole animal cancer model contains a non-arginine residue at codon 132 of IDH1 or at codon 172 of IDH2.
58. A method of detecting or diagnosing glioblastoma multiforme (GBM) or minimal residual disease of GBM or molecular relapse of GBM in a human, comprising the steps of:

determining in a test sample relative to a normal sample of the human, a somatic mutation in a gene or its encoded mRNA or protein, said gene selected from the group consisting of those listed in Fig. 10, Table **S7**;

identifying the human as likely to have glioblastoma multiforme, minimal residual disease, or molecular relapse of GBM when the somatic mutation is determined.

59. The method of claim 58 wherein the mutation is in a gene selected from selected from the group consisting of CDKN2A, TP53, EGFR, PTEN, NF1, CDK4, RB1, IDH1, PIK3CA, and PIK3R1.
60. The method of claim 58 wherein the test sample is a brain tissue sample or a suspected glioblastoma multiforme metastasis.
61. The method of claim 58 wherein the normal sample is a brain tissue sample.

62. A method of characterizing a glioblastoma multiforme in a human, comprising the steps of:

determining a CAN-gene mutational signature for a glioblastoma multiforme by determining in a test sample relative to a normal sample of the human, a somatic mutation in at least one gene or its encoded cDNA or protein, said gene selected from the group consisting of those listed in Fig. 10, Table **S7** ;

assigning the glioblastoma multiforme to a first group of glioblastoma multiforme tumors that have the CAN-gene mutational signature.

63. The method of claim 62 wherein the mutation is in a gene selected from selected from the group consisting of CDKN2A, TP53, EGFR, PTEN, NF1, CDK4, RB1, IDH1, PIK3CA, and PIK3R1.

64. The method of claim 62 wherein the test sample is a glioblastoma multiforme sample or a suspected glioblastoma multiforme metastasis.

65. The method of claim 62 wherein the normal sample is a brain tissue sample.

66. The method of claim 62 further comprising the steps of:

comparing efficacy of a candidate or known anti-cancer therapeutic on the first group to efficacy on a second group of glioblastoma multiforme tumors that has a different CAN-gene mutational signature;

identifying a CAN gene mutational signature which correlates with increased or decreased efficacy of the candidate or known anti-cancer therapeutic relative to other groups.

67. The method of claim 66 wherein the at least one mutation is in a gene selected from the group consisting of CDKN2A, TP53, EGFR, PTEN, NF1, CDK4, RB1, IDH1, PIK3CA, and PIK3R1.

68. The method of claim 66 wherein the test sample is a brain tissue sample or a blood sample.

69. The method of claim 66 wherein the normal sample is a brain tissue sample or a blood sample.

70. The method of claim 62 wherein the CAN-gene mutational signature comprises at least 2 genes selected from Fig. 10, Table **S7**.

71. The method of claim 62 wherein the CAN-gene mutational signature comprises at least 3 genes selected from Fig. 10, Table S7.
72. The method of claim 62 wherein the CAN-gene mutational signature comprises at least 4 genes selected from Fig. 10, Table S7.
73. The method of claim 62 wherein the CAN-gene mutational signature comprises at least 5 genes selected from Fig. 10, Table S7.
74. The method of claim 62 wherein the CAN-gene mutational signature comprises at least 6 genes selected from Fig. 10, Table S7.
75. The method of claim 62 wherein the CAN-gene mutational signature comprises at least 7 genes selected from Fig. 10, Table S7.
76. A method of characterizing a glioblastoma multiforme tumor in a human, comprising the steps of:

determining a mutated pathway selected from the group consisting of TP53, RB1, and PI3K/PTEN in a glioblastoma multiforme tumor by determining at least one somatic mutation in a test sample relative to a normal sample of the human, wherein the at least one somatic mutation is in one or more genes selected from the group consisting of TP53, MDM2, MDM4, RB1, CDK4, CDKN2A, PTEN, PIK3CA, PIK3R1, and IRS1;

assigning the glioblastoma multiforme to a first group of glioblastoma multiforme tumors that have a mutation in one of said pathways, wherein the first group is heterogeneous with respect to the genes in the pathway that have a somatic mutation and homogeneous with respect to the pathway that has a somatic mutation.

77. The method of claim 76 further comprising the steps of:

comparing efficacy of a candidate or known anti-cancer therapeutic on the first group to efficacy on a second group of glioblastoma multiforme tumors that does not have a mutation is said pathway;

identifying a pathway which correlates with increased or decreased efficacy of the candidate or known anti-cancer therapeutic in the first group relative to other groups.

78. A method to detect or diagnose glioblastoma multiforme, or minimal residual disease of GBM or molecular relapse of GBM in a human comprising:

determining expression in a clinical sample of one or more genes listed in Fig. 10, Table S5 or S9 (brain overexpressed genes from SAGE);

comparing expression of the one or more genes in the clinical sample to expression of the one or more genes in a corresponding sample of a control human or control group of humans;

identifying a clinical sample with elevated expression relative to a control as likely to have glioblastoma multiforme, or minimal residual disease of GBM or molecular relapse of GBM in a human.

79. The method of claim 78 wherein the clinical sample is a blood sample.

80. The method of claim 78 wherein the clinical sample is a brain tissue sample.

81. The method of claim 78 wherein protein expression of the one or more genes is determined.

82. The method of claim 78 wherein mRNA expression of the one or more genes is determined.

83. The method of claim 78 wherein the one or more genes is selected from those listed in Fig. 10, Table S10 (extracellular proteins found by SAGE).

84. A method to monitor glioblastoma multiforme burden, comprising:

determining expression in a clinical sample of one or more genes listed in Fig. 10, Table S5 or S9 (brain overexpressed genes from SAGE);

repeating one or more times said step of determining, and

indentifying an increase, decrease or stable level of expression over time.

85. The method of claim 84 wherein the clinical sample is a blood sample.

86. The method of claim 84 wherein protein expression of the one or more genes is determined.

87. The method of claim 86 wherein the one or more genes is selected from those listed in Fig. 10, Table S10 (extracellular proteins found by SAGE).

88. A method to monitor glioblastoma multiforme burden, comprising:

determining a somatic mutation in a clinical sample of one or more genes listed in Fig. 10, Table S7);

repeating one or more times said step of determining, and

indentifying an increase, decrease or stable level of said somatic mutation over time.

89. A method to detect or diagnose gliobastoma multiforme, comprising:

determining expression in a clinical sample of one or more genes listed in Fig. 10, Table S6 (homozygous deletions);

comparing expression of the one or more genes in the clinical sample to expression of the one or more genes in a corresponding sample of a control human or control group of humans;

identifying a clinical sample with reduced expression relative to a control as likely to have gliobastoma multiforme.

90. The method of claim 89 wherein the clinical sample is a blood or lymph node sample.

91. The method of claim 89 wherein protein expression of the one or more genes is determined.

92. A method to monitor gliobastoma multiforme burden, comprising:

determining expression in a clinical sample of one or more genes listed in Fig. 10, Table S6 (homozygous deletions):

repeating one or more times said step of determining, and

identifying an increase, decrease or stable level of expression over time.

93. The method of claim 92 wherein the clinical sample is a blood or lymph node sample.

94. The method of claim 92 wherein protein expression of the one or more genes is determined.

95. The method of claim 89 or 92 wherein the specimen is selected from the group consisting of plasma, serum, whole blood, stool, and breath.

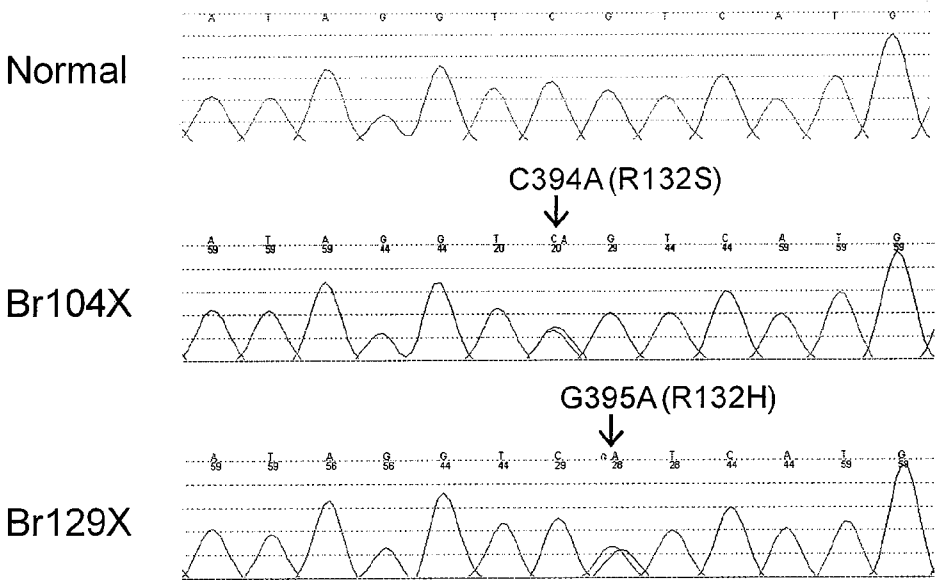

Fig. 1.

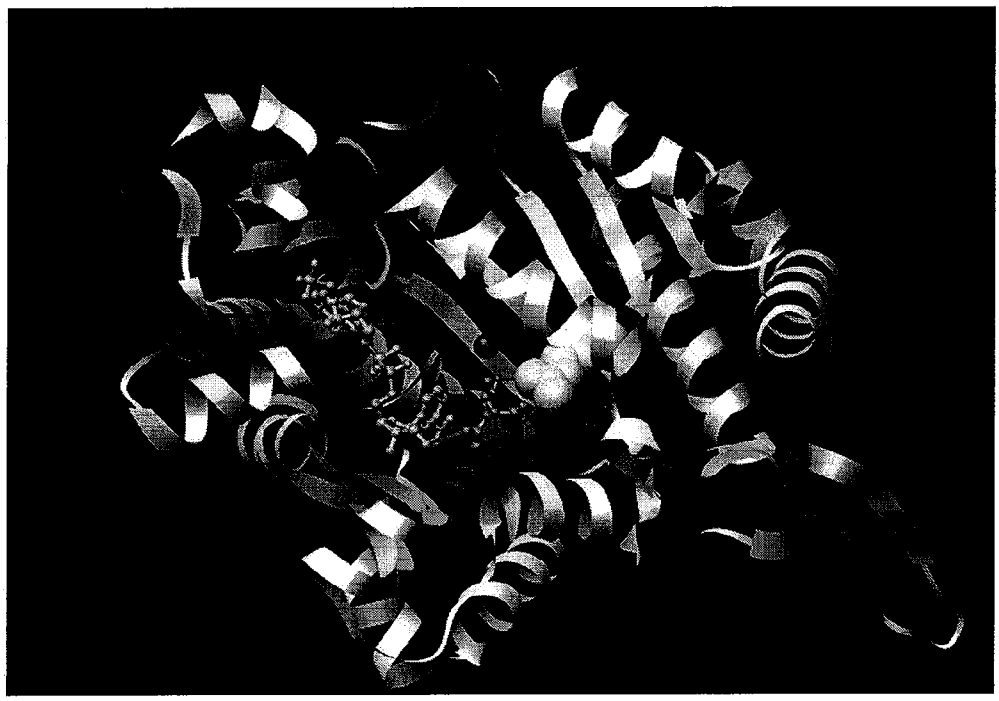

Fig. 2.

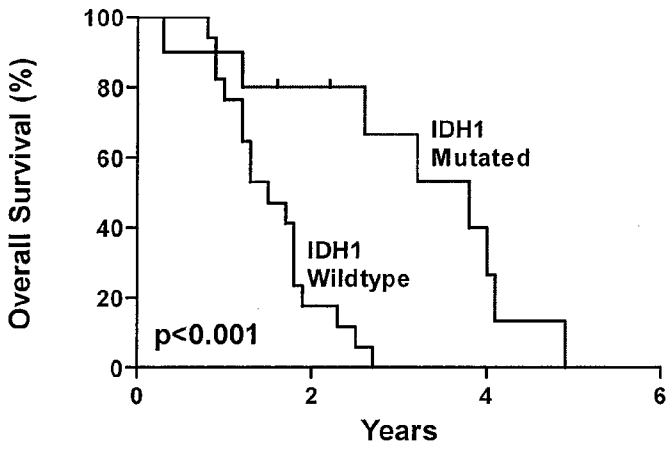
Overall Survival (%)
100
80
60
40
20
0
0
2
4
6
Years
IDH1
Mutated
IDH1
Wildtype
p<0.001

Fig. 3.

Fig. 4A

A

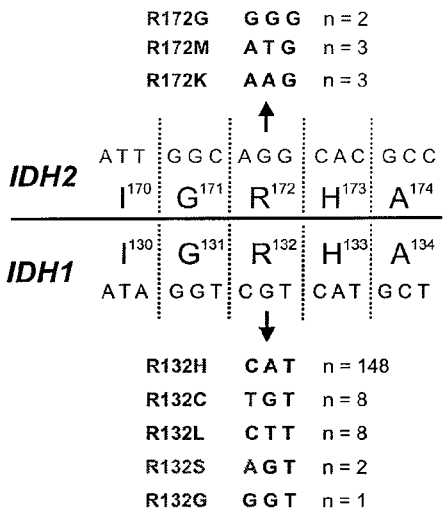

Fig. 4B

B

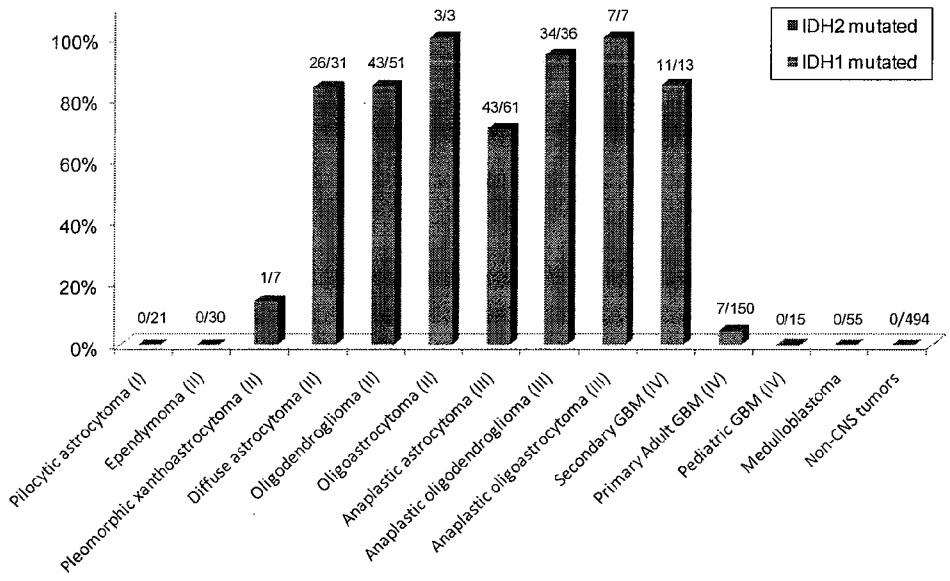

Fig. 5A

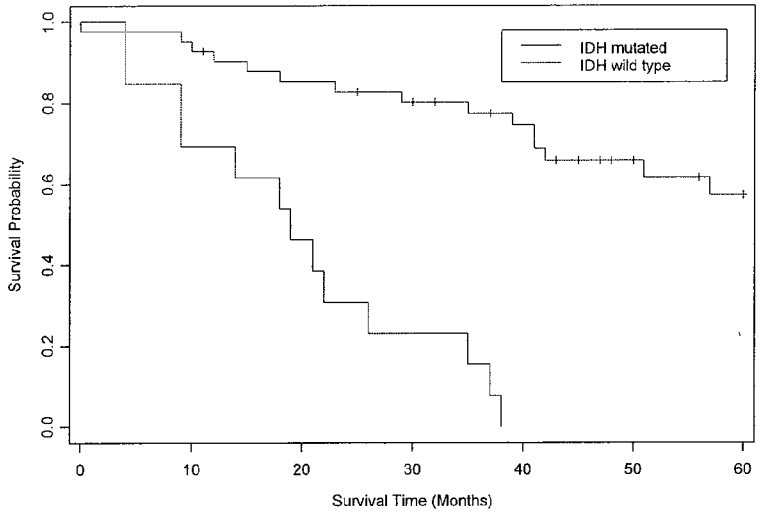
IDH mutated
IDH wild type
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
Survival Time (Months)

Fig. 5B

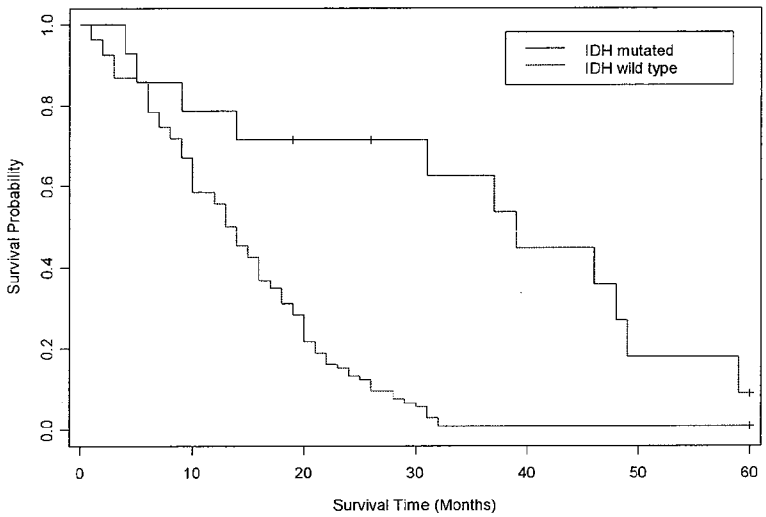
IDH mutated
IDH wild type
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
Survival Time (Months)

Fig. 6

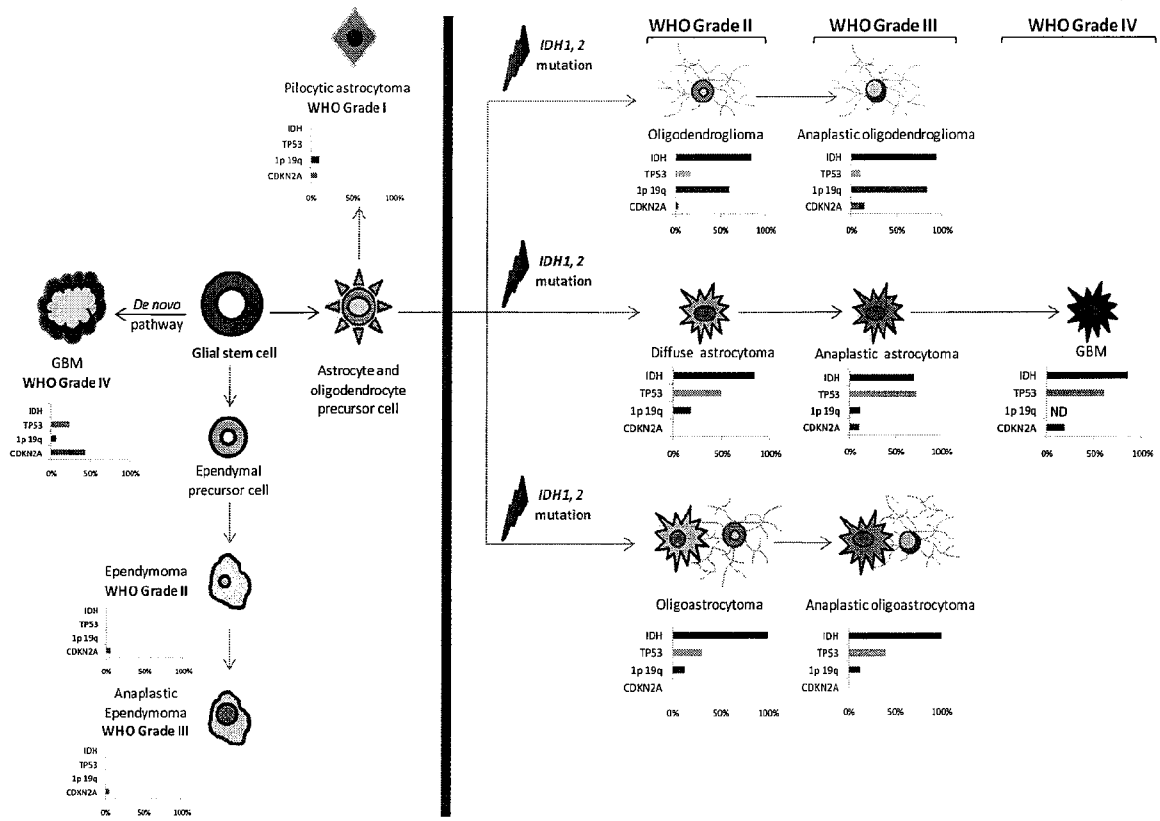
WHO Grade II
WHO Grade III
WHO Grade IV
IDH1, 2 mutation
Pilocytic astrocytoma
WHO Grade I
Oligodendroglioma
Anaplastic oligodendroglioma
IDH
TP53
1p 19q
CDKN2A
0%
50%
100%
De novo pathway
Glial stem cell
Astrocyte and oligodendrocyte precursor cell
GBM
WHO Grade IV
Diffuse astrocytoma
Anaplastic astrocytoma
GBM
ND
Ependymal precursor cell
Ependymoma
WHO Grade II
Anaplastic Ependymoma
WHO Grade III
Oligoastrocytoma
Anaplastic oligoastrocytoma
IDH-independent pathway
IDH-dependent pathway

Fig. 7

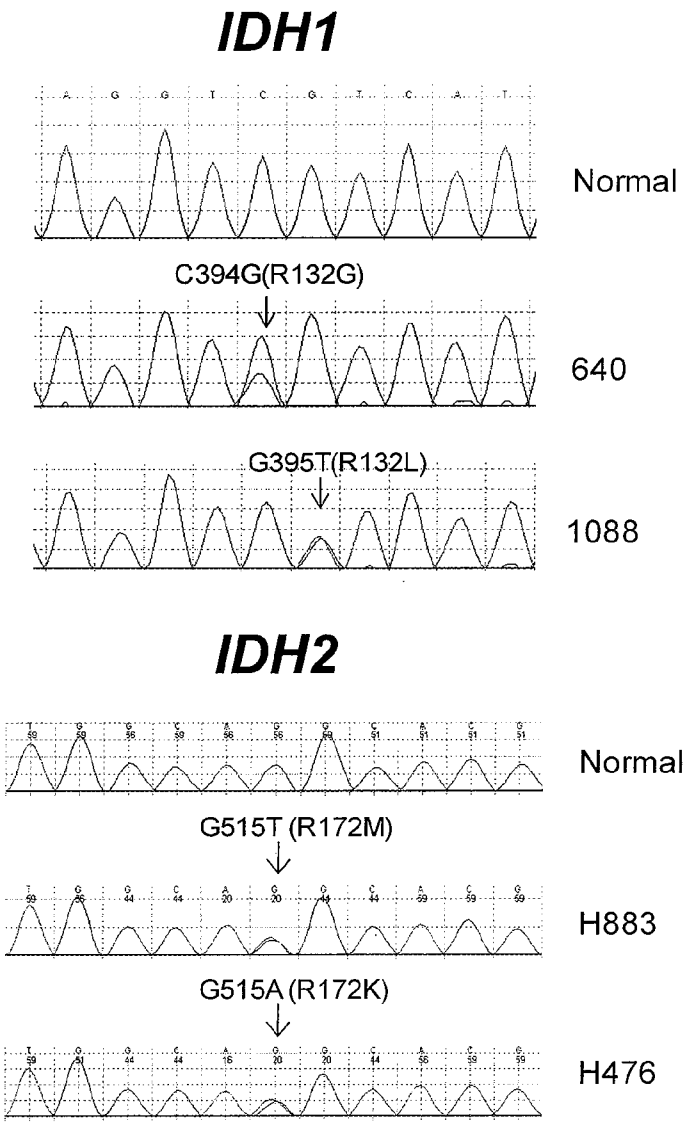
IDH1
Normal
C394G(R132G)
640
G395T(R132L)
1088
IDH2
Normal
G515T (R172M)
H883
G515A (R172K)
H476

Fig. 8

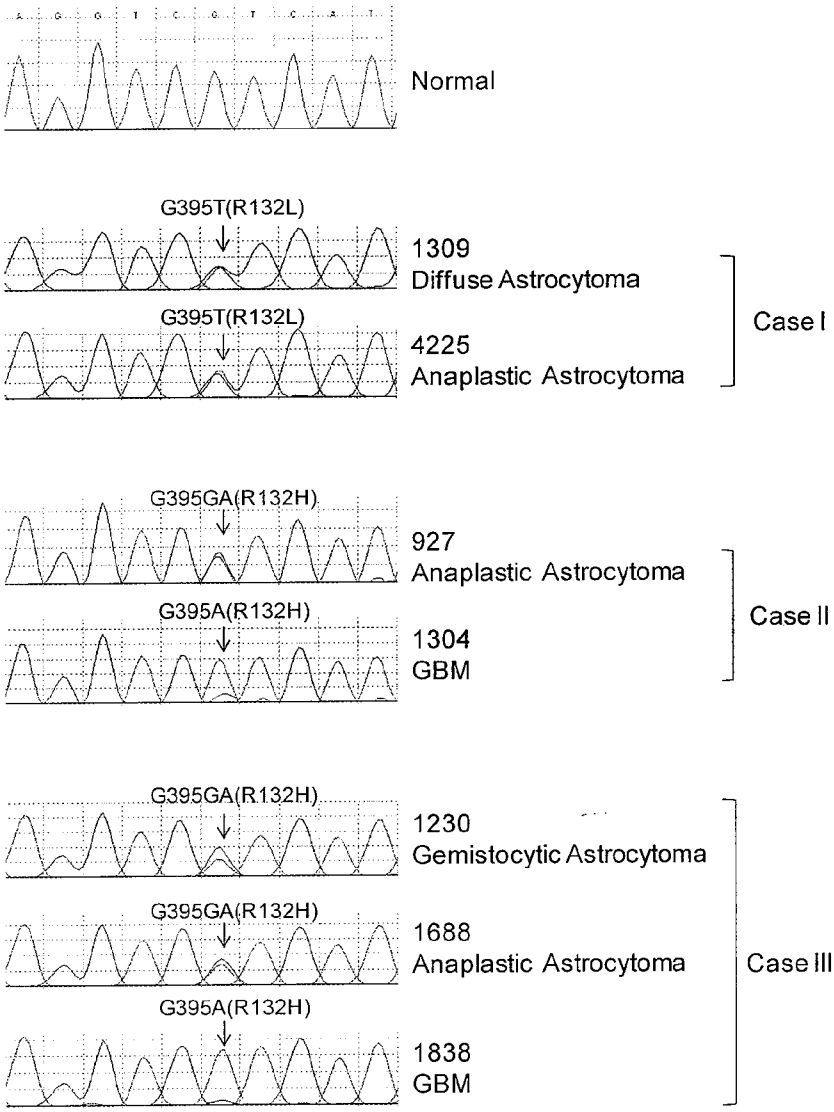
Normal
G395T(R132L)
1309
Diffuse Astrocytoma
G395T(R132L)
4225
Anaplastic Astrocytoma
Case I
G395GA(R132H)
927
Anaplastic Astrocytoma
G395A(R132H)
1304
GBM
Case II
G395GA(R132H)
1230
Gemistocytic Astrocytoma
G395GA(R132H)
1688
Anaplastic Astrocytoma
G395A(R132H)
1838
GBM
Case III

Fig. 9A

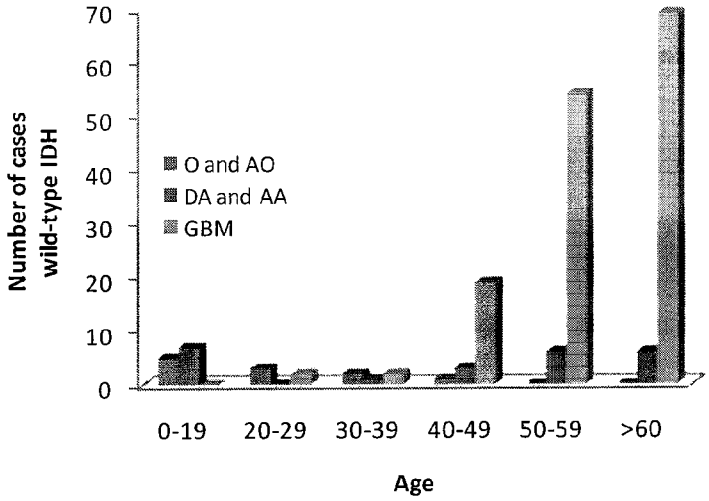
70
60
50
40
30
20
10
0
Number of cases wild-type IDH
O and AO
DA and AA
GBM
0-19
20-29
30-39
40-49
50-59
>60
Age

Fig. 9B

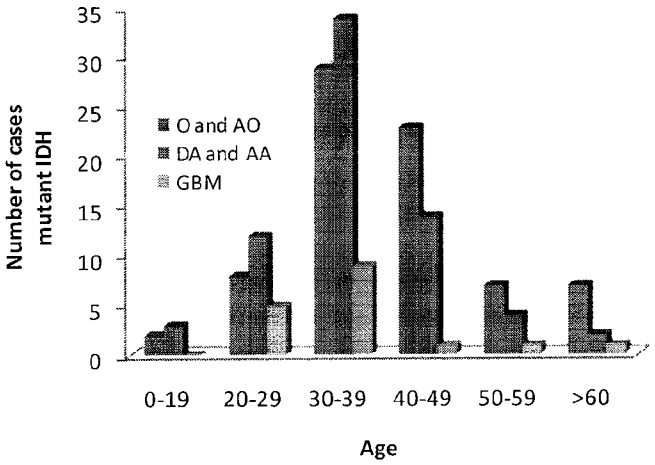
35
30
25
20
15
10
5
0
Number of cases mutant IDH
O and AO
DA and AA
GBM
0-19
20-29
30-39
40-49
50-59
>60
Age

table S3. Somatic mutations identified in GBM Discovery Screen

Gene	Transcript Accession	Tumor	Nucleotide (genomic)*	Nucleotide (cDNA)*†	Amino acid (protein)*‡	Mutation Type
A2M	NM_000014	Br9PT	g.chr12:9150431C>A	c.917C>A	p.T306N	Missense
A4GALT	CCDS14041.1	Br08X	g.chr22:41413510G>A	c.946G>A	p.V316M	Missense
A4GNT	CCDS3097.1	Br13X	g.chr3:139332485T>G	c.312T>G	p.A104A	Synonymous
AACS	CCDS9263.1	Br27P	g.chr12:124116625C>T	c.846C>T	p.S282S	Synonymous
ABCA10	CCDS11684.1	Br11P	g.chr17:64701274G>C	c.1596G>C	p.Q532H	Missense
ABCA12	NM_015657	Br27P	g.chr2:215691839G>A	c.1858G>A	p.E620K	Missense
ABCA13	NM_152701	Br27P	g.chr7:48091360C>T	c.4673C>T	p.S1558F	Missense
ABCA4	CCDS747.1	Br27P	g.chr1:94232842C>T	c.2433C>T	p.R811R	Synonymous
ABCA4	CCDS747.1	Br14X	g.chr1:94199521G>T	c.4675G>T	p.G1559X	Nonsense
ABCA5	CCDS11685.1	Br27P	g.chr17:64781713C>T	c.2746C>T	p.L916F	Missense
ABCA7	CCDS12055.1	Br25X	g.chr19:994398C>T	c.856C>T	p.R286C	Missense
ABCA9	CCDS11681.1	Br05X	g.chr17:64551266G>A	c.759G>A	p.T253T	Synonymous
ABCB1	CCDS5608.1	Br27P	g.chr7:86835309G>A	c.748G>A	p.A250T	Missense
ABCB6	CCDS2436.1	Br25X	g.chr2:219902670C>T	c.1912C>T	p.R638C	Missense
ABCC10	CCDS4896.1	Br27P	g.chr6:43525676C>T	c.4264C>T	p.L1422L	Synonymous
ABCC11	CCDS10732.1	Br27P	g.chr16:46796828C>T	c.1802C>T	p.A601V	Missense
ABCC3	NM_003786	Br14X	g.chr17:46123489G>T	c.4513G>T	p.D1505Y	Missense
ABCC5	NM_005688	Br04X	g.chr3:185178995C>T	c.1294C>T	p.Q432X	Nonsense
ABCD2	CCDS8734.1	Br25X	g.chr12:38266275C>A	c.1738C>A	p.L580M	Missense
ABCF2	CCDS5922.1	Br27P	g.chr7:150349640C>T	c.1707C>T	p.V569V	Synonymous
ABCG2	CCDS3628.1	Br27P	g.chr4:89400087G>A	c.568G>A	p.E190K	Missense
ABHD3	NM_138340	Br27P	g.chr18:17498193C>T	IVS4-4C>T	Splice Site	Splice Site
ABHD4	CCDS9572.1	Br10P	g.chr14:22148578C>T	c.861C>T	p.Y287Y	Synonymous
ABHD7	CCDS736.1	Br27P	g.chr1:92230203G>A	c.824G>A	p.S275N	Missense
ABL2	NM_007314	Br15X	g.chr1:175815771C>T	c.1460C>T	p.P487L	Missense
ABTB2	CCDS7890.1	Br26X	g.chr11:34132451C>A	c.2259C>A	p.C753X	Nonsense
ACAD9	CCDS3053.1	Br27P	g.chr3:130110513G>A	IVS13-1G>A	Splice Site	Splice Site
ACADS	CCDS9207.1	Br15X	g.chr12:119639932G>A	c.1200G>A	p.L400L	Synonymous
ACADS	CCDS9207.1	Br11P	g.chr12:119637983C>T	c.465C>T	p.S155S	Synonymous
ACADSB	CCDS7634.1	Br14X	g.chr10:124800607T>G (homozygous)	c.1043T>G	p.L348X	Nonsense
ACAT2	CCDS5268.1	Br27P	g.chr6:160160062G>A	c.481G>A	p.G161S	Missense
ACCN1	CCDS11276.1	Br27P	g.chr17:28375101C>T	c.1240C>T	p.P414S	Missense
ACCN3	CCDS5914.1	Br27P	g.chr7:150185508C>T	c.829C>T	p.P277S	Missense
ACF	CCDS7241.1	Br27P	g.chr10:52245937G>A	c.976G>A	p.E326K	Missense
ACLY	CCDS11412.1	Br29P	g.chr17:37302840T>G	c.1573T>G	p.S525A	Missense
ACOX3	CCDS3401.1	Br27P	g.chr4:8536193G>A	c.127G>A	p.G43S	Missense
ACP5	CCDS12265.1	Br27P	g.chr19:11549031G>A	c.102G>A	p.W34X	Nonsense
ACRBP	CCDS8554.1	Br14X	g.chr12:6619514C>T	c.1398C>T	p.S466S	Synonymous
ACTG1	CCDS11782.1	Br15X	g.chr17:77092864C>T	c.747C>T	p.T249T	Synonymous
ACTN1	CCDS9792.1	Br27P	g.chr14:68446506C>T	c.434C>T	p.S145L	Missense
ACTR10	NM_018477	Br27P	g.chr14:57739326G>A	c.78G>A	p.K26K	Synonymous
ACTR1A	CCDS7536.1	Br27P	g.chr10:104230676G>A	c.1065G>A	p.K355K	Synonymous
ACTR8	CCDS2875.1	Br27P	g.chr3:53881563C>T	c.1190C>T	p.T397I	Missense
ACTRT1	CCDS14611.1	Br03x	g.chrX:126911559G>A (homozygous)	c.162G>A	p.K54K	Synonymous

Fig. 10

ACTRT1	CCDS14611.1	Br15X	g.chrX:126910589A>T (homozygous)	UTR+1A>T	3'UTR	3'UTR	
ADAM12	CCDS7653.1	Br27P	g.chr10:127796641G>A	c.568G>A	p.A190T	Missense	
ADAM15	CCDS1084.1	Br27P	g.chr1:151842802G>A	c.1214G>A	p.G405E	Missense	
ADAM18	CCDS6113.1	Br13X	g.chr8:39644808T>C	c.1461T>C	p.T487T	Synonymous	
ADAM18	CCDS6113.1	Br03X	g.chr8:39656829C>T	c.1748C>T	p.T583I	Missense	
ADAM28	NM_014265	Br26X	g.chr8:24240084C>T	c.963C>T	p.G321G	Synonymous	
ADAM29	CCDS3823.1	Br07X	g.chr4:176272525T>C	c.1119T>C	p.D373D	Synonymous	
ADAM29	CCDS3823.1	Br07x	g.chr4:176273643C>T (homozygous)	c.2237C>T	p.T746M	Missense	
ADAMTS1	NM_006988	Br27P	g.chr21:27132153C>T	c.2520C>T	p.Y840Y	Synonymous	
ADAMTS13	CCDS6970.1	Br27P	g.chr9:133337114G>A	c.2009G>A	p.R670H	Missense	
ADAMTS13	CCDS6970.1	Br27P	g.chr9:133349273G>A	c.3227G>A	p.W1076X	Nonsense	
ADAMTS17	CCDS10383.1	Br20P	g.chr15:98512929A>G	c.1301A>G	p.D434G	Missense	
ADAMTS20	NM_175851	Br27P	g.chr12:42134010T>C	c.1727T>C	p.I576T	Missense	
ADAMTS20	NM_175851	Br27P	g.chr12:42132735C>T	c.1791C>T	p.G597G	Synonymous	
ADAMTS4	CCDS1223.1	Br17X	g.chr1:157974131G>A	c.2384G>A	p.R795H	Missense	
ADAMTS8	NM_007037	Br27P	g.chr11:129783713C>T	c.1955C>T	p.T652I	Missense	
ADAR	CCDS1071.1	Br27P	g.chr1:151373693C>T	c.3000C>T	p.L1000L	Synonymous	
ADARB2	CCDS7058.1	Br15X	g.chr10:1395335G>A (homozygous)	c.965G>A	p.R322H	Missense	
ADCY1	NM_021116	Br27P	g.chr7:45498885C>T	c.2158C>T	p.P720S	Missense	
ADCY8	CCDS6363.1	Br27P	g.chr8:131966156C>T	c.1945C>T	p.L649L	Synonymous	
ADRBK2	CCDS13832.1	Br27P	g.chr22:24410762G>A	c.1010G>A	p.G337D	Missense	
AGC1	NM_001135	Br27P	g.chr15:87199676G>A	c.2856G>A	p.G952G	Synonymous	
AGL	CCDS759.1	Br27P	g.chr1:100055259G>A	c.1465G>A	p.D489N	Missense	
AGPAT1	CCDS4744.1	Br27P	g.chr6:32247183C>T	c.69C>T	p.P23P	Synonymous	
AGPS	CCDS2275.1	Br27P	g.chr2:178189966G>A	IVS14+1G>A	Splice Site	Splice Site	
AGRN	NM_198576	Br15X	g.chr1:1025272G>C	c.4811G>C	p.R1604P	Missense	
AGRN	NM_198576	Br27P	g.chr1:1030124C>T	IVS35-3C>T	Splice Site	Splice Site	
AHDC1	NM_001029882	Br27P	g.chr1:27561935C>T	c.834C>T	p.P278P	Synonymous	
AHI1	NM_017651	Br27P	g.chr6:135811225C>T	c.1522C>T	p.P508S	Missense	
AIM1L	NM_017977	Br17X	g.chr1:26356608C>T	c.683C>T	p.S228L	Missense	
AIM1L	NM_017977	Br23X	g.chr1:26356352G>A	c.939G>A	p.P313P	Synonymous	
AKAP11	CCDS9383.1	Br27P	g.chr13:41775774G>A	c.4892G>A	p.R1631K	Missense	
AKAP13	NM_007200	Br27P	g.chr15:83924931C>T	c.2628C>T	p.A876A	Synonymous	
AKAP13	NM_007200	Br07X	g.chr15:84052299C>T	c.5510C>T	p.S1837F	Missense	
AKAP13	NM_007200	Br17X	g.chr15:84085604G>A	c.7932G>A	p.K2644K	Synonymous	
AKAP4	CCDS14329.1	Br27P	g.chrX:49660730C>T	c.1670C>T	p.T557I	Missense	
AKAP4	CCDS14329.1	Br27P	g.chrX:49661935C>T	c.465C>T	p.C155C	Synonymous	
AKAP9	CCDS5622.1	Br27P	g.chr7:91318999G>A	c.5189G>A	p.R1730K	Missense	
AKNA	CCDS6805.1	Br05X	g.chr9:114209494G>A	c.1611G>A	p.S537S	Synonymous	
AKNA	CCDS6805.1	Br27P	g.chr9:114198755G>A	c.2788G>A	p.E930K	Missense	
AKR7A2	CCDS194.1	Br27P	g.chr1:19377861C>T	c.875C>T	p.T292I	Missense	
ALDH18A1	CCDS7443.1	Br27P	g.chr10:97356610C>T	c.2287C>T	p.L763L	Synonymous	
ALDH1A2	CCDS10163.1	Br27P	g.chr15:56093392G>A	c.319G>A	p.D107N	Missense	
ALDH1L1	CCDS3034.1	Br27P	g.chr3:127352019C>T	c.912C>T	p.N304N	Synonymous	
ALDH2	CCDS9155.1	Br27P	g.chr12:110700429G>A	IVS10-1G>A	Splice Site	Splice Site	
ALLC	NM_018436	Br07X	g.chr2:3243411C>T	c.1065C>T	p.D355D	Synonymous	
ALOX12	CCDS11084.1	Br27P	g.chr17:6840996C>T	c.263C>T	p.A88V	Missense	
ALOXE3	CCDS11130.1	Br27P	g.chr17:7940771delC	c.2035delC	fs	INDEL	
ALPI	CCDS2492.1	Br15X	g.chr2:233148489C>T	c.1049C>T	p.A350V	Missense	
ALPK2	CCDS11966.1	Br16X	g.chr18:54397977G>A	c.300G>A	p.T100T	Synonymous	

ALPK2	CCDS11966.1	Br27P	g.chr18:54300218C>T	c.5619C>T	p.T1873T	Synonymous
ALPK3	CCDS10333.1	Br26X	g.chr15:83204060G>A	c.4621G>A	p.V1541I	Missense
ALPL	CCDS217.1	Br27P	g.chr1:21649283C>T	c.1411C>T	p.L471L	Synonymous
ALPL	CCDS217.1	Br27P	g.chr1:21634962C>T	c.351C>T	p.Y117Y	Synonymous
ALS2CL	CCDS2743.1	Br27P	g.chr3:46693184G>A	c.1980G>A	p.E660E	Synonymous
ALS2CL	CCDS2743.1	Br27P	g.chr3:46703608C>T	c.403C>T	p.Q135X	Nonsense
ALS2CR12	CCDS2346.1	Br27P	g.chr2:201997816G>A	c.811G>A	p.G271R	Missense
AMACO	CCDS7589.1	Br15X	g.chr10:116036087G>A (homozygous)	c.1397G>A	p.R466H	Missense
AMID	CCDS7297.1	Br27P	g.chr10:71544885C>T	IVS6-3C>T	Splice Site	Splice Site
ANK2	CCDS3702.1	Br27P	g.chr4:114632930C>T	c.5552C>T	p.T1851I	Missense
ANK2	CCDS3702.1	Br27P	g.chr4:114515860C>T	c.597C>T	p.A199A	Synonymous
ANK3	CCDS7258.1	Br17X	g.chr10:61538664C>T (homozygous)	c.3103C>T	p.P1035S	Missense
ANKMY1	CCDS2536.1	Br27P	g.chr2:241171315G>A	c.1972G>A	p.G658S	Missense
ANKRD10	CCDS9520.1	Br27P	g.chr13:110343498A>G	c.569A>G	p.N190S	Missense
ANKRD11	NM_013275	Br27P	g.chr16:87874161C>T	c.6290C>T	p.P2097L	Missense
ANKRD12	CCDS11843.1	Br27P	g.chr18:9246519G>A	c.3254G>A	p.S1085N	Missense
ANKRD15	CCDS6441.1	Br27P	g.chr9:701831G>A	c.591G>A	p.E197E	Synonymous
ANKRD28	NM_015199	Br9PT	g.chr3:15753569A>C	c.437A>C	p.H146P	Missense
ANP32D	NM_012404	Br27P	g.chr12:47152930C>T	c.216C>T	p.S72S	Synonymous
AP3B1	CCDS4041.1	Br27P	g.chr5:77507409G>A	c.1050G>A	p.Q350Q	Synonymous
APG7L	CCDS2605.1	Br27P	g.chr3:11329895G>A	IVS5+1G>A	Splice Site	Splice Site
API5	NM_006595	Br27P	g.chr11:43306005G>A	IVS8+1G>A	Splice Site	Splice Site
APOB	CCDS1703.1	Br27P	g.chr2:21162905T>C	c.1775T>C	p.F592S	Missense
APOB	CCDS1703.1	Br08X	g.chr2:21146371A>G	c.5021A>G	p.E1674G	Missense
APOB	CCDS1703.1	Br07X	g.chr2:21142988G>A	c.8404G>A	p.E2802K	Missense
APOBEC3G	CCDS13984.1	Br27P	g.chr22:37802017G>A	c.508G>A	p.E170K	Missense
APRG1	NM_178339	Br05X	g.chr3:37433846G>A	c.85G>A	p.A29T	Missense
AQP10	CCDS1065.1	Br27P	g.chr1:151108533G>A	c.235G>A	p.A79T	Missense
AR	CCDS14387.1	Br12P	g.chrX:66720414C>T	c.2247C>T	p.A749A	Synonymous
ARD1B	ENST00000286794	Br04X	g.chr4:80603788G>A	c.561G>A	p.G187G	Synonymous
ARHGAP4	CCDS14736.1	Br27P	g.chrX:152708075C>T	c.102C>T	p.C34C	Synonymous
ARHGAP5	NM_001173	Br27P	g.chr14:31632997C>T	c.3371C>T	p.S1124L	Missense
ARHGAP8	CCDS14058.1	Br27P	g.chr22:43451484G>A	c.596G>A	p.R199H	Missense
ARHGDIG	CCDS10404.1	Br27P	g.chr16:272477G>A	c.424G>A	p.E142K	Missense
ARHGEF9	NM_015185	Br27P	g.chrX:62646878A>C	IVS9+3A>C	Splice Site	Splice Site
ARID1A	CCDS285.1	Br27P	g.chr1:26740387G>A	c.1241G>A	p.G414E	Missense
ARID1A	CCDS285.1	Br27P	g.chr1:26707082C>T	c.46C>T	p.P16S	Missense
ARL1	NM_001177	Br14X	g.chr12:100292678C>T	c.482C>T	p.T161I	Missense
ARNT2	NM_014862	Br15X	g.chr15:78659938C>A	c.1745C>A	p.P582Q	Missense
ARNT2	NM_014862	Br11P	g.chr15:78549732A>G	c.313A>G	p.I105V	Missense
ARP10	CCDS13985.1	Br03x	g.chr22:37821842C>T	c.251C>T	p.P84L	Missense
ARSE	CCDS14122.1	Br9PT	g.chrX:2871804_2871802delACA	UTR-2_1delACA	Unknown	INDEL
ASB4	CCDS5641.1	Br27P	g.chr7:94801932C>T	c.644C>T	p.A215V	Missense
ASCL4	NM_203436	Br27P	g.chr12:106671712C>T	c.250C>T	p.R84W	Missense
ASCL5	ENST00000344317	Br27P	g.chr1:19781627 6C>T	c.26C>T	p.S9F	Missense
ASGR1	CCDS11089.1	Br27P	g.chr17:7017734G>A	c.844G>A	p.D282N	Missense
ASH1L	CCDS1113.1	Br15X	g.chr1:152262607G>C	c.3127G>C	p.G1043R	Missense
ASIP	CCDS13232.1	Br07X	g.chr20:32320560G>A	c.325G>A	p.D109N	Missense
ASTN	CCDS1319.1	Br9PT	g.chr1:173733563G>A	c.551G>A	p.R184H	Missense
ASTN	CCDS1319.1	Br04X	g.chr1:173733513A>G	c.601A>G	p.I201V	Missense

Fig. 10

ATAD2B	ENST00000295142	Br27P	g.chr2:24061283C>T	c.9C>T	p.N3N	Synonymous
ATP10B	ENST00000327245	Br03X	g.chr5:159958513T>A	c.3406T>A	p.F1136I	Missense
ATP12A	NM_001676	Br27P	g.chr13:24170838C>T	c.1555C>T	p.L519F	Missense
ATP12A	NM_001676	Br13X	g.chr13:24178566C>G	c.2134C>G	p.Q712E	Missense
ATP13A1	NM_020410	Br27P	g.chr19:19626975G>A	c.1254G>A	p.G418G	Synonymous
ATP13A2	CCDS175.1	Br27P	g.chr1:17060192C>T	c.2693C>T	p.A898V	Missense
ATP1A2	CCDS1196.1	Br27P	g.chr1:156918456G>A	c.2275G>A	p.V759M	Missense
ATP2A1	CCDS10643.1	Br27P	g.chr16:28820696C>T	c.2112C>T	p.G704G	Synonymous
ATP2A3	CCDS11041.1	Br9PT	g.chr17:3787662C>T	c.2118C>T	p.N706N	Synonymous
ATP2B1	CCDS9035.1	Br12P	g.chr12:88531401T>A	c.502T>A	p.L168I	Missense
ATP2B2	CCDS2601.1	Br27P	g.chr3:10392328G>A	c.1067G>A	p.G356D	Missense
ATP6V1G3	CCDS1396.1	Br26X	g.chr1:195237514A>T	IVS1-3A>T	Splice Site	Splice Site
ATP7B	NM_000053	Br27P	g.chr13:51407782G>A	c.4072G>A	p.A1358T	Missense
ATP8A1	CCDS3466.1	Br27P	g.chr4:42421311G>A	c.1022G>A	p.G341E	Missense
ATP8B1	CCDS11965.1	Br27P	g.chr18:53503330C>T	c.1445C>T	p.A482V	Missense
ATP8B1	CCDS11965.1	Br16X	g.chr18:53512891C>A	c.950C>A	p.T317N	Missense
ATRNL1	CCDS7592.1	Br27P	g.chr10:117476771G>A	c.3819G>A	p.Q1273Q	Synonymous
ATXN1	NM_000332	Br27P	g.chr6:16436254G>A	c.267G>A	p.P89P	Synonymous
AUTS2	CCDS5539.1	Br27P	g.chr7:69699995C>T	c.3142C>T	p.P1048S	Missense
AXIN2	CCDS11662.1	Br27P	g.chr17:60962242C>T	c.2201C>T	p.A734V	Missense
AZI1	NM_001009811	Br27P	g.chr17:76790689G>A	c.734G>A	p.G245E	Missense
B3Gn-T6	NM_138706	Br27P	g.chr11:76429072C>T	c.829C>T	p.P277S	Missense
BAD	CCDS8065.1	Br27P	g.chr11:63795668C>T	c.371C>T	p.S124F	Missense
BAI2	CCDS346.1	Br25X	g.chr1:31865600C>T	c.4238C>T	p.P1413L	Missense
BAMBI	CCDS7162.1	Br06X	g.chr10:29011167dupA	c.614dupA	fs	INDEL
BAT2D1	CCDS1296.1	Br27P	g.chr1:168241275G>A	c.3006G>A	p.R1002R	Synonymous
BAZ1A	CCDS9651.1	Br27P	g.chr14:34333728G>A	c.1341G>A	p.E447E	Synonymous
BCAR3	CCDS745.1	Br17X	g.chr1:93760355C>T	c.1210C>T	p.P404S	Missense
BCL2L1	CCDS13188.1	Br27P	g.chr20:29717517G>A	c.409G>A	p.A137T	Missense
BCL2L12	CCDS12776.1	Br27P	g.chr19:54865490C>T	c.887C>T	p.T296I	Missense
BCL2L2	CCDS9591.1	Br9PT	g.chr14:22847208A>G	c.392A>G	p.E131G	Missense
BCL6	CCDS3289.1	Br27P	g.chr3:188930420G>A	c.475G>A	p.G159S	Missense
BCOR	CCDS14250.1	Br08X	g.chrX:39670947C>T	c.4537C>T	p.R1513X	Nonsense
BFSP1	CCDS13126.1	Br27P	g.chr20:17423130G>A	c.1587G>A	p.Q529Q	Synonymous
BIN1	CCDS2137.1	Br07X	g.chr2:127524280C>G	c.1204C>G	p.L402V	Missense
BIN1	CCDS2137.1	Br27P	g.chr2:127537450G>A	c.608G>A	p.R203H	Missense
BIRC1	CCDS4009.1	Br26X	g.chr5:70344085C>T	c.414C>T	p.Y138Y	Synonymous
BIRC6	NM_016252	Br27P	g.chr2:32565957G>A	c.2881G>A	p.E961K	Missense
BMP3	CCDS3588.1	Br08X	g.chr4:82324498C>G	c.744C>G	p.A248A	Synonymous
BMPER	CCDS5442.1	Br17X	g.chr7:33965986C>T	c.1919C>T	p.P640L	Missense
BNC2	CCDS6482.1	Br27P	g.chr9:16572987G>A	c.193G>A	p.A65T	Missense
BOC	CCDS2971.1	Br27P	g.chr3:114474608C>T	c.964C>T	p.P322S	Missense
BPY2IP1	NM_018174	Br08X	g.chr19:17698128G>A	c.935G>A	p.R312H	Missense
BRAF	CCDS5863.1	Br27P	g.chr7:139953397C>T	c.929C>T	p.T310I	Missense
BRF1	CCDS10001.1	Br20P	g.chr14:104756379G>A	IVS14+1G>A	Splice Site	Splice Site
BRP44L	CCDS5293.1	Br27P	g.chr6:166749339G>A	c.319G>A	p.A107T	Missense
BRPF1	CCDS2575.1	Br27P	g.chr3:9760305C>T	c.2337C>T	p.H779H	Synonymous
BSN	CCDS2800.1	Br27P	g.chr3:49673702C>T	c.9420C>T	p.A3140A	Synonymous
BST1	CCDS3416.1	Br04X	g.chr4:15409723A>C	c.943A>C	p.R315R	Synonymous
BTAF1	CCDS7419.1	Br27P	g.chr10:93776485G>A	c.5232G>A	p.G1744G	Synonymous

Fig. 10

BTBD1	CCDS10322.1	Br27P	g.chr15:81489969G>A	c.978G>A	p.R326R	Synonymous
BTBD3	CCDS13113.1	Br27P	g.chr20:11851652G>A	c.907G>A	p.A303T	Missense
BTC	CCDS3566.1	Br27P	g.chr4:76033011G>A	c.379G>A	p.V127I	Missense
BTK	CCDS14482.1	Br27P	g.chrX:100417280C>T	c.1471C>T	p.H491Y	Missense
BTNL2	CCDS4749.1	Br27P	g.chr6:32471943G>A	c.929G>A	p.G310E	Missense
BTNL9	CCDS4460.1	Br07X	g.chr5:180407717G>A (homozygous)	c.294G>A	p.P98P	Synonymous
BUCS1	CCDS10587.1	Br27P	g.chr16:20609893G>A	c.119G>A	p.W40X	Nonsense
C10orf18	ENST00000263123	Br05X	g.chr10:5843371G>A	c.3784G>A	p.E1262K	Missense
C10orf26	CCDS7540.1	Br27P	g.chr10:104562539C>T	c.490C>T	p.P164S	Missense
C10orf33	CCDS7474.1	Br27P	g.chr10:100133609G>T	c.1682G>T	p.G561V	Missense
C10orf47	CCDS7085.1	Br04X	g.chr10:11948752G>T	c.355G>T	p.E119X	Nonsense
C10orf64	ENST00000265453	Br14X	g.chr10:49710728C>T (homozygous)	c.889C>T	p.R297W	Missense
C10orf71	ENST00000323868	Br27P	g.chr10:50203424G>A	c.215G>A	p.S72N	Missense
C10orf80	NM_001008723	Br27P	g.chr10:106118299G>A	c.921G>A	p.L307L	Synonymous
C10orf81	CCDS7583.1	Br27P	g.chr10:115516387C>T	c.144C>T	p.I48I	Synonymous
C11orf11	NM_006133	Br27P	g.chr11:61264574G>A	c.1917G>A	p.E639E	Synonymous
C11ORF4	CCDS8066.1	Br27P	g.chr11:63812220G>A	c.741G>A	p.R247R	Synonymous
C12orf11	CCDS8708.1	Br27P	g.chr12:26955452C>T	c.1871C>T	p.P624L	Missense
C12orf42	NM_198521	Br27P	g.chr12:102297915C>T	c.84C>T	p.S28S	Synonymous
C14orf115	CCDS9830.1	Br9PT	g.chr14:73894110G>A	c.871G>A	p.V291I	Missense
C14orf131	NM_018335	Br27P	g.chr14:101878133C>T	c.1151C>T	p.S384F	Missense
C14orf133	CCDS9862.1	Br26X	g.chr14:76965843G>C	c.1200G>C	p.K400N	Missense
C14orf145	NM_152446	Br26X	g.chr14:80398895C>T	c.721C>T	p.R241C	Missense
C14orf155	CCDS9679.1	Br17X	g.chr14:44045852G>A	c.89G>A	p.R30H	Missense
C14orf159	NM_024952	Br27P	g.chr14:90725215C>T	c.1128C>T	p.D376D	Synonymous
C14orf159	NM_024952	Br27P	g.chr14:90735956C>T	c.1383C>T	p.D461D	Synonymous
C14orf31	CCDS9704.1	Br02X	g.chr14:51264389C>T	c.1737C>T	p.C579C	Synonymous
C14orf43	CCDS9819.1	Br05X	g.chr14:73276371C>T	c.94C>T	p.L32L	Synonymous
C14orf49	CCDS9935.1	Br27P	g.chr14:94991706G>A	c.898G>A	p.G300R	Missense
C15orf2	CCDS10015.1	Br23X	g.chr15:22472605G>A	c.498G>A	p.P166P	Synonymous
C15orf42	ENST00000268138	Br17X	g.chr15:87920396T>C	c.575T>C	p.L192S	Missense
C15orf42	ENST00000268138	Br27P	g.chr15:87920406G>A	c.585G>A	p.K195K	Synonymous
C16orf9	CCDS10402.1	Br11P	g.chr16:254837G>A	c.1474G>A	p.A492T	Missense
C17orf27	NM_020914	Br27P	g.chr17:75961478G>A	c.7079G>A	p.R2360Q	Missense
C17orf31	CCDS11016.1	Br27P	g.chr17:2086668C>T	c.2737C>T	p.P913S	Missense
C17orf31	CCDS11016.1	Br27P	g.chr17:2149981C>T	c.816C>T	p.G272G	Synonymous
C18orf25	NM_001008239	Br07X	g.chr18:42087709C>T	c.764C>T	p.A255V	Missense
C18orf4	CCDS11995.1	Br25X	g.chr18:63330753C>G	c.2103C>G	p.S701R	Missense
C19orf29	ENST00000221899	Br04X	g.chr19:3569902G>C	c.929G>C	p.R310P	Missense
C1orf147	NM_001025592	Br27P	g.chr1:203059417C>T	c.29C>T	p.S10F	Missense
C1orf151	NM_001032363	Br27P	g.chr1:19695301C>T	c.140C>T	p.S47F	Missense
C1orf16	CCDS1355.1	Br15X	g.chr1:180234495G>A	c.1034G>A	p.C345Y	Missense
C1orf173	NM_001002912	Br27P	g.chr1:74750303G>A	c.3112G>A	p.A1038T	Missense
C1orf84	NM_015284	Br27P	g.chr1:43582385C>T	c.6666C>T	p.Y2222Y	Synonymous
C1orf84	NM_015284	Br27P	g.chr1:43577029T>A	IVS39-3T>A	Splice Site	Splice Site
C1QDC1	CCDS8720.1	Br27P	g.chr12:30754328G>A	c.3009G>A	p.K1003K	Synonymous
C20orf10	CCDS13352.1	Br27P	g.chr20:43435985G>A	c.849G>A	p.W283X	Nonsense
C20orf102	CCDS13299.1	Br27P	g.chr20:35965280C>T	c.114C>T	p.S38S	Synonymous
C20orf114	CCDS13218.1	Br27P	g.chr20:31355429C>T	c.1145C>T	p.A382V	Missense
C20orf114	CCDS13218.1	Br27P	g.chr20:31355490C>T	c.1206C>T	p.I402I	Synonymous

Fig. 10

C20orf23	CCDS13122.1	Br27P	g.chr20:16307605G>A	c.3042G>A	p.R1014R	Synonymous
C20orf78	ENST00000278779	Br08X	g.chr20:18753915delA	c.111delA	fs	INDEL
C21orf29	CCDS13712.1	Br17X	g.chr21:44771612C>T	c.1140C>T	p.I380I	Synonymous
C21orf29	CCDS13712.1	Br9PT	g.chr21:44749134T>A	c.1813T>A	p.S605T	Missense
C21orf29	CCDS13712.1	Br05X	g.chr21:44772876C>T	c.809C>T	p.T270M	Missense
C21orf5	CCDS13643.1	Br29P	g.chr21:36508719A>T	c.1124A>T	p.E375V	Missense
C21orf69	NM_058189	Br27P	g.chr21:45178476C>T	c.51C>T	p.A17A	Synonymous
C2orf17	CCDS2434.1	Br02X	g.chr2:219872581C>T	c.1357C>T	p.L453F	Missense
C2orf29	CCDS2050.1	Br27P	g.chr2:101332905G>A	c.649G>A	p.D217N	Missense
C2orf3	CCDS1961.1	Br27P	g.chr2:75845376G>A	c.322G>A	p.E108K	Missense
C3orf14	CCDS2896.1	Br27P	g.chr3:62292081C>T	c.219C>T	p.H73H	Synonymous
C4orf7	CCDS3537.1	Br03X	g.chr4:71277680A>T	c.9A>T	p.K3N	Missense
C5AR1	NM_001736	Br9PT	g.chr19:52515442G>A	c.568G>A	p.V190M	Missense
C6	CCDS3936.1	Br27P	g.chr5:41189823C>T	c.2136C>T	p.V712V	Synonymous
C6	CCDS3936.1	Br13X	g.chr5:41189744G>T	c.2215G>T	p.A739S	Missense
C6orf103	ENST00000326929	Br9PT	g.chr6:147063896T>C	c.1704T>C	p.S568S	Synonymous
C6orf150	CCDS4978.1	Br27P	g.chr6:74191797G>A	c.1443G>A	p.E481E	Synonymous
C6orf163	NM_001010868	Br27P	g.chr6:88131789C>T	c.568C>T	p.P190S	Missense
C6orf165	CCDS5009.1	Br27P	g.chr6:88180261G>A	c.207G>A	p.R69R	Synonymous
C6orf168	NM_032511	Br27P	g.chr6:99878221C>T	c.643C>T	p.R215W	Missense
C6orf170	NM_152730	Br04X	g.chr6:121680381C>T (homozygous)	c.454C>T	p.R152C	Missense
C6orf21	NM_001003693	Br04X	g.chr6:121680365C>T (homozygous)	c.470C>T	p.S157F	Missense
C6orf213	NM_001010852	Br27P	g.chr6:31786174G>A	c.869G>A	p.G290D	Missense
C6orf29	CCDS4724.1	Br27P	g.chr6:123373937C>T	c.498C>T	p.N166N	Synonymous
C6orf4	CCDS5092.1	Br27P	g.chr6:31940771G>A	c.1832G>A	p.G611D	Missense
C6orf68	CCDS5118.1	Br27P	g.chr6:111987373G>A	c.1653G>A	p.R551R	Synonymous
C7orf16	CCDS5436.1	Br20P	g.chr6:118103684G>A	c.158G>A	p.G53D	Missense
C8A	CCDS606.1	Br03X	g.chr7:31508388G>A	c.148G>A	p.V50I	Missense
C8B	NM_000066	Br27P	g.chr1:57090167G>A	c.1451G>A	p.R484H	Missense
C8B	NM_000066	Br27P	g.chr1:57107246C>T	c.1628C>T	p.P543L	Missense
C8orf77	NM_001039382	Br29P	g.chr1:57137786C>T	c.177C>T	p.T59T	Synonymous
C8ORFK23	NM_001039112	Br9PT	g.chr8:146199285_146199288delGAAG	c.109_112delGAAG	fs	INDEL
C9orf126	NM_173690	Br07x	g.chr8:125037438A>C	c.19A>C	p.K7Q	Missense
C9orf19	CCDS6598.1	Br27P	g.chr9:124813204G>A (homozygous)	c.1742G>A	p.R581Q	Missense
C9orf5	NM_032012	Br04X	g.chr9:36152520C>T	UTR+1C>T	3'UTR	3'UTR
C9orf50	NM_199350	Br27P	g.chr9:108878134C>T	c.2306C>T	p.T769I	Missense
CA2	CCDS6239.1	Br15X	g.chr9:129462058G>A	c.350G>A	p.R117K	Missense
CAB39	CCDS2478.1	Br27P	g.chr8:86564771A>C	c.53A>C	p.K18T	Missense
CABIN1	CCDS13823.1	Br27P	g.chr2:231450239G>A	c.18G>A	p.G6G	Synonymous
CABP1	CCDS9204.1	Br27P	g.chr22:22785070C>T	c.1903C>T	p.L635L	Synonymous
CACNA1A	NM_000068	Br15X	g.chr12:119561719G>A	c.456G>A	p.G152G	Synonymous
CACNA1C	NM_000719	Br17X	g.chr19:13184518C>T	c.5980C>T	p.P1994S	Missense
CACNA1C	NM_000719	Br27P	g.chr12:2094747C>A	c.146C>A	p.A49D	Missense
CACNA1E	NM_000721	Br27P	g.chr12:2585197G>A	c.3140G>A	p.G1047E	Missense
CACNA1E	NM_000721	Br27P	g.chr1:178439999C>T	c.3672C>T	p.I1224I	Synonymous
CACNA1H	NM_021098	Br15X	g.chr1:178476959C>T	c.5205C>T	p.I1735I	Synonymous
CACNA1H	NM_021098	Br05X	g.chr16:1199144C>T	c.3475C>T	p.Q1159X	Nonsense
CACNA1I	NM_001003406	Br27P	g.chr16:1201735G>A	c.4495G>A	p.V1499M	Missense
CACNA1S	CCDS1407.1	Br27P	g.chr22:38321132C>T	c.456C>T	p.R152R	Synonymous
			g.chr1:197748332C>T	c.4521C>T	p.D1507D	Synonymous

Fig. 10

CACNA2D3	NM_018398	Br07X	g.chr3:54905889G>A	c.2320G>A	p.A774T	Missense
CACNB2	CCDS7125.1	Br27P	g.chr10:18730945G>A	c.300G>A	p.E100E	Synonymous
CACNG4	CCDS11667.1	Br05X	g.chr17:62451481C>A	c.348C>A	p.I116I	Synonymous
CADPS	CCDS2898.1	Br27P	g.chr3:62553378G>A	c.1411G>A	p.A471T	Missense
CADPS	CCDS2898.1	Br08X	g.chr3:62360136C>T	c.3810C>T	p.D1270D	Synonymous
CADPS2	NM_017954	Br23X	g.chr7:121627314C>T	c.2796C>T	p.I932I	Synonymous
CALM1	CCDS9892.1	Br27P	g.chr14:89937439C>T	c.118C>T	p.L40L	Synonymous
CAMSAP1	NM_015447	Br27P	g.chr9:135939001G>A	c.2617G>A	p.D873N	Missense
CAPN12	CCDS12519.1	Br27P	g.chr19:43920121C>T	IVS8-3C>T	Splice Site	Splice Site
CAPN3	CCDS10084.1	Br08X	g.chr15:40419220T>C (homozygous)	c.1905T>C	p.A635A	Synonymous
CAPN3	CCDS10084.1	Br08X	g.chr15:40419268G>A (homozygous)	c.1953G>A	p.K651K	Synonymous
CAPZA3	CCDS8681.1	Br12P	g.chr12:18782589T>C	c.120T>C	p.D40D	Synonymous
CARD11	CCDS5336.1	Br27P	g.chr7:2719519G>A	c.3438G>A	p.Q1146Q	Synonymous
CART1	CCDS9028.1	Br02X	g.chr12:84197515G>C	c.775G>C	p.D259H	Missense
CASC5	NM_170589	Br27P	g.chr15:38702625C>T	c.2949C>T	p.S983S	Synonymous
CASQ1	CCDS1198.1	Br27P	g.chr1:156978791A>G	c.665A>G	p.E222G	Missense
CCDC15	NM_025004	Br27P	g.chr11:124352627G>A	c.674G>A	p.G225E	Missense
CCNF	CCDS10467.1	BR27P	g.chr16:2438947C>G	c.1185C>G	p.G395G	Synonymous
CCNL2	ENST00000321423	Br05x	g.chr1:1419932G>T	c.22G>T	p.A8S	Missense
CCNYL1	ENST00000339882	Br27P	g.chr19:33166187C>T	c.634C>T	p.L212L	Synonymous
CD19	CCDS10644.1	Br27P	g.chr16:28855877G>A	c.1117G>A	p.G373S	Missense
CD84	CCDS1206.1	Br27P	g.chr1:157348537C>T	c.118C>T	p.P40S	Missense
CD96	CCDS2958.1	Br15X	g.chr3:112802268T>C	c.904T>C	p.Y302H	Missense
CDA08	CCDS10728.1	Br27P	g.chr16:46042831C>T	c.537C>T	p.N179N	Synonymous
CDC2L6	CCDS5085.1	Br04X	g.chr6:111049193C>T (homozygous)	c.1184C>T	p.A395V	Missense
CDC7	CCDS734.1	Br27P	g.chr1:91689195G>A	c.356G>A	p.G119E	Missense
CDCA8	CCDS424.1	Br27P	g.chr1:37843121C>T	c.833C>T	p.T278I	Missense
CDH23	NM_022124	Br27P	g.chr10:73120311G>A	c.2140G>A	p.E714K	Missense
CDH23	NM_022124	Br27P	g.chr10:73134729C>T	c.2789C>T	p.P930L	Missense
CDH24	CCDS9585.1	Br27P	g.chr14:22594316G>A	c.288G>A	p.E96E	Synonymous
CDH26	CCDS13485.1	Br27P	g.chr20:58009809C>T	c.2114C>T	p.P705L	Missense
CDH5	CCDS10804.1	Br27P	g.chr16:64980825T>A	c.680T>A	p.V227E	Missense
CDK5	NM_004935	Br27P	g.chr7:150191887G>A	c.46G>A	p.G16R	Missense
CDK6	CCDS5628.1	Br27P	g.chr7:91889102C>T	UTR+3C>T	3'UTR	3'UTR
CDT1	NM_030928	Br27P	g.chr16:87399960C>T	c.863C>T	p.A288V	Missense
CDX1	CCDS4304.1	Br9PT	g.chr5:149527044C>T	c.412C>T	p.R138C	Missense
CDYL2	NM_152342	Br25X	g.chr16:79212311C>A	c.857C>A	p.A286E	Missense
CEACAM1	CCDS12609.1	Br02X	g.chr19:47717317C>T	c.900C>T	p.H300H	Synonymous
CELSR3	CCDS2775.1	Br27P	g.chr3:48671847G>A	c.3225G>A	p.R1075R	Synonymous
CELSR3	CCDS2775.1	Br25X	g.chr3:48655321G>A	c.8407G>A	p.G2803R	Missense
CENPF	NM_016343	Br27P	g.chr1:211204488G>A	c.4412G>A	p.G1471E	Missense
CENTG3	NM_031946	Br27P	g.chr7:150258594G>A	c.1086G>A	p.G362G	Synonymous
CENTG3	NM_031946	Br27P	g.chr7:150278288C>T	c.2378C>T	p.S793F	Missense
CEP135	NM_025009	Br11P	g.chr4:56678377G>A	c.1124G>A	p.C375Y	Missense
Cep164	NM_014956	Br27P	g.chr11:116737794C>T	c.427C>T	p.P143S	Missense
CEP2	CCDS13255.1	Br27P	g.chr20:33530983C>T	c.2387C>T	p.T796I	Missense
CETP	CCDS10772.1	Br27P	g.chr16:55569609G>A	c.1087G>A	p.V363M	Missense
CFTR	CCDS5773.1	Br20P	g.chr7:116844526_116844528delGTT	c.2991_2993delGTT	p.L997del	INDEL
CGI-38	CCDS10835.1	Br17X	g.chr16:65981979G>A	c.246G>A	p.L82L	Synonymous
CGI-96	CCDS14036.1	Br27P	g.chr22:41235186G>A	c.558G>A	p.E186E	Synonymous

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CGNL1	CCDS10161.1	Br27P	g.chr15:55518870C>T	c.1381C>T	p.P461S	Missense
CHAD	CCDS11568.1	Br20P	g.chr17:45898161C>G	c.844C>G	p.Q282E	Missense
CHD4	CCDS8552.1	Br27P	g.chr12:6575522G>A	c.1935G>A	p.R645R	Synonymous
CHD4	CCDS8552.1	Br27P	g.chr12:6561156G>A	c.4601G>A	p.G1534E	Missense
CHD5	CCDS57.1	Br05X	g.chr1:6106151C>T	c.5199C>T	p.Y1733Y	Synonymous
CHD6	CCDS13317.1	Br27P	g.chr20:39574945G>A	c.806G>A	p.G269D	Missense
CHD9	NM_025134	Br11P	g.chr16:51906311delA	c.7441delA	fs	INDEL
CHDH	CCDS2873.1	Br29P	g.chr3:53832926G>A	c.150G>A	p.S50S	Synonymous
CHEK1	CCDS8459.1	Br27P	g.chr11:125019230G>A	c.958G>A	p.E320K	Missense
ChGn	CCDS6010.1	Br27P	g.chr8:19320489A>G	c.1185A>G	p.I395M	Missense
ChGn	CCDS6010.1	Br27P	g.chr8:19320471A>C	c.1203A>C	p.A401A	Synonymous
CHKA	CCDS8178.1	Br27P	g.chr11:67589923G>A	c.1031G>A	p.G344E	Missense
CHL1	CCDS2556.1	Br14X	g.chr3:342738C>A (homozygous)	c.188C>A	p.P63Q	Missense
CHL1	CCDS2556.1	Br27P	g.chr3:336466C>T	c.7C>T	p.P3S	Missense
CHRM2	CCDS5843.1	Br27P	g.chr7:136156899G>A	c.32G>A	p.S11N	Missense
CHRM5	CCDS10031.1	Br07X	g.chr15:32143031C>T	c.821C>T	p.S274F	Missense
CHRNA3	CCDS10305.1	Br14X	g.chr15:76681620T>C	c.419T>C	p.L140S	Missense
CHRNA4	CCDS13517.1	Br16X	g.chr20:61452004G>C	c.1203G>C	p.L401L	Synonymous
CHRNA9	CCDS3459.1	Br15X	g.chr4:40197220C>T	c.1195C>T	p.R399C	Missense
CHST13	CCDS3039.1	Br07X	g.chr3:127743526G>A	c.433G>A	p.A145T	Missense
CIDEA	CCDS11856.1	Br27P	g.chr18:12267216G>A	c.607G>A	p.E203K	Missense
CIDEC	CCDS2587.1	Br27P	g.chr3:9883918C>T	c.617C>T	p.S206F	Missense
CIZ1	CCDS6894.1	Br27P	g.chr9:128011331C>T	c.2053C>T	p.P685S	Missense
CIZ1	CCDS6894.1	Br04X	g.chr9:128010960C>A	c.2220C>A	p.F740L	Missense
CKLFSF5	CCDS9599.1	Br27P	g.chr14:22916453C>T	c.153C>T	p.A51A	Synonymous
CLASP1	NM_015282	Br27P	g.chr2:122079677C>T	c.25C>T	p.L9L	Synonymous
CLASP2	NM_015097	Br27P	g.chr3:33700903G>A	c.596G>A	p.G199E	Missense
CLCN1	CCDS5881.1	Br02X	g.chr7:142560556A>G	c.2332A>G	p.R778G	Missense
CLCN5	CCDS14328.1	Br27P	g.chrX:49554214G>A	c.998G>A	p.G333E	Missense
CLDN11	CCDS3213.1	Br27P	g.chr3:171623728C>T	c.302C>T	p.T101I	Missense
CLEC1A	CCDS8612.1	Br08X	g.chr12:10125204C>G	c.290C>G	p.S97C	Missense
CLEC4E	CCDS8594.1	Br29P	g.chr12:8578507T>C	c.654T>C	p.S218S	Synonymous
CLEC7A	CCDS8613.1	Br27P	g.chr12:10169201G>A	c.316G>A	p.G106S	Missense
CLIC6	CCDS13638.1	Br27P	g.chr21:34963705G>A	c.148G>A	p.A50T	Missense
CLN8	CCDS5956.1	Br27P	g.chr8:1706692G>A	c.65G>A	p.G22E	Missense
CLSPN	CCDS396.1	Br15X	g.chr1:35895144C>T	c.1471C>T	p.R491W	Missense
CLSTN2	CCDS3112.1	Br27P	g.chr3:141748193C>T	c.1646C>T	p.S549F	Missense
CLTA	CCDS6600.1	Br27P	g.chr9:36181248C>T	c.195C>T	p.H65H	Synonymous
CMIP	NM_198390	Br27P	g.chr16:80290889G>A	c.1635G>A	p.G545G	Synonymous
CMYA1	CCDS2683.1	Br10P	g.chr3:39205833G>A	c.108G>A	p.P36P	Synonymous
CMYA4	CCDS11292.1	Br27P	g.chr17:30521366G>A	c.1668G>A	p.Q556Q	Synonymous
CMYA4	CCDS11292.1	Br27P	g.chr17:30522577C>T	c.1819C>T	p.P607S	Missense
CNNM2	CCDS7543.1	Br27P	g.chr10:104668323C>T	c.96C>T	p.S32S	Synonymous
CNOT1	CCDS10799.1	Br27P	g.chr16:57172165C>T	c.1216C>T	p.L406F	Missense
CNOT1	CCDS10799.1	Br27P	g.chr16:57137819G>A	c.3913G>A	p.D1305N	Missense
CNOT10	CCDS2655.1	Br27P	g.chr3:32789963G>A	c.2091G>A	p.Q697Q	Synonymous
CNOT7	CCDS6000.1	Br27P	g.chr8:17134378C>T	c.589C>T	p.R197W	Missense
CNR2	CCDS245.1	Br12P	g.chr1:23946683C>G	c.731C>G	p.A244G	Missense
CNTN4	CCDS2558.1	Br27P	g.chr3:2942424C>T	c.335C>T	p.T112I	Missense
CNTNAP2	CCDS5889.1	Br02X	g.chr7:147038402C>T	c.2196C>T	p.I732I	Synonymous

Fig. 10

COCH	CCDS9640.1	Br27P	g.chr14:30424416C>T	c.799C>T	p.P267S	Missense
COG5	CCDS5742.1	Br27P	g.chr7:106798271G>A	c.115G>A	p.V39I	Missense
COG5	CCDS5742.1	Br15X	g.chr7:106515735A>G	c.1629A>G	p.A543A	Synonymous
COH1	CCDS6280.1	Br27P	g.chr8:100229314C>T	c.1913C>T	p.T638I	Missense
COH1	CCDS6280.1	Br11P	g.chr8:100916970A>C	c.9845A>C	p.K3282T	Missense
COL14A1	NM_021110	Br07X	g.chr8:121391472C>T (homozygous)	c.4445C>T	p.P1482L	Missense
COL18A1	NM_030582	Br27P	g.chr21:45724863G>A	IVS11+1G>A	Splice Site	Splice Site
COL23A1	CCDS4436.1	Br10P	g.chr5:177605917C>G	IVS23-3C>G	Splice Site	Splice Site
COL24A1	NM_152890	Br27P	g.chr1:85964126G>A	c.3991G>A	p.A1331T	Missense
COL3A1	CCDS2297.1	Br9PT	g.chr2:189684824C>T	c.1345C>T	p.R449C	Missense
COL3A1	CCDS2297.1	Br11P	g.chr2:189693990C>T	c.2632C>T	p.R878C	Missense
COL3A1	CCDS2297.1	Br25X	g.chr2:189693991G>A	c.2633G>A	p.R878H	Missense
COL4A2	NM_001846	Br27P	g.chr13:109941590G>A	c.3356G>A	p.G1119E	Missense
COL4A2	NM_001846	Br27P	g.chr13:109889015G>A	c.911G>A	p.R304K	Missense
COL4A4	NM_000092	Br15X	g.chr2:227772380G>A	c.1652G>A	p.G551D	Missense
COL4A4	NM_000092	Br27P	g.chr2:227746289C>T	c.2593C>T	p.P865S	Missense
COL4A4	NM_000092	Br13X	g.chr2:227698287A>G	c.4761A>G	p.P1587P	Synonymous
COL4A5	CCDS14543.1	Br04X	g.chrX:107656189C>T	c.2317C>T	p.P773S	Missense
COL5A3	CCDS12222.1	Br27P	g.chr19:9941335C>T	c.4014C>T	p.P1338P	Synonymous
COL6A3	NM_004369	Br15X	g.chr2:238071893C>T	c.1562C>T	p.S521L	Missense
COL6A3	NM_057167	Br27P	g.chr2:238062591G>T	c.3451G>T	p.V1151L	Missense
COL8A2	CCDS403.1	Br27P	g.chr1:36233584G>A	c.791G>A	p.G264E	Missense
COPB	CCDS7815.1	Br17X	g.chr11:14444432G>A	c.2262G>A	p.Q754Q	Synonymous
COQ2	NM_015697	Br27P	g.chr4:84551918C>T	c.602C>T	p.A201V	Missense
CPB1	NM_001871	Br27P	g.chr3:150060415C>T	c.1182C>T	p.I394I	Synonymous
CPN1	CCDS7486.1	Br04X	g.chr10:101831232G>A (homozygous)	c.141G>A	p.R47R	Synonymous
CPN1	CCDS7486.1	Br14X	g.chr10:101825715G>A (homozygous)	c.363G>A	p.T121T	Synonymous
CPNE2	CCDS10774.1	Br27P	g.chr16:55710629C>T	c.529C>T	p.P177S	Missense
CPNE4	CCDS3072.1	Br27P	g.chr3:132751540C>T	c.1251C>T	p.I417I	Synonymous
CPS1	CCDS2393.1	Br04X	g.chr2:211266579C>T	c.240C>T	p.Y80Y	Synonymous
CPS1	CCDS2393.1	Br25X	g.chr2:211281096G>C	c.907G>C	p.A303P	Missense
CPS1	CCDS2393.1	Br27P	g.chr2:211358515G>A	IVS34+1G>A	Splice Site	Splice Site
CPSF4	CCDS5664.1	Br27P	g.chr7:98696339G>A	c.670G>A	p.V224I	Missense
CPT1B	CCDS14098.1	Br27P	g.chr22:49298869C>T	c.2139C>T	p.G713G	Synonymous
CPT1C	CCDS12779.1	Br27P	g.chr19:54905550C>T	c.1728C>T	p.F576F	Synonymous
CRA	CCDS942.1	Br27P	g.chr1:146718400C>T	c.741C>T	p.H247H	Synonymous
CRAT	CCDS6919.1	Br27P	g.chr9:128942508G>A	c.820G>A	p.D274N	Missense
CREB1	CCDS2374.1	Br27P	g.chr2:208265665C>T	c.669C>T	p.S223S	Synonymous
CRIM2	ENST00000257704	Br27P	g.chr7:128124271C>T	c.2406C>T	p.C802C	Synonymous
CRISPLD1	CCDS6219.1	Br27P	g.chr8:76087316C>T	c.352C>T	p.Q118X	Nonsense
CRR9	CCDS3862.1	Br20P	g.chr5:1371499G>A	c.1602G>A	p.A534A	Synonymous
CRX	CCDS12706.1	Br10P	g.chr19:53034727G>A	c.591G>A	p.P197P	Synonymous
CRY2	CCDS7915.1	Br27P	g.chr11:45847672C>T	c.922C>T	p.Q308X	Nonsense
CRYAA	CCDS13695.1	Br27P	g.chr21:43463779C>T	c.273C>T	p.D91D	Synonymous
CSK	CCDS10269.1	Br27P	g.chr15:72878223C>T	c.133C>T	p.P45S	Missense
CSMD1	NM_033225	Br27P	g.chr8:3032853C>T	c.5568C>T	p.S1856S	Synonymous
CSN3	CCDS3538.1	Br13X	g.chr4:71295569A>G	c.182A>G	p.N61S	Missense
CSNK2A2	CCDS10794.1	Br27P	g.chr16:56758648G>A	c.690G>A	p.R230R	Synonymous
CSPG2	CCDS4060.1	Br27P	g.chr5:82869679G>A	c.5101G>A	p.V1701M	Missense
CSPG5	CCDS2757.1	Br27P	g.chr3:47594194G>A	c.326G>A	p.G109E	Missense

Fig. 10

CSPG6	NM_005445	Br20P	g.chr10:112325084C>T	c.131C>T	p.A44V	Missense
CSTF1	CCDS13452.1	Br27P	g.chr20:54404114C>T	c.99C>T	p.G33G	Synonymous
CTEN	CCDS11368.1	Br05X	g.chr17:35896828C>A	c.1274C>A	p.T425N	Missense
CTNNA2	NM_004389	Br07X	g.chr2:80747066G>A	c.2398G>A	p.V800M	Missense
CTNNA3	CCDS7269.1	Br27P	g.chr10:68610122C>T	c.1006C>T	p.R336C	Missense
CTSW	CCDS8117.1	Br27P	g.chr11:65407132G>A	c.762G>A	p.L254L	Synonymous
CUBN	CCDS7113.1	Br12P	g.chr10:17123136A>T	c.3919A>T	p.N1307Y	Missense
CUGBP1	CCDS7938.1	Br27P	g.chr11:47462615C>T	c.347C>T	p.S116F	Missense
CUGBP1	CCDS7939.1	Br27P	g.chr11:47455001G>A	c.967G>A	p.A323T	Missense
CUL4B	NM_003588	Br27P	g.chrX:119476321G>A	c.109G>A	p.E37K	Missense
CUTL1	CCDS5721.1	Br27P	g.chr7:101438232C>T	c.2220C>T	p.I740I	Synonymous
CX40.1	CCDS7191.1	Br27P	g.chr10:35937292C>T	c.845C>T	p.S282F	Missense
CXCR3	CCDS14416.1	Br05X	g.chrX:70619233C>T (homozygous)	UTR+3C>T	3'UTR	3'UTR
CXorf17	CCDS14356.1	Br27P	g.chrX:54069008C>T	c.762C>T	p.F254F	Synonymous
CXorf20	CCDS14184.1	Br23X	g.chrX:17955368G>A	c.1608G>A	p.P536P	Synonymous
CXorf27	ENST00000341016	Br02X	g.chrX:37606403G>A (homozygous)	c.94G>A	p.V32M	Missense
CXorf37	CCDS14322.1	Br25X	g.chrX:48856200G>A (homozygous)	c.615G>A	p.S205S	Synonymous
CXXC5	NM_016463	Br27P	g.chr5:139041147G>A	c.570G>A	p.K190K	Synonymous
CYBB	CCDS14242.1	Br27P	g.chrX:37414473G>C	c.727G>C	p.V243L	Missense
CYP26C1	CCDS7425.1	Br03X	g.chr10:94818111G>A (homozygous)	c.1236G>A	p.R412R	Synonymous
CYP2C19	CCDS7436.1	Br07x	g.chr10:96592767C>T	c.1145C>T	p.P382L	Missense
CYP2R1	CCDS7818.1	Br27P	g.chr11:14858371C>T	c.887C>T	p.S296F	Missense
CYP4F12	NM_023944	Br05X	g.chr19:15667782C>T	c.1152C>T	p.C384C	Synonymous
CYP4F12	NM_023944	Br9PT	g.chr19:15650138C>T	c.266C>T	p.T89M	Missense
DAB2IP	CCDS6832.1	Br11P	g.chr9:121614666G>A	c.1933G>A	p.V645I	Missense
DCBLD2	NM_080927	Br27P	g.chr3:100001354G>C	c.1880G>C	p.G627A	Missense
DCC	CCDS11952.1	Br27P	g.chr18:48937844C>T	c.1382C>T	p.T461I	Missense
DCT	CCDS9470.1	Br27P	g.chr13:93912394G>A	c.914G>A	p.G305D	Missense
DCTN4	CCDS4310.1	Br06X	g.chr5:150078134G>T	c.968G>T	p.S323I	Missense
DDB1	NM_001923	Br27P	g.chr11:60853576C>T	c.384C>T	p.C128C	Synonymous
DDR1	CCDS4690.1	Br27P	g.chr6:30972618G>A	c.1755G>A	p.G585G	Synonymous
DDX1	CCDS1686.1	Br27P	g.chr2:15711008G>A	c.1285G>A	p.V429I	Missense
DDX1	CCDS1686.1	Br27P	g.chr2:15693314G>A	c.352G>A	p.E118K	Missense
DDX31	CCDS6951.1	Br27P	g.chr9:132574954G>A	c.237G>A	p.S79S	Synonymous
DDX54	NM_024072	Br25X	g.chr12:112063803C>G	IVS15-4C>G	Splice Site	Splice Site
DEFB112	NM_001037498	Br14X	g.chr6:50124236C>T (homozygous)	c.88C>T	p.R30X	Nonsense
DEFB125	CCDS12989.1	Br14X	g.chr20:24953G>T	c.354G>T	p.M118I	Missense
DELGEF	CCDS7828.1	Br27P	g.chr11:17973973C>T	c.568C>T	p.P190S	Missense
DEPDC5	NM_014662	Br13X	g.chr22:30567431G>T	c.3052G>T	p.E1018X	Nonsense
DFNB31	CCDS6806.1	Br27P	g.chr9:114320539G>A	c.685G>A	p.V229I	Missense
DGCR6	CCDS13753.1	Br27P	g.chr22:17273070G>A	c.488G>A	p.G163D	Missense
DGKD	CCDS2504.1	Br27P	g.chr2:234140016G>A	c.1882G>A	p.E628K	Missense
DHPS	CCDS12276.1	Br14X	g.chr19:12653377C>T (homozygous)	c.204C>T	p.A68A	Synonymous
DHX29	NM_019030	Br27P	g.chr5:54601040G>A	c.3252G>A	p.K1084K	Synonymous
DIO3	NM_001362	Br27P	g.chr14:101097940G>A	c.276G>A	p.W92X	Nonsense
DKFZp434I099	CCDS10787.1	Br17X	g.chr16:56314542C>T	c.1536C>T	p.R512R	Synonymous
DKFZp547A023	CCDS845.1	Br27P	g.chr1:112711988C>T	c.1832C>T	p.T611I	Missense
DKFZp547A023	CCDS845.1	Br27P	g.chr1:112711154C>T	c.998C>T	p.T333I	Missense
DKFZp547B1713	CCDS1591.1	Br27P	g.chr1:227683603C>T	c.20C>T	p.A7V	Missense
DKFZP564B1023	CCDS1403.1	Br05X	g.chr1:19736481 4G>C	c.862G>C	p.E288Q	Missense

Fig. 10

DKFZp564I1922	CCDS14124.1	Br07x	g.chrX:3234086C>T	c.3001C>T	p.L1001F	Missense
DKFZp761L1417	CCDS5658.1	Br08X	g.chr7:98090906T>C	c.1070T>C	p.I357T	Missense
DKFZp761N1114	CCDS1455.1	Br27P	g.chr1:202293007G>A	c.1232G>A	p.G411D	Missense
DLD	CCDS5749.1	Br27P	g.chr7:107152438G>A	c.1355G>A	p.G452E	Missense
DLEC1	ENST00000337335	Br27P	g.chr3:38114268C>T	c.560C>T	p.P187L	Missense
DLEC1	ENST00000337335	Br27P	g.chr3:38114287C>T	c.579C>T	p.S193S	Synonymous
DLGAP2	NM_004745	Br27P	g.chr8:1612130A>G	c.1987A>G	p.T663A	Missense
DLGAP2	NM_004745	Br26X	g.chr8:1632768T>A	c.2605T>A	p.W869R	Missense
DLGAP2	NM_004745	Br27P	g.chr8:1636761G>A	c.2710G>A	p.E904K	Missense
DLGAP2	NM_004745	Br27P	g.chr8:1485167G>A	c.901G>A	p.E301K	Missense
DMN	NM_015286	Br08X	g.chr15:97487568G>A	c.1480G>A	p.V494I	Missense
DMTF1	CCDS5601.1	Br27P	g.chr7:86458488C>T	c.945C>T	p.T315T	Synonymous
DNAH1	NM_015512	Br27P	g.chr3:52372148C>T	c.5192C>T	p.A1731V	Missense
DNAH10	CCDS9255.1	Br27P	g.chr12:122799405G>A	c.943G>A	p.G315R	Missense
DNAH11	NM_003777	Br27P	g.chr7:21713926C>T	c.13386C>T	p.C4462C	Synonymous
DNAH3	CCDS10594.1	Br27P	g.chr16:20867333C>T	c.11316C>T	p.Y3772Y	Synonymous
DNAH3	CCDS10594.1	Br11P	g.chr16:20960912G>A	c.4576G>A	p.A1526T	Missense
DNAH5	CCDS3882.1	Br27P	g.chr5:13864853G>A	c.7310G>A	p.R2437H	Missense
DNAH8	CCDS4838.1	Br17X	g.chr6:38810301G>A	c.33G>A	p.P11P	Synonymous
DNAH9	CCDS11160.1	Br03X	g.chr17:11781538G>A	c.12634G>A	p.G4212R	Missense
DNAH9	CCDS11160.1	Br27P	g.chr17:11786432C>T	c.12748C>T	p.P4250S	Missense
DNAI2	CCDS11697.1	Br27P	g.chr17:69789555G>A	c.4G>A	p.E2K	Missense
DNCH1	CCDS9966.1	Br27P	g.chr14:101511876G>A	c.331G>A	p.V111I	Missense
DNCH1	CCDS9966.1	Br20P	g.chr14:101558902C>T	c.8569C>T	p.H2857Y	Missense
DNCLI2	CCDS10818.1	Br17X	4032_65334009dupGTACCACACAAAGGCCT	c.339_362dupGTACCACACAAAGGCCTGCTGCTGAAATT	indel	INDEL
DNHD3	NM_020877	Br25X	g.chr17:7635980G>A	c.6921G>A	p.E2307E	Synonymous
DNTTIP1	CCDS13369.1	Br27P	g.chr20:43863128G>A	c.381G>A	p.L127L	Synonymous
DOCK4	NM_014705	Br27P	g.chr7:110999193C>T	c.3925C>T	p.Q1309X	Nonsense
DOCK8	CCDS6440.1	Br27P	g.chr9:4049422G>A	c.3487G>A	p.D1163N	Missense
DOCK9	NM_015296	Br27P	g.chr13:98281996G>A	c.4294G>A	p.V1432I	Missense
DOK6	NM_152721	Br25X	g.chr18:65576033C>T	c.800C>T	p.A267V	Missense
DONSON	CCDS13632.1	Br23X	g.chr21:33882755C>G	c.63C>G	p.L21L	Synonymous
DRCTNNB1A	CCDS5377.1	Br16X	g.chr7:22758535C>T	c.1479C>T	p.Y493Y	Synonymous
DRD3	CCDS2978.1	Br05X	g.chr3:115332900G>A	c.761G>A	p.R254H	Missense
DRG1	CCDS13897.1	Br15X	g.chr22:30143902G>A	c.665G>A	p.R222H	Missense
DSG1	CCDS11896.1	Br27P	g.chr18:27170353T>C	c.1044T>C	p.S348S	Synonymous
DSG2	NM_001943	Br26X	g.chr18:27332233C>T	c.21C>T	p.R7R	Synonymous
DSG3	CCDS11898.1	Br27P	g.chr18:27303304C>T	c.1891C>T	p.L631L	Synonymous
DSG4	CCDS11897.1	Br16X	g.chr18:27240203C>T	c.1802C>T	p.A601V	Missense
DSG4	CCDS11897.1	Br26X	g.chr18:27225138G>A	c.784G>A	p.V262I	Missense
DSPP	NM_014208	Br27P	g.chr4:88892193G>A	c.1200G>A	p.E400E	Synonymous
DST	CCDS4959.1	Br27P	g.chr6:56604068G>A	c.2431G>A	p.A811T	Missense
DST	CCDS4959.1	Br27P	g.chr6:56613211C>T	c.568C>T	p.P190S	Missense
DTX1	CCDS9164.1	Br27P	g.chr12:111978112C>T	c.423C>T	p.D141D	Synonymous
DTX4	ENST00000227451	Br27P	g.chr11:58706180G>A	c.96G>A	p.A286T	Missense
DULLARD	CCDS11093.1	Br27P	g.chr17:7088593G>A	IVS7+1G>A	Splice Site	Splice Site
DUSP22	CCDS4468.1	Br07X	g.chr6:293155G>A	c.316G>A	p.V106I	Missense
DUSP3	CCDS11469.1	Br9PT	g.chr17:39202506delC	c.555delC	fs	INDEL
DYRK3	NM_001004023	Br27P	g.chr1:203209612G>A	c.614G>A	p.R205K	Missense
DZIP3	CCDS2952.1	Br27P	g.chr3:109874107G>A	c.2503G>A	p.E835K	Missense

Fig. 10

E2F4	NM_001950	Br04X	g.chr16:65784512C>T	c.345C>T	p.D115D	Synonymous
EAF1	CCDS2626.1	Br08X	g.chr3:154530486>T	c.722G>T	p.S241I	Missense
EBF	CCDS4343.1	Br08X	g.chr5:158071816C>T	c.1473C>T	p.Y491Y	Synonymous
EBF3	NM_001005463	Br27P	g.chr10:131556126G>T	c.795G>T	p.W265C	Missense
ECEL1	CCDS2493.1	Br13X	g.chr2:233174379C>T	c.1244C>T	p.P415L	Missense
ECEL1	CCDS2493.1	Br27P	g.chr2:233171842G>A	c.1868G>A	p.G623D	Missense
ECHDC2	CCDS571.1	Br07X	g.chr1:53085564A>G	c.361A>G	p.I121V	Missense
ECOP	NM_030796	Br05X	g.chr7:55334248G>A	c.264G>A	p.P88P	Synonymous
EDD1	NM_015902	Br23X	g.chr8:103354043G>A	c.6863G>A	p.G2288D	Missense
EDG3	CCDS6680.1	Br27P	g.chr9:88846179C>T	c.510C>T	p.A170A	Synonymous
EDG8	CCDS12240.1	Br17X	g.chr19:10486558C>T	c.130C>T	p.L44L	Synonymous
EEF1A1	ENST00000331523	Br26X	g.chr5:99360721A>G	c.551A>G	p.Y184C	Missense
EFCBP1	NM_022351	Br27P	g.chr8:92032543C>T	c.965C>T	p.T322I	Missense
EFHC2	NM_025184	Br27P	g.chrX:43857775G>A	c.1126G>A	p.V376I	Missense
EGF	CCDS3689.1	Br27P	g.chr4:111192180C>T	c.85C>T	p.P29S	Missense
EGFR	CCDS5514.1	Br02X	g.chr7:55007252G>T (homozygous)	c.1793G>T	p.G598V	Missense
EGFR	CCDS5514.1	Br20P	g.chr7:54994474T>G	c.655T>G	p.C219G	Missense
EHBP1L1	ENST00000309295	Br14X	g.chr11:65106679C>T	c.1921C>T	p.Q641X	Nonsense
EIF2A	NM_032025	Br27P	g.chr3:151782223C>T	c.1618C>T	p.L540L	Synonymous
EIF3S12	CCDS12517.1	Br27P	g.chr19:43806626C>T	c.228C>T	p.N76N	Synonymous
EIF4G1	CCDS3259.1	Br04X	g.chr3:185525375A>T	c.2627A>T	p.E876V	Missense
EIF4G2	NM_001418	Br27P	g.chr11:10784151C>T	c.127C>T	p.P43S	Missense
EME2	NM_001010865	Br26X	g.chr16:1766094C>T	c.1189C>T	p.R397W	Missense
EML4	CCDS1807.1	Br15X	g.chr2:42456214C>A	IVS18-4C>A	Splice Site	Splice Site
EMR4	ENST00000359590	Br06X	g.chr19:6932130G>A	c.502G>A	p.A168T	Missense
EN2	CCDS5940.1	Br03X	g.chr7:154754861C>T	UTR+3C>T	3'UTR	3'UTR
ENO1	CCDS97.1	Br27P	g.chr1:8859757G>A	c.718G>A	p.V240M	Missense
ENPP2	CCDS6329.1	Br14X	g.chr8:120677325A>G	c.1071A>G	p.K357K	Synonymous
ENPP2	CCDS6329.1	Br13X	g.chr8:120667672C>G	c.1458C>G	p.H486Q	Missense
ENPP6	CCDS3834.1	Br05X	g.chr4:185413167A>G (homozygous)	c.846A>G	p.K282K	Synonymous
ENPP7	CCDS11763.1	Br27P	g.chr17:75323463C>T	c.426C>T	p.Y142Y	Synonymous
ENPP7	CCDS11763.1	Br27P	g.chr17:75323749C>T	c.712C>T	p.R238C	Missense
ENSA	CCDS958.1	Br27P	g.chr1:147413099G>A	c.100G>A	p.E34K	Missense
ENST00000294635	ENST00000294635	Br27P	g.chr1:74657904C>T	c.858C>T	p.L286L	Synonymous
ENST00000310882	ENST00000310882	Br17X	g.chr19:22112927G>A	c.178G>A	p.E60K	Missense
ENST00000326382	ENST00000326382	Br27P	g.chr7:75509139C>T	c.104C>T	p.A35V	Missense
ENST00000328067	ENST00000328067	Br08X	g.chr7:143292764G>A	c.752G>A	p.R251Q	Missense
ENST00000331583	ENST00000331583	Br27P	g.chr1:209990554G>A	c.261G>A	p.R87R	Synonymous
ENST00000334627	ENST00000334627	Br03X	g.chr2:106363959C>T	c.69C>T	p.I23I	Synonymous
ENST00000336168	ENST00000336168	Br27P	g.chr22:23607224G>A	c.2297G>A	p.G766E	Missense
ENST00000336168	ENST00000336168	Br27P	g.chr22:23576119C>T	c.848C>T	p.S283F	Missense
ENST00000355177	ENST00000355177	Br07X	g.chr8:27261015G>A (homozygous)	c.327G>A	p.W109X	Nonsense
ENST00000355324	ENST00000355324	Br14X	g.chr6:32535582C>A	c.261C>A	p.H87Q	Missense
ENST00000355324	ENST00000355324	Br13X	g.chr6:32535582C>G (homozygous)	c.261C>G	p.H87Q	Missense
ENST00000355607	ENST00000355607	Br27P	g.chr11:4867746G>A	c.608G>A	p.G203D	Missense
ENST00000357689	ENST00000357689	Br02X	g.chr18:31241610upA	c.108dupA	fs	INDEL
ENST00000358347	ENST00000358347	Br27P	g.chr19:53875256C>T	c.164C>T	p.P55L	Missense
ENST00000359736	ENST00000359736	Br27P	g.chr14:69108537G>A	c.1508G>A	p.R503Q	Missense
EPB41L2	CCDS5141.1	Br27P	g.chr6:131232577C>T	c.2426C>T	p.T809I	Missense
EPB41L4B	NM_019114	Br07X	g.chr9:109055589G>A (homozygous)	c.1698G>A	p.L566L	Synonymous

Fig. 10

EPB49	CCDS6020.1	Br27P	g.chr8:21983345C>T	c.402C>T	p.S134S	Synonymous
EPC1	CCDS7172.1	Br27P	g.chr10:32600999G>A	c.2035G>A	p.V679M	Missense
EPHA2	CCDS169.1	Br27P	g.chr1:16203547C>T	c.2450C>T	p.P817L	Missense
EPHA5	CCDS3513.1	Br07X	g.chr4:66042690delT	IVS14-3delT	Splice Site	INDEL
EPHA6	ENST00000334709	Br05X	g.chr3:98839497G>C	c.838G>C	p.V280L	Missense
EPHA8	CCDS225.1	Br04X	g.chr1:22670819C>T (homozygous)	c.2361C>T	p.D787D	Synonymous
EPO	CCDS5705.1	Br26X	g.chr7:99964998C>T	c.307C>T	p.R103W	Missense
ERCC5	NM_000123	Br11P	g.chr13:102313361C>G	c.1861C>G	p.Q621E	Missense
ERF	CCDS12600.1	Br27P	g.chr19:47444614G>A	c.1490G>A	p.G497D	Missense
ERN1	NM_001433	Br27P	g.chr17:59495158C>T	c.1007C>T	p.P336L	Missense
ESCO2	NM_001017420	Br27P	g.chr8:27706167C>T	c.1417C>T	p.P473S	Missense
ESPNP	ENST00000270691	Br27P	g.chr1:16771684C>T	c.1308C>T	p.R436R	Synonymous
ESR1	CCDS5234.1	Br07X	g.chr6:152357683C>T	c.1022C>T	p.S341L	Missense
ESR2	CCDS9762.1	Br17X	g.chr14:63786151delG	c.1091delG	fs	INDEL
ETV1	NM_004956	Br27P	g.chr7:13744503C>G	c.666C>G	p.F222L	Missense
EVI1	CCDS3205.1	Br27P	g.chr3:170290545G>A	c.2782G>A	p.D928N	Missense
EVPL	CCDS11737.1	Br27P	g.chr17:71523187C>T	c.1828C>T	p.L610F	Missense
EXOC6B	ENST00000272427	Br15X	g.chr2:72318160G>T	c.1006G>T	p.A336S	Missense
EXOC6B	ENST00000272427	Br27P	g.chr2:72518562C>T	c.684C>T	p.L228L	Synonymous
EXTL1	CCDS271.1	Br27P	g.chr1:26045806G>T	c.1857G>T	p.G619G	Synonymous
F13B	CCDS1388.1	Br16X	g.chr1:193756636T>C	c.1220T>C	p.V407A	Missense
F2RL1	CCDS4033.1	Br14X	g.chr5:76164865G>C	c.677G>C	p.C226S	Missense
F3	CCDS750.1	Br27P	g.chr1:94713672G>A	c.282G>A	p.E94E	Synonymous
F5	CCDS1281.1	Br07X	g.chr1:166251632G>A	c.1300G>A	p.V434M	Missense
FAD158	CCDS725.1	Br27P	g.chr1:89891718G>A	c.1568G>A	p.G523D	Missense
FADS1	CCDS8011.1	Br27P	g.chr11:61340759C>T	c.48C>T	p.T16T	Synonymous
FAM43A	NM_153690	Br27P	g.chr3:195889463G>A	c.611G>A	p.R204Q	Missense
FAM46B	CCDS294.1	Br27P	g.chr1:27017291C>T	c.561C>T	p.S187S	Synonymous
FAM47A	NM_203408	Br27P	g.chrX:33908975T>A	c.1078T>A	p.S360T	Missense
FAM48A	ENST00000360252	Br27P	g.chr13:36510638C>G	c.104C>G	p.T35R	Missense
FAM63B	NM_019092	Br27P	g.chr15:56850904G>A	c.18G>A	p.E6E	Synonymous
FAM78B	NM_001017961	Br27P	g.chr1:162867048G>A	c.96G>A	p.T32T	Synonymous
FAM92B	NM_198491	Br27P	g.chr16:83696470G>A	c.501G>A	p.V167V	Synonymous
FANCA	NM_000135	Br27P	g.chr16:88352505C>T	c.2962C>T	p.L988L	Synonymous
FANCD2	CCDS2595.1	Br02X	g.chr3:10091272dupT	c.2774dupT	fs	INDEL
FASN	CCDS11801.1	Br27P	g.chr17:77644540G>A	c.499G>A	p.A167T	Missense
FAT	NM_005245	Br15X	g.chr4:187885152A>G	c.13510A>G	p.K4504E	Missense
FBN3	CCDS12196.1	Br14X	g.chr19:8044008G>A	c.7876G>A	p.A2626T	Missense
FBXO40	NM_016298	Br03X	g.chr3:122823199G>A	c.233G>A	p.R78H	Missense
FBXW7	CCDS3777.1	Br27P	g.chr4:153604789C>T	c.1618C>T	p.H540Y	Missense
FCGBP	CCDS12546.1	Br15X	g.chr19:45100663C>A	c.4016C>A	p.P1339H	Missense
FCHSD1	NM_033449	Br27P	g.chr5:141004098G>A	c.1734G>A	p.R578R	Synonymous
FECH	CCDS11964.1	Br27P	g.chr18:53372525C>T	c.1042C>T	p.L348L	Synonymous
FEZ1	NM_005103	Br04X	g.chr11:124864772dupC	c.112dupC	fs	INDEL
FGD1	CCDS14359.1	Br27P	g.chrX:54356791G>A	c.2554G>A	p.V852M	Missense
FGD4	CCDS8727.1	Br02X	g.chr12:32669913G>A	c.1694G>A	p.C565Y	Missense
FGF2	NM_002006	Br14X	g.chr4:124155122A>G	c.619A>G	p.I207V	Missense
FGFR3	CCDS3353.1	Br08X	g.chr4:1773911G>A	c.1396G>A	p.E466K	Missense
FGIF	CCDS8300.1	Br27P	g.chr11:93870897C>T	c.271C>T	p.R91W	Missense
FIGF	CCDS14166.1	Br23X	g.chrX:15130895A>G	c.694A>G	p.K232E	Missense

Fig. 10

FLII	CCDS11192.1	Br27P	g.chr17:18091971G>A	c.2292G>A	p.R764R	Synonymous
FLJ10276	CCDS363.1	Br05X	g.chr1:32513483A>G	c.514A>G	p.K172E	Missense
FLJ10514	CCDS1311.1	Br27P	g.chr1:170554272G>A	c.1473G>A	p.E491E	Synonymous
FLJ10514	CCDS1311.1	Br17X	g.chr1:170539044A>G	c.830A>G	p.E277G	Missense
FLJ11088	CCDS8716.1	Br27P	g.chr12:28351015G>A	c.341G>A	p.G114E	Missense
FLJ11535	CCDS12043.1	Br27P	g.chr19:772530C>T	c.30C>T	p.I10I	Synonymous
FLJ12529	CCDS8006.1	Br27P	g.chr11:60940424C>T	c.694C>T	p.L232F	Missense
FLJ12644	CCDS12843.1	Br27P	g.chr19:57086230G>A	c.971G>A	p.G324E	Missense
FLJ12671	CCDS1153.1	Br27P	g.chr1:153510252G>A	c.266G>A	p.G89E	Missense
FLJ12700	CCDS5898.1	Br27P	g.chr7:148756207C>T	c.116C>T	p.T39I	Missense
FLJ13273	CCDS3672.1	Br27P	g.chr4:106996452C>T	c.78C>T	p.I26I	Synonymous
FLJ13576	CCDS5757.1	Br13X	g.chr7:1120180937>A	c.739T>A	p.S247T	Missense
FLJ13725	CCDS10840.1	Br27P	g.chr16:66136884G>A	c.3136G>A	p.E1046K	Missense
FLJ13841	CCDS11819.1	Br27P	g.chr17:78381727G>A	c.1752G>A	p.K584K	Synonymous
FLJ13941	CCDS40.1	Br26X	g.chr1:2349494C>T	c.363C>T	p.H121H	Synonymous
FLJ14397	CCDS1945.1	Br27P	g.chr2:74520958G>A	c.662G>A	p.S221N	Missense
FLJ16165	NM_001004318	Br27P	g.chr19:44289446C>T	c.1133C>T	p.T378M	Missense
FLJ16331	NM_001004326	Br27P	g.chr11:64738196G>A	c.277G>A	p.A93T	Missense
FLJ16478	NM_001004341	Br27P	g.chr1:153875934C>T	c.666C>T	p.V222V	Synonymous
FLJ20035	NM_017631	Br11P	g.chr4:169571321C>T	c.2209C>T	p.R737W	Missense
FLJ20097	ENST00000317751	Br27P	g.chr7:92565717C>T	c.187C>T	p.L63L	Synonymous
FLJ20186	CCDS10989.1	Br04X	g.chr16:88548186C>T	c.208C>T	p.R70C	Missense
FLJ20232	CCDS13995.1	Br27P	g.chr22:38234449G>A	c.1013G>A	p.R338Q	Missense
FLJ20272	NM_017735	Br25X	g.chr2:32895125G>A	c.1568G>A	p.R523Q	Missense
FLJ20294	NM_017749	Br11P	g.chr11:46411689C>T	c.2617C>T	p.R873X	Nonsense
FLJ20298	CCDS14522.1	Br13X	g.chrX:105890141G>A	c.1601G>A	p.R534H	Missense
FLJ21159	CCDS3792.1	Br27P	g.chr4:156639161G>A	c.814G>A	p.E272K	Missense
FLJ21963	CCDS9022.1	Br27P	g.chr12:80149797G>A	c.1875G>A	p.Q625Q	Synonymous
FLJ22709	CCDS12351.1	Br27P	g.chr19:17198552G>A	c.120G>A	p.R40R	Synonymous
FLJ23049	CCDS3199.1	Br27P	g.chr3:168489411G>A	c.991G>A	p.G331S	Missense
FLJ23447	CCDS12300.1	Br27P	g.chr19:13905800C>T	c.679C>T	p.L227F	Missense
FLJ23577	ENST00000303168	Br27P	g.chr5:35775790delT	c.1534delT	fs	INDEL
FLJ23577	CCDS3910.1	Br17X	g.chr5:35690509C>G	c.902C>G	p.A301G	Missense
FLJ23790	CCDS6346.1	Br05X	g.chr8:124887510G>A	c.1166G>A	p.R389H	Missense
FLJ25715	NM_182570	Br27P	g.chr18:75540448C>T	c.157C>T	p.Q53X	Nonsense
FLJ25715	NM_182570	Br27P	g.chr18:75503080G>A	c.437G>A	p.R146K	Missense
FLJ25715	NM_182570	Br27P	g.chr18:75502987G>A	c.530G>A	p.R177K	Missense
FLJ25801	CCDS3850.1	Br08X	g.chr4:189401232T>A	c.43T>A	p.L15I	Missense
FLJ25801	CCDS3850.1	Br17X	g.chr4:189388102G>A	c.738G>A	p.A246A	Synonymous
FLJ27465	NM_001039843	Br26X	g.chr15:99346452C>T	c.515C>T	p.T172M	Missense
FLJ27465	NM_001039843	Br26X	g.chr15:99282375G>A	c.6G>A	p.S2S	Synonymous
FLJ30525	CCDS787.1	Br04X	g.chr1:108905031C>T	c.600C>T	p.R200R	Synonymous
FLJ30655	CCDS3740.1	Br27P	g.chr4:130235848G>A	c.1084G>A	p.E362K	Missense
FLJ30707	CCDS9427.1	Br27P	g.chr13:50753176C>T	c.1532C>T	p.A511V	Missense
FLJ31438	NM_152385	Br17X	g.chr2:55316398G>A	c.1555G>A	p.G519S	Missense
FLJ32796	CCDS1507.1	Br27P	g.chr1:209187813G>A	c.1199G>A	p.S400N	Missense
FLJ32934	CCDS1082.1	Br27P	g.chr1:151819045G>A	c.206G>A	p.G69D	Missense
FLJ33167	CCDS3837.1	Br27P	g.chr4:185978613G>A	c.1070G>A	p.G357E	Missense
FLJ33387	CCDS9783.1	Br27P	g.chr14:67010125C>T	c.269C>T	p.T90I	Missense
FLJ34512	CCDS10424.1	Br27P	g.chr16:714935C>T	c.1017C>T	p.G339G	Synonymous

Fig. 10

FLJ34658	CCDS3913.1	Br27P	g.chr5:35990085G>A	c.1548G>A	p.G516G	Synonymous
FLJ35709	CCDS7767.1	Br27P	g.chr11:6476395A>G	c.374A>G	p.D125G	Missense
FLJ35728	CCDS1537.1	Br13X	g.chr1:219939893C>T	c.1297C>T	p.R433W	Missense
FLJ36004	CCDS8704.1	Br11P	g.chr12:25590734C>T	c.269C>T	p.P90L	Missense
FLJ36208	NM_145270	Br20P	g.chr16:554064C>T	c.769C>T	p.R257C	Missense
FLJ36601	CCDS14238.1	Br03x	g.chrX:35851101G>T	c.379G>T	p.G127X	Nonsense
FLJ37440	CCDS2095.1	Br27P	g.chr2:112659027G>A	c.827G>A	p.G276D	Missense
FLJ38964	NM_173527	Br27P	g.chr14:22425960C>T	UTR+2C>T	3'UTR	3'UTR
FLJ38973	NM_153689	Br27P	g.chr2:200615404G>A	c.99G>A	p.V33V	Synonymous
FLJ39058	CCDS8489.1	Br27P	g.chr11:130048243G>A	c.160G>A	p.V54I	Missense
FLJ39198	NM_001039769	Br27P	g.chr8:64053832G>A	c.173G>A	p.S58N	Missense
FLJ39873	CCDS2980.1	Br27P	g.chr3:115501183C>T	c.441C>T	p.A147A	Synonymous
FLJ40243	NM_173489	Br23X	g.chr5:41040284T>C	c.4115T>C	p.I1372T	Missense
FLJ40342	CCDS11512.1	Br17X	g.chr5:41040244C>T	c.4155C>T	p.F1385F	Synonymous
FLJ40869	CCDS1691.1	Br14X	g.chr17:42793835C>T	c.754C>T	p.P252S	Missense
FLJ41170	NM_001004332	Br27P	g.chr2:17875627C>T	c.901C>T	p.H301Y	Missense
FLJ41766	ENST00000338573	Br11P	g.chr14:100542038T>C	c.112T>C	p.W38R	Missense
FLJ43706	NM_001039774	Br26X	g.chr16:21235757G>A	c.134G>A	p.R45H	Missense
FLJ44186	CCDS5854.1	Br27P	g.chr4:62122281G>A	c.409G>A	p.G137S	Missense
FLJ44861	CCDS11778.1	Br07X	g.chr7:138595683C>T	c.1135C>T	p.L379L	Synonymous
FLJ45300	NM_001001681	Br27P	g.chr17:76755104C>T	c.214C>T	p.P72S	Missense
FLJ45744	CCDS12424.1	Br27P	g.chr11:119007338C>T	c.41C>T	p.A14V	Missense
FLJ45964	CCDS2530.1	Br27P	g.chr19:37859283G>A	c.274G>A	p.D92N	Missense
FLJ45974	NM_001001707	Br07X	g.chr2:240236539C>T	c.166C>T	p.Q56X	Nonsense
FLJ46072	CCDS6410.1	Br08x	g.chr7:53653463C>T	c.363C>T	p.Y121Y	Synonymous
FLJ90650	CCDS4124.1	Br23X	g.chr8:144882513C>T	c.227C>T	p.P76L	Missense
FLT1	CCDS9330.1	Br26X	g.chr5:115374362G>A	c.2119G>A	p.A707T	Missense
FLT1	CCDS9330.1	Br27P	g.chr13:27899451A>T	c.1281A>T	p.K427N	Missense
FMN2	NM_020066	Br27P	g.chr13:27811340G>A	c.2453G>A	p.S818N	Missense
FMNL2	NM_001004417	Br27P	g.chr1:236581393G>A	c.372G>A	p.E124E	Synonymous
FMNL2	NM_001004417	Br27P	g.chr2:153301602C>T	c.1699C>T	p.P567S	Missense
FN1	CCDS2399.1	Br27P	g.chr2:153314055G>A	c.2576G>A	p.R859K	Missense
FNBP1	NM_015033	Br05X	g.chr2:216123657A>G	c.311A>G	p.N104S	Missense
FNDC1	NM_032532	Br26X	g.chr9:129769094G>C	c.723G>C	p.V241V	Synonymous
FOXA2	CCDS13147.1	Br13X	g.chr6:159625258G>A	c.3147G>A	p.K1049K	Synonymous
FOXB1	NM_012182	Br07X	g.chr20:22510578G>A	c.1284G>A	p.T428T	Synonymous
FOXI1	CCDS4372.1	Br17X	g.chr15:58084861G>A	c.407G>A	p.R136Q	Missense
FOXM1	CCDS8515.1	Br20P	g.chr5:169465925C>T	c.386C>T	p.S129L	Missense
FOXR2	NM_198451	Br27P	g.chr12:2838919G>A	c.1438G>A	p.E480K	Missense
FRAS1	NM_025074	Br26X	g.chrX:55533654C>T	c.489C>T	p.D163D	Synonymous
FREM2	NM_207361	Br26X	g.chr4:79710934C>T	c.5211C>T	p.Y1737Y	Synonymous
FRMD3	NM_174938	Br27P	g.chr13:38163333G>A	c.3852G>A	p.G1284G	Synonymous
FRMD4B	ENST00000264546	Br27P	g.chr9:83194176C>T	c.346C>T	p.P116S	Missense
FRMPD1	CCDS6612.1	Br27P	g.chr3:69434212G>A	c.472G>A	p.G158S	Missense
FRMPD1	CCDS6612.1	Br17X	g.chr9:37730100C>T	c.1575C>T	p.D525D	Synonymous
FRMPD4	NM_014728	Br15X	g.chr9:37719830G>A (homozygous)	c.718G>A	p.E240K	Missense
FRMPD4	NM_014728	Br9PT	g.chrX:12479743G>A (homozygous)	c.1027G>A	p.V343I	Missense
FSD2	NM_001007122	Br27P	g.chrX:12493874C>T	c.1639C>T	p.L547F	Missense
FSTL1	CCDS2998.1	Br11P	g.chr15:81244621G>A	c.1062G>A	p.L354L	Synonymous
			g.chr3:121613429G>C	c.260G>C	p.G87A	Missense

Fig. 10

FSTL4	NM_015082	Br27P	g.chr5:132562801T>A	c.2414T>A	p.L805H	Missense
FSTL5	CCDS3802.1	Br03X	g.chr4:163390100G>A	c.54G>A	p.S18S	Synonymous
FUBP1	CCDS683.1	Br27P	g.chr1:78127001G>A	c.1786G>A	p.A596T	Missense
FUBP1	CCDS683.1	Br27P	g.chr1:78142058C>T	c.842C>T	p.P281L	Missense
FUT2	NM_000511	Br27P	g.chr19:53898686C>T	c.661C>T	p.R221X	Nonsense
FXYD6	CCDS8387.1	Br27P	g.chr11:117217109G>A	c.173G>A	p.S58N	Missense
FYCO1	CCDS2734.1	Br27P	g.chr3:45984943C>T	c.887C>T	p.A296V	Missense
FZD10	CCDS9267.1	Br14X	g.chr12:129172394G>T	c.27G>T	p.W9C	Missense
FZD3	CCDS6069.1	Br07x	g.chr8:28441140C>A	c.944C>A	p.A315D	Missense
FZD6	CCDS6298.1	Br27P	g.chr8:104409743C>T	c.1464C>T	p.I488I	Synonymous
FZD9	CCDS5548.1	Br27P	g.chr7:72294706C>T	c.1718C>T	p.T573I	Missense
G3BP2	CCDS3571.1	Br27P	g.chr4:76927904G>A	c.1338G>A	p.M446I	Missense
GABPA	CCDS13575.1	Br27P	g.chr21:26058805G>A	c.972G>A	p.Q324Q	Synonymous
GABRA6	CCDS4356.1	Br15X	g.chr5:161048645C>T	c.338C>T	p.T113M	Missense
GABRD	CCDS36.1	BR14X	g.chr1:1993815G>A	c.1291G>A	p.A431T	Missense
GAD2	CCDS7149.1	Br06X	g.chr10:26615288G>A	c.1245G>A	p.M415I	Missense
GALNT13	CCDS2199.1	Br27P	g.chr2:154626633G>A	c.115G>A	p.E39K	Missense
GALNT3	CCDS2226.1	Br27P	g.chr2:166446952C>T	c.637C>T	p.P213S	Missense
GALNT3	CCDS2226.1	Br27P	g.chr2:166441475C>T	c.951C>T	p.N317N	Synonymous
GALNT7	CCDS3815.1	Br27P	g.chr4:174597947G>A	c.1168G>A	p.G390R	Missense
GALNTL1	NM_020692	Br27P	g.chr14:68883523G>A	c.1285G>A	p.E429K	Missense
GANAB	CCDS8026.1	Br27P	g.chr11:62152974G>A	c.2023G>A	p.A675T	Missense
GAPVD1	NM_015635	Br27P	g.chr9:125154427G>A	c.1584G>A	p.G528G	Synonymous
GAS6	CCDS9540.1	Br27P	g.chr13:113583934C>T	c.1437C>T	p.F479F	Synonymous
GAS6	CCDS9540.1	Br12P	g.chr13:113588931G>A	c.1801G>A	p.A601T	Missense
GATA4	CCDS5983.1	Br17X	g.chr8:11653376G>A	c.1312G>A	p.D438N	Missense
GATA6	CCDS11872.1	Br02X	g.chr18:18005370G>T	c.267G>T	p.G89G	Synonymous
GBF1	CCDS7533.1	Br27P	g.chr10:104125238G>A	c.3790G>A	p.A1264T	Missense
GCGR	NM_000160	Br27P	g.chr17_random:1868957C>T	c.1101C>T	p.V367L	Missense
GCGR	NM_000160	Br27P	g.chr17_random:1869577G>A	c.1228G>A	p.E410K	Missense
GCM1	CCDS4950.1	Br15X	g.chr6:53101613C>T	c.661C>T	p.H221Y	Missense
GCM2	CCDS4517.1	Br11P	g.chr6:10982864C>G	c.871C>G	p.L291V	Missense
GCNT3	CCDS10172.1	Br20P	g.chr15:57698490C>T	c.761C>T	p.S254L	Missense
GDF3	CCDS8581.1	Br27P	g.chr12:7739324G>A	c.268G>A	p.G90S	Missense
GEFT	CCDS8947.1	Br27P	g.chr12:56294613G>A	c.774G>A	p.K258K	Synonymous
GFI1B	CCDS6957.1	Br27P	g.chr9:132894043C>T	c.552C>T	p.R184R	Synonymous
GFM1	NM_024996	Br27P	g.chr3:159846698G>A	c.277G>A	p.E93K	Missense
GGA2	CCDS10611.1	Br08X	g.chr16:23412191G>A	c.342G>A	p.L114L	Synonymous
GGPS1	CCDS1604.1	Br27P	g.chr1:231831786G>A	c.561G>A	p.R187R	Synonymous
GHSR	CCDS3218.1	Br08X	g.chr3:173648161G>A	c.745G>A	p.V249M	Missense
GIMAP1	CCDS5906.1	Br27P	g.chr7:149855143G>A	c.403G>A	p.V135M	Missense
GIMAP5	CCDS5907.1	Br20P	g.chr7:149877039C>A	c.164C>A	p.S55Y	Missense
GIMAP8	NM_175571	Br27P	g.chr7:149612139G>A	c.1621G>A	p.D541N	Missense
GIT2	CCDS9138.1	Br27P	g.chr12:108860392G>A	c.1079G>A	p.S360N	Missense
GJA4	NM_002060	Br27P	g.chr1:34929843C>T	c.936C>T	p.P312P	Synonymous
GJB4	CCDS383.1	Br27P	g.chr1:34896194C>T	c.246C>T	p.I82I	Synonymous
GK	CCDS14225.1	Br04X	g.chrX:30497838C>T	c.1205C>T	p.A402V	Missense
GLRA1	CCDS4320.1	Br15X	g.chr5:151211320C>T	c.736C>T	p.R246W	Missense
GMCL1L	CCDS4433.1	Br27P	g.chr5:177545346C>T	c.1561C>T	p.P521S	Missense
GMDS	CCDS4474.1	Br27P	g.chr6:2062772G>A	c.165G>A	p.R55R	Synonymous

Fig. 10

GML	CCDS6391.1	Br07X	g.chr8:143919589C>G (homozygous)	c.127C>G	p.P43A	Missense
GNAI2	CCDS2813.1	Br04X	g.chr3:50269450C>T	c.801C>T	p.L267L	Synonymous
GNAT1	CCDS2812.1	Br27P	g.chr3:50205604G>A	c.141G>A	p.K47K	Synonymous
GNL2	CCDS421.1	Br10P	g.chr1:37709400T>A	c.1261T>A	p.F421I	Missense
GNPTG	CCDS10436.1	Br27P	g.chr16:1352223G>A	c.427G>A	p.G143R	Missense
GNS	CCDS8970.1	Br27P	g.chr12:63424926C>T	c.554C>T	p.T185I	Missense
GOLGA3	CCDS9281.1	Br27P	g.chr12:131994862G>A	c.1143G>A	p.G381G	Synonymous
GOLGA3	CCDS9281.1	Br27P	g.chr12:131995273G>A	c.732G>A	p.R244R	Synonymous
GOLGA4	CCDS2666.1	Br27P	g.chr3:37331992G>A	c.1312G>A	p.D438N	Missense
GORASP2	NM_015530	Br23X	g.chr2:171633368C>G	c.459C>G	p.I153M	Missense
GOT2	CCDS10801.1	Br27P	g.chr16:57309940G>A	c.589G>A	p.D197N	Missense
GP6	NM_016363	Br26X	g.chr19:60218165G>A	c.956G>A	p.R319Q	Missense
GPBP1	NM_022913	Br27P	g.chr5:56577880G>A	IVS4-4G>A	Splice Site	Splice Site
GPI7	CCDS3336.1	Br04X	g.chr4:517677T>C	c.2618T>C	p.I873T	Missense
GPR114	CCDS10785.1	Br27P	g.chr16:56156501C>T	c.484C>T	p.H162Y	Missense
GPR116	CCDS4919.1	Br03X	g.chr6:46944735delT	c.1465delT	fs	INDEL
GPR132	CCDS9997.1	Br14X	g.chr14:104589052G>A	c.467G>A	p.R156Q	Missense
GPR142	CCDS11698.1	Br27P	g.chr17:69879732C>T	c.787C>T	p.P263S	Missense
GPR144	NM_182611	Br27P	g.chr9:124295843G>A	c.991G>A	p.E331K	Missense
GPR145	CCDS5044.1	Br27P	g.chr6:100475803G>A	c.757G>A	p.V253M	Missense
GPR174	CCDS14443.1	Br9PT	g.chrX:78233393C>A	c.744C>A	p.F248L	Missense
GPR37	CCDS5792.1	Br27P	g.chr7:123998902C>T	c.80C>T	p.A27V	Missense
GPR37L1	CCDS1420.1	Br27P	g.chr1:198828929G>A	c.1034G>A	p.C345Y	Missense
GPR40	CCDS12458.1	Br26X	g.chr19:40534646C>T	c.352C>T	p.R118W	Missense
GPR43	CCDS12461.1	Br27P	g.chr19:40633189G>A	c.733G>A	p.G245R	Missense
GPR61	CCDS801.1	Br27P	g.chr1:109797705C>T	c.19C>T	p.P7S	Missense
GPR61	CCDS801.1	Br27P	g.chr1:109798263C>T	c.577C>T	p.P193S	Missense
GPR73L1	CCDS13089.1	Br27P	g.chr20:5231346G>A	c.495G>A	p.M165I	Missense
GPR74	CCDS3551.1	Br17X	g.chr4:73378053T>C	c.1058T>C	p.V353A	Missense
GPR78	CCDS3403.1	Br08X	g.chr4:8700870C>T	c.90C>T	p.C30C	Synonymous
GPR83	CCDS8297.1	Br27P	g.chr11:93773974G>A	c.88G>A	p.E30K	Missense
GPR83	CCDS8297.1	Br27P	g.chr11:93766298G>A	IVS3+1G>A	Splice Site	Splice Site
GPR85	CCDS5758.1	Br23X	g.chr7:112317674A>C	c.1054A>C	p.T352P	Missense
GPRC5C	CCDS11699.1	Br14X	g.chr17:69948219C>T	c.844C>T	p.R282C	Missense
GPS1	CCDS11800.1	Br11P	g.chr17:77604512T>C	c.227T>C	p.V76A	Missense
GPS2	NM_032442	Br27P	g.chr17:7164907G>A	c.3420G>A	p.K1140K	Synonymous
GPSM2	CCDS792.1	Br27P	g.chr1:109156547C>T	c.870C>T	p.D290D	Synonymous
GPT	CCDS6430.1	Br27P	g.chr8:145702560C>T	c.1094C>T	p.P365L	Missense
GRAP2	CCDS13999.1	Br13X	g.chr22:38691505T>C (homozygous)	c.910T>C	p.S304P	Missense
GRASP	CCDS8817.1	Br27P	g.chr12:50694842G>A	c.780G>A	p.G260G	Synonymous
GRCA	CCDS8563.1	Br04X	g.chr12:6805701C>T	c.1137C>T	p.S379S	Synonymous
GREB1	NM_014668	Br15X	g.chr2:11689443C>T	c.2192C>T	p.T731M	Missense
GRIA4	CCDS8333.1	Br27P	g.chr11:105302713G>A	c.1884G>A	p.W628X	Nonsense
GRIK4	CCDS8433.1	Br17X	g.chr11:120343207G>A	c.2360G>A	p.G787E	Missense
GRIN2B	CCDS8662.1	Br04X	g.chr12:13910212C>A	c.198C>A	p.P66P	Synonymous
GRIN2B	CCDS8662.1	Br13X	g.chr12:13608123G>A	c.3316G>A	p.E1106K	Missense
GRIN2B	CCDS8662.1	Br27P	g.chr12:13607612C>T	c.3827C>T	p.A1276V	Missense
GRIN3A	CCDS6758.1	Br29P	g.chr9:101512338A>G	c.1911A>G	p.A637A	Synonymous
GRINA	NM_001009184	Br27P	g.chr8:145138181C>T	c.640C>T	p.L214F	Missense
GRM1	CCDS5209.1	Br15X	g.chr6:146761918C>T	c.2050C>T	p.R684C	Missense

Fig. 10

GRM3	CCDS5600.1	Br08X	g.chr7:86113754C>T	c.2273C>T	p.T758M	Missense
GRM3	CCDS5600.1	Br15X	g.chr7:86060570G>A	c.811G>A	p.V271I	Missense
GSR	NM_000637	Br27P	g.chr8:30656684G>A	c.1464G>A	p.L488L	Synonymous
GSTO2	CCDS7556.1	Br27P	g.chr10:106029187G>A	c.436G>A	p.A146T	Missense
GTF2A2	CCDS10173.1	Br27P	g.chr15:57718645C>T	c.308C>T	p.T103I	Missense
GTF2H4	NM_020442	Br20P	g.chr6:31001736G>C	c.3062G>C	p.G1021A	Missense
GTF3C4	CCDS6953.1	Br27P	g.chr9:132584539G>A	c.1979G>A	p.G660E	Missense
GUCY1A3	NM_000856	Br08X	g.chr4:156989502dupG	c.580dupG	fs	INDEL
GUCY1B2	CCDS9426.1	Br27P	g.chr13:50500400G>A	c.344G>A	p.R115K	Missense
GZMH	CCDS9632.1	Br17X	g.chr14:24145771G>A	c.619G>A	p.V207M	Missense
HAMP	CCDS12454.1	Br27P	g.chr19:40467743C>T	c.213C>T	p.G71G	Synonymous
HBB	NM_000519	Br07X	g.chr11:5211942G>C	c.170G>C	p.G57A	Missense
HBXAP	CCDS8253.1	Br27P	g.chr11:77063772T>C	c.3519T>C	p.D1173D	Synonymous
HBXAP	CCDS8253.1	Br27P	g.chr11:77091173G>A	c.749G>A	p.S250N	Missense
HCFC2	CCDS9097.1	Br06X	g.chr12:102977024G>A	c.716G>A	p.G239E	Missense
HDAC2	NM_001527	Br03X	g.chr6:114381275G>C	c.498G>C	p.K166N	Missense
HDAC9	NM_178425	Br27P	g.chr7:18398170G>A	c.49G>A	p.G17S	Missense
HDAC9	NM_178425	Br25X	g.chr7:18447540A>G	c.847A>G	p.N283D	Missense
HDC	CCDS10134.1	Br27P	g.chr15:48333110C>T	c.766C>T	p.L256L	Synonymous
HECW2	NM_020760	Br27P	g.chr2:196982979G>A	c.2816G>A	p.S939N	Missense
HERC1	NM_003922	Br27P	g.chr15:61754010C>T	c.7430C>T	p.S2477F	Missense
HERC1	NM_003922	Br06X	g.chr15:61748950G>A	c.8046G>A	p.R2682R	Synonymous
HERC2	CCDS10021.1	Br15X	g.chr15:26088302C>T	c.10152C>T	p.L3384L	Synonymous
HGSNAT	ENST00000332689	Br27P	g.chr8:43114876G>A	c.68G>A	p.G23D	Missense
HHIP	CCDS3762.1	Br11P	g.chr4:146013538delG	c.1801delG	fs	INDEL
HIF3A	CCDS12681.1	Br27P	g.chr19:51524515G>A	c.1652G>A	p.C551Y	Missense
HIP1	NM_005338	Br27P	g.chr7:74832210G>A	c.1376G>A	p.R459K	Missense
HIVEP1	NM_002114	Br23X	g.chr6:12232178C>A	c.4164C>A	p.F1388L	Missense
HIVEP2	NM_006734	Br9PT	g.chr6:143137172G>A	c.397G>A	p.V133I	Missense
HIVEP3	CCDS463.1	Br27P	g.chr1:41719464C>T	c.98C>T	p.S33F	Missense
HMG20A	CCDS10295.1	Br02X	g.chr15:75558704G>A	c.1036G>A	p.D346N	Missense
HMGCL	CCDS243.1	Br27P	g.chr1:23888551G>A	c.268G>A	p.E90K	Missense
HMP19	CCDS4391.1	Br27P	g.chr5:173423841G>A	c.130G>A	p.V44M	Missense
HNT	CCDS8491.1	Br27P	g.chr11:131710194G>A	c.979G>A	p.A327T	Missense
HORMAD1	CCDS967.1	Br27P	g.chr1:147493950C>T	c.402C>T	p.N134N	Synonymous
HOXA6	CCDS5407.1	Br07X	g.chr7:26958628C>T	c.591C>T	p.R197R	Synonymous
HP	NM_005143	Br14X	g.chr16:70651895G>A	c.826G>A	p.G276R	Missense
HP1BP3	NM_016287	Br17X	g.chr1:20829004_20829000delAGAAC	c.942_946delAGAAC	fs	INDEL
HPCAL4	CCDS441.1	Br04X	g.chr1:39819340C>A	c.29C>A	p.P10H	Missense
HRB	CCDS2467.1	Br26X	g.chr2:228243952_228243955delCAAA	c.1565_1568delCAAA	fs	INDEL
HRBL	CCDS5697.1	Br27P	g.chr7:99792782G>A	c.428G>A	p.R143K	Missense
HRG	CCDS3280.1	Br27P	g.chr3:187878168G>A	c.1372G>A	p.V458M	Missense
HS2ST1	CCDS712.1	Br27P	g.chr1:87310212C>T	c.423C>T	p.G141G	Synonymous
HS2ST1	CCDS711.1	Br27P	g.chr1:87282172A>T	IVS6-2A>T	Splice Site	Splice Site
HSA9761	CCDS3981.1	Br23X	g.chr5:61730453G>A	c.253G>A	p.E85K	Missense
HSD17B2	CCDS10936.1	Br15X	g.chr16:80659286C>T	c.276C>T	p.C92C	Synonymous
HSD17B8	CCDS4769.1	Br27P	g.chr6:33281662G>A	c.646G>A	p.D216N	Missense
HSPA4L	CCDS3734.1	Br9PT	g.chr4:129086786T>C	c.1275T>C	p.P425P	Synonymous
HSPC111	NM_016391	Br27P	g.chr5:175743906C>T	c.469C>T	p.R157C	Missense
HSPG2	NM_005529	Br27P	g.chr1:21936825C>T	c.4443C>T	p.L1481L	Synonymous

Fig. 10

HTR3C	CCDS3250.1	Br26X	g.chr3:185256780C>T	IVS4+4C>T	Splice Site	Splice Site
HTR3E	CCDS3251.1	Br10P	g.chr3:185300897G>A	c.35G>A	p.R12H	Missense
HXMA	CCDS10586.1	Br14X	g.chr16:20461790C>T	c.1456C>T	p.P486S	Missense
HYPB	CCDS2749.1	Br27P	g.chr3:47133202T>G	c.2992T>G	p.C998G	Missense
IBTK	NM_015525	Br02X	g.chr6:82979143G>C	c.2291G>C	p.C764S	Missense
IBTK	NM_015525	Br27P	g.chr6:82939856C>T	c.3744C>T	p.T1248T	Synonymous
ICAM3	CCDS12235.1	Br17X	g.chr19:10310614G>A	c.87G>A	p.G29G	Synonymous
ICEBERG	NM_021571	Br26X	g.chr11:104514773G>A	c.250G>A	p.A84T	Missense
IDE	CCDS7421.1	Br27P	g.chr10:94281604G>A	c.542G>A	p.R181K	Missense
IDH1	CCDS2381.1	Br10P	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br11P	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br12P	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br27P	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br29P	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IFI44	CCDS688.1	Br26X	g.chr1:78833091C>T	c.714C>T	p.D238D	Synonymous
IFIT3	CCDS7402.1	Br27P	g.chr10:91089032G>A	c.640G>A	p.G214S	Missense
IFNAR1	CCDS13624.1	Br17X	g.chr21:33639513G>A	c.765G>A	p.M255I	Missense
IFRD1	NM_001007245	Br27P	g.chr7:11168474 4G>A	c.50G>A	p.G17D	Missense
IGF1	CCDS9091.1	Br27P	g.chr12:101372044G>A	c.64G>A	p.V22M	Missense
IGF2	CCDS7728.1	Br27P	g.chr11:2110805C>T	c.531C>T	p.S177S	Synonymous
IGFBP7	CCDS3512.1	Br27P	g.chr4:57739618G>A	c.731G>A	p.G244E	Missense
IGSF1	CCDS14629.1	Br03X	g.chrX:130135064A>G (homozygous)	c.3107A>G	p.Y1036C	Missense
IGSF10	CCDS3160.1	Br03X	g.chr3:152646824C>G	c.3643C>G	p.P1215A	Missense
IGSF9	CCDS1190.1	Br27P	g.chr1:156713171G>A	c.1897G>A	p.V633I	Missense
IGSF9	CCDS1190.1	Br27P	g.chr1:156720567G>A	c.382G>A	p.V128M	Missense
IKBKE	NM_014002	Br27P	g.chr1:203054848G>A	IVS17+1G>A	Splice Site	Splice Site
IL12RB2	CCDS638.1	Br23X	g.chr1:67498069G>T	UTR-4G>T	5'UTR	5'UTR
IL17B	CCDS4297.1	Br17X	g.chr5:148734262C>T	c.406C>T	p.R136C	Missense
IL17RE	CCDS2589.1	Br27P	g.chr3:9920722C>T	c.155C>T	p.S52F	Missense
IL1F9	CCDS2108.1	Br9PT	g.chr2:113452488C>T	c.42C>T	p.A14A	Synonymous
IL1RL1	CCDS2057.1	Br27P	g.chr2:102418056G>A	c.725G>A	p.G242D	Missense
IL3	CCDS4149.1	Br27P	g.chr5:131424345C>T	c.47C>T	p.P16L	Missense
ILT7	CCDS12890.1	Br03X	g.chr19:59541295G>A (homozygous)	c.379G>A	p.A127T	Missense
IMP4	CCDS2160.1	Br03X	g.chr2:130816898G>A	c.13G>A	p.E5K	Missense
IMP4	CCDS2160.1	Br29P	g.chr2:130819902T>C	c.676T>C	p.Y226H	Missense
IMPDH1	NM_183243	Br27P	g.chr7:127643797G>A	c.110G>A	p.S37N	Missense
INDO	NM_002164	Br27P	g.chr8:39904750C>T	c.1101C>T	p.T367T	Synonymous
INDO	NM_002164	Br27P	g.chr8:39896791G>A	IVS5+1G>A	Splice Site	Splice Site
INSIG2	CCDS2122.1	Br27P	g.chr2:118570375G>A	c.13G>A	p.E5K	Missense
IPO13	CCDS503.1	Br08X	g.chr1:44091688_44091690delTGA	c.1218_1220delTGA	p.D406del	INDEL
IPO8	CCDS8719.1	Br27P	g.chr12:30683785C>T	c.2420C>T	p.P807L	Missense
IQGAP2	NM_006633	Br27P	g.chr5:76003350G>A	c.2854G>A	p.D952N	Missense
IQWD1	CCDS1267.1	Br27P	g.chr1:164745940G>A	c.863G>A	p.S288N	Missense
IRS1	CCDS2463.1	Br02X	g.chr2:227488820A>G	c.140A>G	p.Y47C	Missense
IRTA2	CCDS1165.1	Br26X	g.chr1:154327353C>A	c.616C>A	p.P206T	Missense
IRX6	NM_024335	Br14X	g.chr16:53917924C>A	c.221C>A	p.P74H	Missense
IRX6	NM_024335	Br27P	g.chr16:53920286G>A	c.895G>A	p.A299T	Missense
IRX6	NM_024335	Br04X	:hr16:53917796_53917806delACGCTCTGT	c.93_103delACGCTCTGTCT	fs	INDEL
ISL1	NM_002202	Br27P	g.chr5:50721259G>A	c.492G>A	p.Q164Q	Synonymous
ITGA4	NM_000885	Br25X	g.chr2:182224557C>A	c.2837C>A	p.P946Q	Missense

Fig. 10

ITGA7	CCDS8888.1	Br27P	g.chr12:54383206C>T	c.230C>T	p.A77V	Missense
ITGAL	NM_002209	Br04X	g.chr16:30436684G>T	c.3099G>T	p.V1033V	Synonymous
ITGAL	NM_002209	Br26X	g.chr16:30398277G>A	c.570G>A	p.S190S	Synonymous
ITGAX	CCDS10711.1	Br17X	g.chr16:31282136G>T	c.1650G>T	p.R550R	Synonymous
ITIH5	NM_032817	Br12P	g.chr10:76452170>T	c.2022G>T	p.V674V	Synonymous
ITIH5	NM_032817	Br27P	g.chr10:76619780>A	c.522G>A	p.V174V	Synonymous
ITLN1	CCDS1211.1	Br05X	g.chr1:157666290G>A	IVS2+1G>A	Splice Site	Splice Site
ITPKB	CCDS1555.1	Br27P	g.chr1:2231321140>A	IVS6+1G>A	Splice Site	Splice Site
ITPR3	CCDS4783.1	Br16X	g.chr6:33761264G>A	c.5458G>A	p.E1820K	Missense
IVNS1ABP	CCDS1368.1	Br05X	g.chr1:181999070_181999067delGTTT	c.1683_1686delGTTT	fs	INDEL
JMJD1A	CCDS1990.1	Br27P	g.chr2:86605545G>A	c.1400G>A	p.C467Y	Missense
JMJD1B	NM_016604	Br27P	g.chr5:137736306G>A	c.237G>A	p.W79X	Nonsense
JUNB	CCDS12280.1	Br27P	g.chr19:12763638C>T	c.53C>T	p.T18M	Missense
K0574_HUMAN	ENST00000261275	Br27P	g.chr15:27205831G>A	c.757G>A	p.V253M	Missense
KATNAL2	NM_031303	Br27P	g.chr18:42849857G>T	c.680G>T	p.G227V	Missense
KBTBD3	CCDS8334.1	Br27P	g.chr11:105429606C>T	c.1020C>T	p.Y340Y	Synonymous
KBTBD4	CCDS7940.1	Br27P	g.chr11:47551919G>A	IVS2-1G>A	Splice Site	Splice Site
KCNA4	NM_002233	Br29P	g.chr11:29990620C>T	c.182C>T	p.S61F	Missense
KCNA7	CCDS12755.1	Br02X	g.chr19:54265675C>T	c.828C>T	p.I276I	Synonymous
KCNB2	CCDS6209.1	Br11P	g.chr8:74011087G>A	c.943G>A	p.A315T	Missense
KCNC4	CCDS821.1	Br20P	g.chr1:110478374C>T	c.1425C>T	p.F475F	Synonymous
KCND2	CCDS5776.1	Br27P	g.chr7:119976568C>T	c.1428C>T	p.T476T	Synonymous
KCND2	CCDS5776.1	Br03X	g.chr7:119979914C>T	c.1597C>T	p.R533X	Nonsense
KCNG3	CCDS1809.1	Br26X	g.chr2:42631881G>A	c.412G>A	p.D138N	Missense
KCNH1	CCDS1496.1	Br9PT	g.chr1:207365704G>T	c.1662G>T	p.K554N	Missense
KCNH5	CCDS9756.1	Br08X	g.chr14:62316201C>T	c.2017C>T	p.R673W	Missense
KCNJ15	CCDS13656.1	Br03X	g.chr21:38593138G>A	c.85G>A	p.V29I	Missense
KCNK1	CCDS1599.1	Br26X	g.chr1:230109198G>A	c.478G>A	p.V160I	Missense
KCNK5	CCDS4841.1	Br27P	g.chr6:39304718C>T	c.148C>T	p.P50S	Missense
KCNN1	NM_002248	Br27P	g.chr19:17946067G>A	c.370G>A	p.E124K	Missense
KCNQ3	NM_004519	Br27P	g.chr8:133211412G>A	c.1898G>A	p.G633E	Missense
KCNQ4	CCDS456.1	Br27P	g.chr1:40954145G>A	c.742G>A	p.V248M	Missense
KCTD7	CCDS5534.1	Br27P	g.chr7:65538336G>A	c.135G>A	p.L45L	Synonymous
KCTD8	CCDS3467.1	Br27P	g.chr4:44291341C>T	c.128C>T	p.P43L	Missense
KCTD8	CCDS3467.1	Br27P	g.chr4:44291181C>T	c.288C>T	p.R96R	Synonymous
KDELR2	CCDS5351.1	Br27P	g.chr7:6276044C>T	c.607C>T	p.L203F	Missense
KDR	CCDS3497.1	Br03X	g.chr4:55797122G>A	c.3121G>A	p.V1041M	Missense
KEL	NM_000420	Br27P	g.chr7:142158572G>A	c.1408G>A	p.D470N	Missense
KIAA0082	CCDS4835.1	Br16X	g.chr6:37555001C>T	c.2367C>T	p.A789A	Synonymous
KIAA0101	CCDS10193.1	Br27P	g.chr15:62456131C>T	c.154C>T	p.P52S	Missense
KIAA0103	CCDS6309.1	Br20P	g.chr8:109551279G>A	c.412G>A	p.V138M	Missense
KIAA0133	NM_014777	Br07X	g.chr1:226080304T>A	c.3209T>A	p.F1070Y	Missense
KIAA0133	NM_014777	Br17X	g.chr1:226077736G>A	c.641G>A	p.G214E	Missense
KIAA0143	NM_015137	Br17X	g.chr8:133035700G>C	c.1600G>C	p.D534H	Missense
KIAA0153	CCDS14047.1	Br27P	g.chr22:41901418C>T	c.374C>T	p.T125M	Missense
KIAA0317	NM_001039479	Br27P	g.chr14:74206524G>A	c.1667G>A	p.G556E	Missense
KIAA0329	NM_014844	Br27P	g.chr14:101970983C>T	c.2076C>T	p.H692H	Synonymous
KIAA0350	NM_015226	Br17X	g.chr16:11052915C>G	c.1911C>G	p.I637M	Missense
KIAA0367	NM_015225	Br03X	g.chr9:76552682G>A	c.2985G>A	p.G995G	Synonymous
KIAA0404	NM_015104	Br27P	g.chr11:64434704C>T	c.1667C>T	p.A556V	Missense

Fig. 10

KIAA0406	CCDS13300.1	Br27P	g.chr20:36068178C>T	c.2338C>T	p.L780F	Missense
KIAA0528	NM_014802	Br27P	g.chr12:22557563G>A	c.970G>A	p.A324T	Missense
KIAA0649	CCDS6988.1	Br23X	g.chr9:135605495G>A	c.3194G>A	p.G1065D	Missense
KIAA0652	CCDS7921.1	Br05X	t g.chr11:46627297_46627301delAAATG	c.305_309delAAATG	fs	INDEL
KIAA0664	NM_015229	Br27P	g.chr17:2542135C>T	c.3450C>T	p.H1150H	Synonymous
KIAA0664	NM_015229	Br27P	g.chr17:2544166G>A	IVS17+1G>A	Splice Site	Splice Site
KIAA0672	NM_014859	Br15X	g.chr17:12802872G>A	c.1456G>A	p.E486K	Missense
KIAA0672	NM_014859	Br27P	g.chr17:12740531G>A	c.176G>A	p.G59E	Missense
KIAA0690	CCDS7457.1	Br06X	g.chr10:99113648G>A	c.3520G>A	p.E1174K	Missense
KIAA0701	NM_001006947	Br27P	g.chr12:98979356C>T	c.1313C>T	p.T438I	Missense
KIAA0703	NM_014861	Br20P	g.chr16:83006699G>A	IVS5+1G>A	Splice Site	Splice Site
KIAA0748	ENST00000316577	Br27P	g.chr12:53643162G>A	c.373G>A	p.D125N	Missense
KIAA0759	CCDS9852.1	Br27P	g.chr14:76345743C>T	IVS1-4C>T	Splice Site	Splice Site
KIAA0774	NM_001033602	Br15X	g.chr13:28506145C>T (homozygous)	c.2359C>T	p.R787C	Missense
KIAA0774	NM_001033602	Br05X	g.chr13:28497704C>T	c.899C>T	p.S300L	Missense
KIAA0802	CCDS11841.1	Br9PT	g.chr18:8774394C>T	c.1284C>T	p.F428F	Synonymous
KIAA0831	NM_014924	Br9PT	g.chr14:54918591C>A	c.719C>A	p.A240D	Missense
KIAA0863	NM_014913	Br27P	g.chr18:75996793G>A	c.2506G>A	p.E836K	Missense
KIAA0980	NM_025176	Br27P	g.chr20:25404789G>A	c.3138G>A	p.E1046E	Synonymous
KIAA1024	NM_015206	Br27P	g.chr15:77547735C>T	c.2705C>T	p.T902I	Missense
KIAA1033	NM_015275	Br27P	g.chr12:104011475G>A	IVS5+1G>A	Splice Site	Splice Site
KIAA1086	ENST00000262961	Br04X	g.chr19:3771285G>C	c.1524G>C	p.R508R	Synonymous
KIAA1109	ENST00000264501	Br27P	g.chr4:123583744G>A	IVS20+1G>A	Splice Site	Splice Site
KIAA1223	NM_020337	Br25X	g.chr4:125947835A>T	c.4202A>T	p.E1401V	Missense
KIAA1274	NM_014431	Br27P	g.chr10:71962517G>A	c.768G>A	p.R256R	Synonymous
KIAA1328	NM_020776	Br27P	g.chr18:32901211G>A	c.937G>A	p.D313N	Missense
KIAA1377	NM_020802	Br13X	g.chr11:101338494A>T	c.1518A>T	p.K506N	Missense
KIAA1411	NM_020819	Br27P	g.chr6:71247348C>T	c.437C>T	p.T146I	Missense
KIAA1441	CCDS992.1	Br04X	g.chr1:148073883G>C	c.2043G>C	p.Q681H	Missense
KIAA1441	CCDS992.1	Br04X	g.chr1:148073884T>A	c.2044T>A	p.C682S	Missense
KIAA1441	CCDS992.1	Br27P	g.chr1:148076695C>T	c.3651C>T	p.T1217T	Synonymous
KIAA1467	NM_020853	Br11P	2:13124806_13124822delCGATAACTCTTT	IVS12-20_IVS12-4delCGATAACTCTTTTTCCA	Splice Site	INDEL
KIAA1505	NM_020879	Br27P	g.chr7:76530454_76530455delTT	c.661_662delTT	fs	INDEL
KIAA1524	NM_020890	Br17X	g.chr3:109766959_109766955delTTGAT	c.1448_1452delTTGAT	fs	INDEL
KIAA1576	NM_020927	Br27P	g.chr16:76416695G>A	c.415G>A	p.V139I	Missense
KIAA1618	CCDS11772.1	Br27P	g.chr17:75876486G>A	c.539G>A	p.G180E	Missense
KIAA1754L	NM_178495	Br26X	g.chr2:96415170C>T	c.951C>T	p.T317T	Synonymous
KIAA1804	CCDS1598.1	Br07X	g.chr1:229822156A>C	c.2669A>C	p.H890P	Missense
KIAA1804	CCDS1598.1	Br07X	g.chr1:229822168T>C	c.2681T>C	p.M894T	Missense
KIAA1862	NM_032534	Br27P	g.chr7:148857534G>A	c.611G>A	p.G204E	Missense
KIAA1909	NM_052909	Br27P	g.chr5:216616C>T	c.2361C>T	p.P787P	Synonymous
KIAA1909	NM_052909	Br26X	g.chr5:196353G>A	c.601G>A	p.G201R	Missense
KIAA1946	NM_177454	Br06X	g.chr2:187452911C>T	c.2336C>T	p.S779L	Missense
KIAA1967	NM_021174	Br07X	g.chr8:22529222C>T (homozygous)	c.1460C>T	p.A487V	Missense
KIAA2022	NM_001008537	Br05X	g.chrX:73746128C>G	c.1285C>G	p.L429V	Missense
KIAA2026	NM_001017969	Br12P	g.chr9:5912152G>T	c.1369G>T	p.V457F	Missense
KIDINS220	NM_020738	Br27P	g.chr2:8840972G>A	c.3282G>A	p.G1094G	Synonymous
KIFC2	CCDS6427.1	Br27P	g.chr8:145668629C>T	c.1685C>T	p.A562V	Missense
KIFC3	CCDS10789.1	Br27P	g.chr16:56362003G>A	c.459G>A	p.V153V	Synonymous
KIRREL2	CCDS12479.1	Br27P	g.chr19:41049219C>T	c.1843C>T	p.P615S	Missense

KIRREL3	NM_032531	Br27P	g.chr11:125800102C>T	c.1920C>T	p.V640V	Synonymous
KLHDC5	NM_020782	Br02X	g.chr12:27825052A>G	c.522A>G	p.Q174Q	Synonymous
KLHL10	NM_152467	Br04X	g.chr17:37257996G>A	c.1738G>A	p.E580K	Missense
KLHL4	CCDS14456.1	Br27P	g.chrX:86695014C>T	c.1670C>T	p.S557L	Missense
KLK9	CCDS12816.1	Br11P	g.chr19:56198214T>G	c.718T>G	p.Y240D	Missense
KLP1	CCDS12926.1	Br29P	g.chr19:60689674G>A	c.160G>A	p.G54S	Missense
KLRG1	CCDS8599.1	Br07X	g.chr12:9039068G>A (homozygous)	c.274G>A	p.E92K	Missense
KNTC1	NM_014708	Br06X	g.chr12:121580488A>G	c.1954A>G	p.I652V	Missense
KREMEN2	CCDS10484.1	Br27P	g.chr16:2957845G>A	c.1133G>A	p.R378Q	Missense
KREMEN2	CCDS10483.1	Br27P	g.chr16:2955005G>A	c.239G>A	p.R80H	Missense
KRT9	NM_000226	Br27P	g.chr17:36978068G>A	c.1266G>A	p.Q422Q	Synonymous
KRTAP12-3	NM_198697	Br27P	g.chr21:44902470C>T	c.146C>T	p.S49F	Missense
KRTAP20-2	CCDS13604.1	Br27P	g.chr21:30929456G>A	c.3G>A	p.M1I	Missense
KRTHA4	CCDS11390.1	Br04X	g.chr17:36787862C>A	c.1286C>A	p.T429N	Missense
KSR1	NM_014238	Br27P	g.chr17:22956841C>T	c.1524C>T	p.G508G	Synonymous
L1CAM	CCDS14733.1	Br20P	g.chrX:152654161C>T	c.1880C>T	p.T627M	Missense
L3MBTL2	CCDS14011.1	Br27P	g.chr22:39944621C>T	c.1040C>T	p.T347I	Missense
LACE1	CCDS5067.1	Br9PT	g.chr6:108784598delC	c.529delC	fs	INDEL
LACRT	CCDS8883.1	Br27P	g.chr12:53313235G>A	c.108G>A	p.G36G	Synonymous
LAMA1	NM_005559	Br12P	g.chr18:6967742G>A	c.6329G>A	p.R2110H	Missense
LAMA3	CCDS11880.1	Br14X	g.chr18:19738532G>A	c.1664G>A	p.S555N	Missense
LAMA4	NM_002290	Br20P	g.chr6:112558910C>T	c.3900C>T	p.Y1300Y	Synonymous
LAMB3	CCDS1487.1	Br27P	g.chr1:206188654G>A	c.1550G>A	p.R517H	Missense
LAMB3	CCDS1487.1	Br17X	g.chr1:206180232G>A	c.2869G>A	p.A957T	Missense
LAMP3	CCDS3242.1	Br15X	g.chr3:184354455C>A	c.476C>A	p.T159N	Missense
LAP1B	CCDS1335.1	Br27P	g.chr1:176618341C>T	c.1062C>T	p.F354F	Synonymous
LARGE	CCDS13912.1	Br27P	g.chr22:31994964C>T	UTR+3C>T	3'UTR	3'UTR
LARP5	NM_015155	Br17X	g.chr10:848909G>A	c.2174G>A	p.R725H	Missense
LATS1	NM_004690	Br27P	g.chr6:150093563G>A	c.2155G>A	p.V719I	Missense
LATS2	CCDS9294.1	Br27P	g.chr13:20451877G>A	c.2725G>A	p.G909R	Missense
LAX	CCDS1441.1	Br27P	g.chr1:200475255G>A	c.758G>A	p.G253E	Missense
LBP	CCDS13304.1	Br04X	g.chr20:36431158G>A	c.1087G>A	p.E363K	Missense
LCA10	NM_001039768	Br27P	g.chrX:152673310C>T	c.343C>T	p.P115S	Missense
LCT	CCDS2178.1	Br04X	g.chr2:136408656T>A	c.1694T>A	p.V565E	Missense
LCT	CCDS2178.1	Br03x	g.chr2:136400046C>T	c.3603C>T	p.A1201A	Synonymous
LDLRAD3	NM_174902	Br27P	g.chr11:36059887G>A	c.302G>A	p.S101N	Missense
LEMD2	CCDS4785.1	Br27P	g.chr6:33864496C>T	c.376C>T	p.P126S	Missense
LENG8	CCDS12894.1	Br12P	g.chr19:59657433G>A	c.439G>A	p.G147S	Missense
LETM1	CCDS3355.1	Br27P	g.chr4:1791230G>A	c.1517G>A	p.R506K	Missense
LETMD1	CCDS8806.1	Br27P	g.chr12:49739469G>A	c.1071G>A	p.G357G	Synonymous
LETMD1	CCDS8806.1	Br04X	g.chr12:49735994A>G	c.583A>G	p.I195V	Missense
LIP8	CCDS11126.1	Br20P	g.chr17:7784239C>G	c.1265C>G	p.A422G	Missense
LIPM	ENST00000282673	Br26X	g.chr10:90569974T>C (homozygous)	c.861T>C	p.T287T	Synonymous
LMNB1	CCDS4140.1	Br27P	g.chr5:126141304G>A	c.205G>A	p.E69K	Missense
LMX1A	CCDS1247.1	Br23X	g.chr1:162054049G>A	c.185G>A	p.C62Y	Missense
LMX1A	CCDS1247.1	Br16X	g.chr1:161911626G>A	c.715G>A	p.V239I	Missense
LMX1A	CCDS1247.1	Br15X	g.chr1:161904931C>T	c.993C>T	p.A331A	Synonymous
LNX	CCDS3492.1	Br27P	g.chr4:54188918C>T	c.1094C>T	p.S365F	Missense
LNX	CCDS3492.1	Br27P	g.chr4:54185756G>A	c.1279G>A	p.A427T	Missense
LNX2	CCDS9323.1	Br27P	g.chr13:27022629G>A	IVS7-1G>A	Splice Site	Splice Site

Fig. 10

LOC113655	CCDS6431.1	Br27P	g.chr8:145705898A>C	c.374A>C	p.Q125P	Missense
LOC113655	CCDS6431.1	Br27P	g.chr8:145705899G>T	c.375G>T	p.Q125H	Missense
LOC124842	CCDS11283.1	Br27P	g.chr17:29984030C>T	c.1407C>T	p.L469L	Synonymous
LOC126248	CCDS12429.1	Br27P	g.chr19:38343191G>A	c.1029G>A	p.R343R	Synonymous
LOC131368	CCDS2947.1	Br16X	g.chr3:103657744A>T	c.393A>T	p.G131G	Synonymous
LOC131873	ENST00000358511	Br05X	g.chr3:131767096C>T	c.1147C>T	p.R383W	Missense
LOC134145	NM_199133	Br27P	g.chr5:10289727G>A	c.307G>A	p.V103I	Missense
LOC146562	CCDS10521.1	BR27P	g.chr16:4730662G>A	IVS3+1G>A	Splice Site	Splice Site
LOC158830	NM_001025265	Br27P	g.chrX:70106912C>T	c.498C>T	p.D166D	Synonymous
LOC200312	NM_001017981	Br27P	g.chr22:29106470C>T	c.564C>T	p.T188T	Synonymous
LOC221955	CCDS5350.1	Br27P	g.chr7:6229509G>A	c.1416G>A	p.R472R	Synonymous
LOC257106	CCDS1215.1	Br27P	g.chr1:157831186C>T	c.2065C>T	p.P689S	Missense
LOC257106	CCDS1215.1	Br27P	g.chr1:157839375G>A	c.221G>A	p.R74Q	Missense
LOC283537	CCDS9332.1	Br15X	g.chr13:28189947G>C	c.189G>C	p.E63D	Missense
LOC284912	CCDS13918.1	Br11P	g.chr22:34348002C>T	c.230C>T	p.A77V	Missense
LOC284948	CCDS1976.1	Br07X	g.chr2:85573774C>T	c.38C>T	p.S13F	Missense
LOC339977	NM_001024611	Br27P	g.chr4:52703222G>A	c.894G>A	p.R298R	Synonymous
LOC374768	NM_199339	Br27P	g.chr17:7267592C>T	c.461C>T	p.A154V	Missense
LOC387755	NM_001031853	Br16X	g.chr11:15213745A>T	c.1333A>T	p.M445L	Missense
LOC387856	NM_001013635	Br27P	g.chr12:46864265G>A	c.93G>A	p.V31V	Synonymous
LOC388595	NM_001013641	Br27P	g.chr1:15814859C>T	c.200C>T	p.A67V	Missense
LOC388969	NM_001013649	Br15X	g.chr2:85748258C>T	c.336C>T	p.Y112Y	Synonymous
LOC391123	NM_001013661	Br27P	g.chr1:156641726C>T	c.99C>T	p.Y33Y	Synonymous
LOC392617	ENST00000333066	Br03X	g.chr7:1559311C>T	c.1796C>T	p.A599V	Missense
LOC392617	ENST00000333066	Br16X	g.chr7:1557860C>T	c.387C>T	p.R129R	Synonymous
LOC400707	NM_001013673	Br27P	g.chr19:51690107C>T	c.378C>T	p.A126A	Synonymous
LOC441136	NM_001013719	Br27P	g.chr6:27465110G>A	c.498G>A	p.R166R	Synonymous
LOC441233	NM_001013724	Br15X	g.chr7:57282870G>A	c.170G>A	p.R57H	Missense
LOC442213	NM_001013732	Br27P	g.chr6:47954784C>T	c.1704C>T	p.F568F	Synonymous
LOC494115	NM_001008662	Br27P	g.chr1:89126934C>T	c.900C>T	p.D300D	Synonymous
LOC51058	CCDS476.1	Br27P	g.chr1:42985811G>A	c.89G>A	p.G30D	Missense
LOC54103	NM_017439	Br27P	g.chr7:76636587G>A	c.268G>A	p.G90R	Missense
LOC54499	CCDS12511.1	Br13X	g.chr1:162469112A>G	c.123A>G	p.A41A	Synonymous
LOC550631	NM_001017437	Br27P	g.chr22:29094218C>T	c.1261C>T	p.L421L	Synonymous
LOC63928	CCDS10617.1	Br27P	g.chr16:23674524G>A	c.109G>A	p.A37T	Missense
LOC643866	NM_001039771	Br02X	g.chr14:23967927G>A	c.174G>A	p.G58G	Synonymous
LOC648272	ENST00000343945	Br27P	g.chr19:14054377G>A	c.548G>A	p.G183D	Missense
LOC651746	ENST00000296657	BR02X	g.chr5:10702532G>A	c.792G>A	p.P264P	Synonymous
LOC651863	ENST00000333744	Br26X	g.chr5:17688134C>T	c.230C>T	p.A77V	Missense
LOC90379	NM_138353	Br27P	g.chr19:13932775G>A	c.1771G>A	p.D591N	Missense
LOC90826	CCDS3771.1	Br15X	g.chr4:148932669G>A	c.1984G>A	p.D662N	Missense
LOC92154	NM_138383	Br27P	g.chr16:69256483C>T	c.1146C>T	p.G382G	Synonymous
LOC93349	NM_138402	Br27P	g.chr2:231082415G>A	c.812G>A	p.R271H	Missense
LPAL2	ENST00000342479	Br9PT	g.chr6:160858400C>T	c.299C>T	p.T100M	Missense
LPHN1	CCDS12307.1	Br27P	g.chr19:14122991G>A	c.4104G>A	p.R1368R	Synonymous
LPHN2	CCDS689.1	Br15X	g.chr1:82133746A>G	c.1947A>G	p.S649S	Synonymous
LPHN3	NM_015236	Br07X	g.chr4:62604044T>A (homozygous)	c.1684T>A	p.L562M	Missense
LPIN3	NM_022896	Br27P	g.chr20:39414891C>T	c.1497C>T	p.S499S	Synonymous
LPL	CCDS6012.1	Br04X	g.chr8:19853707C>A	c.397C>A	p.Q133K	Missense
LRAT	CCDS3789.1	Br02X	g.chr4:156023524G>C	c.441G>C	p.K147N	Missense

Fig. 10

LRCH1	NM_015116	Br14X	g.chr13:46177267C>G	c.1464C>G	p.A488A	Synonymous
LRFN5	CCDS9678.1	Br26X	g.chr14:41425765G>A	c.187G>A	p.V63I	Missense
LRP1	CCDS8932.1	Br17X	g.chr12:55857636C>T	c.4356C>T	p.D1452D	Synonymous
LRP10	CCDS9578.1	Br27P	g.chr14:22414270G>A	c.382G>A	p.G128S	Missense
LRP1B	CCDS2182.1	Br27P	g.chr2:141405026G>A	c.5291G>A	p.G1764D	Missense
LRP1B	CCDS2182.1	Br27P	g.chr2:141047846C>T	c.9873C>T	p.A3291A	Synonymous
LRP2	CCDS2232.1	Br27P	g.chr2:169928866G>A	c.3046G>A	p.D1016N	Missense
LRP2	CCDS2232.1	Br03x	g.chr2:169926886G>A	c.3254G>A	p.R1085H	Missense
LRP2	CCDS2232.1	Br05X	g.chr2:169886257G>A	c.7747G>A	p.V2583M	Missense
LRP2	CCDS2232.1	Br17X	g.chr2:169870167G>A	c.9148G>A	p.V3050I	Missense
LRRC16	NM_017640	Br27P	g.chr6:25689597C>T	c.2957C>T	p.T986I	Missense
LRRC4	CCDS5799.1	Br27P	g.chr7:127264318C>T	c.327C>T	p.N109N	Synonymous
LRRC4B	ENST00000253728	Br03X	g.chr19:55713328C>T	c.809C>T	p.T270I	Missense
LRRC7	CCDS645.1	Br16X	g.chr1:70214215_70214218delCTCA	c.2061_2064delCTCA	fs	INDEL
LRRC7	CCDS645.1	Br04X	g.chr1:70216830G>C	c.3188G>C	p.S1063T	Missense
LRRIQ1	NM_032165	Br20P	g.chr12:84018016C>T	c.3451C>T	p.R1151C	Missense
LRRK1	NM_024652	Br9PT	g.chr15:99410752C>A	c.1677C>A	p.G559G	Synonymous
LRRK1	NM_024652	Br11P	g.chr15:99424368delG	c.3654delG	fs	INDEL
LRRN1	NM_020873	Br27P	g.chr3:3862281C>T	c.956C>T	p.A319V	Missense
LRRN3	CCDS5754.1	Br26X	g.chr7:110357189C>T	c.410C>T	p.S137F	Missense
LRRN5	CCDS1448.1	Br27P	g.chr1:201319504C>T	c.1274C>T	p.S425F	Missense
LTB4R2	CCDS9624.1	Br14X	g.chr14:23843301G>A	c.1625G>A	p.R542H	Missense
LTBP1	NM_000627	Br27P	g.chr2:33502134G>A	c.3649G>A	p.G1217S	Missense
LTBP3	CCDS8103.1	Br27P	g.chr11:65005753C>T	c.2619C>T	p.D873D	Synonymous
LTBP4	NM_003573	Br03X	g.chr19:45824922G>T	c.4278G>T	p.E1426D	Missense
LTK	CCDS10077.1	Br13X	g.chr15:39590689C>T	c.962C>T	p.A321V	Missense
LUC7L	CCDS10401.1	Br27P	g.chr16:1980777G>A	IVS4+1G>A	Splice Site	Splice Site
LY6K	CCDS6385.1	Br10P	g.chr8:143778899C>T	c.126C>T	p.G42G	Synonymous
LYNX1	ENST00000317543	Br04X	g.chr8:143848208_143848207delCT	c.19_20delCT	fs	INDEL
LYPLA1	CCDS6157.1	Br08X	g.chr8:55127795G>T	c.435G>T	p.W145C	Missense
LYRIC	CCDS6274.1	Br27P	g.chr8:98800512C>T	c.1440C>T	p.T480T	Synonymous
LYST	NM_000081	Br27P	g.chr1:232176318C>T	c.10772C>T	p.A3591V	Missense
LYST	NM_000081	Br27P	g.chr1:232282899G>A	c.4061G>A	p.C1354Y	Missense
LYZL4	CCDS2697.1	Br20P	g.chr3:42413815G>A	c.387G>A	p.R129R	Synonymous
LZTR2	NM_033127	Br27P	g.chr1:174652727G>A	c.1524G>A	p.G508G	Synonymous
M160	CCDS8577.1	Br27P	g.chr12:7413219G>A	IVS15+1G>A	Splice Site	Splice Site
MACF1	CCDS435.1	Br27P	g.chr1:39570389C>T	c.11665C>T	p.L3889L	Synonymous
MACF1	CCDS435.1	Br27P	g.chr1:39583523G>A	c.14076G>A	p.V4692V	Synonymous
MACF1	CCDS435.1	Br17X	g.chr1:39493468C>T	c.5764C>T	p.R1922X	Nonsense
MAEA	NM_001017405	Br27P	g.chr4:1322210C>T	c.1070C>T	p.P357L	Missense
MAGEA4	CCDS14702.1	Br27P	g.chrX:150763365G>A	c.661G>A	p.E221K	Missense
MAGEB10	NM_182506	Br9PT	g.chrX:27599243G>T	c.163G>T	p.D55Y	Missense
MAGEC1	NM_005462	Br02X	g.chrX:140721711A>T (homozygous)	c.3001A>T	p.I1001F	Missense
MAGEH1	CCDS14369.1	Br23X	g.chrX:55361867G>A	c.39G>A	p.A13A	Synonymous
MAGI-3	CCDS859.1	Br27P	g.chr1:113905733G>T	c.2378G>T	p.R793L	Missense
MAK10	CCDS6673.1	Br27P	g.chr9:85854359G>A	c.1249G>A	p.A417T	Missense
MALT1	CCDS11967.1	Br27P	g.chr18:54565995G>A	c.2416G>A	p.E806K	Missense
MAMDC2	CCDS6631.1	Br27P	g.chr9:70070265G>A	c.1957G>A	p.A653T	Missense
MAN1B1	CCDS7029.1	Br27P	g.chr9:137277846G>A	c.1791G>A	p.R597R	Synonymous
MAN2A1	NM_002372	Br27P	g.chr5:109148487G>A	c.1721G>A	p.G574E	Missense

Fig. 10

MAN2B1	NM_000528	Br17X	g.chr19:12619121G>A	c.2849G>A	p.R950H	Missense
MAN2B1	NM_000528	Br27P	g.chr19:12619070G>A	c.2900G>A	p.R967K	Missense
MAP1B	CCDS4012.1	Br27P	g.chr5:71526970G>A	c.2032G>A	p.E678K	Missense
MAP3K11	CCDS8107.1	Br9PT	g.chr11:65123671G>A	c.1976G>A	p.R659H	Missense
MAP3K14	NM_003954	Br27P	g.chr17:40719883C>T	c.850C>T	p.L284L	Synonymous
MAP3K8	CCDS7166.1	Br27P	g.chr10:30788322G>A	c.1159G>A	p.A387T	Missense
MAP3K9	NM_033141	Br14X	g.chr14:70267227G>A	c.2980G>A	p.D994N	Missense
MAP4K4	NM_004834	Br27P	g.chr2:101944678delC	c.2054delC	fs	INDEL
MAP7D3	ENST00000218318	Br27P	g.chrX:135039435C>T	c.796C>T	p.L266L	Synonymous
MARCO	CCDS2124.1	Br27P	g.chr2:119443935C>T	c.215C>T	p.A72V	Missense
MARK3	NM_002376	Br11P	chr14:103039090_103039098delATCCGCA	c.1963_1971delATCCGCAAA	p.I655_K657del	INDEL
MARS	CCDS8942.1	Br27P	g.chr12:56180468G>A	c.1189G>A	p.A397T	Missense
MARS2	NM_138395	Br27P	g.chr2:198396070G>A	c.435G>A	p.V145V	Synonymous
MASS1	NM_032119	Br17X	g.chr5:90172179G>A	c.16640G>A	p.R5547H	Missense
MASS1	NM_032119	Br16X	g.chr5:90017395C>T	c.6317C>T	p.A2106V	Missense
MASS1	NM_032119	Br25X	g.chr5:90048295G>A	c.9440G>A	p.R3147Q	Missense
MAST4	ENST00000261569	Br27P	g.chr5:66494362C>T	c.2799C>T	p.D933D	Synonymous
MATN1	CCDS336.1	Br27P	g.chr1:30863523C>T	c.263C>T	p.T88I	Missense
MBD1	CCDS11941.1	Br15X	g.chr18:46053264G>T	c.1338G>T	p.K446N	Missense
MBNL1	CCDS3163.1	Br27P	g.chr3:153656050C>T	c.983C>T	p.P328L	Missense
MCCC1	CCDS3241.1	Br27P	g.chr3:184223000G>A	c.1776G>A	p.E592E	Synonymous
MCF2L	ENST00000261963	Br27P	g.chr13:112797752G>A	c.184G>A	p.E62K	Missense
MCFD2	NM_139279	Br23X	g.chr2:47047893C>T	c.69C>T	p.G23G	Synonymous
MCM10	CCDS7095.1	Br27P	g.chr10:132546640G>A	c.485G>A	p.R162K	Missense
MCPH1	NM_024596	Br15X	g.chr8:6466515G>A	c.2062G>A	p.G688R	Missense
MDGA1	NM_153487	Br27P	g.chr6:37739725C>T	c.203C>T	p.P68L	Missense
MDGA1	NM_153487	Br27P	g.chr6:37731507C>T	c.526C>T	p.L176L	Synonymous
MDH2	CCDS5581.1	Br27P	g.chr7:75338323G>A	c.649G>A	p.D217N	Missense
MEA	CCDS4879.1	Br27P	g.chr6:43088213C>T	c.531C>T	p.A177A	Synonymous
MED12	NM_005120	Br27P	g.chrX:70140738C>T	c.5968C>T	p.H1990Y	Missense
MEFV	CCDS10498.1	Br02X	g.chr16:3237215G>A	c.1389G>A	p.Q463Q	Synonymous
MEFV	CCDS10498.1	Br20P	g.chr16:3244459C>T	c.610C>T	p.R204C	Missense
MEN1	CCDS8083.1	Br27P	g.chr11:64331062C>T	c.924C>T	p.H308H	Synonymous
METTL5	NM_014168	Br27P	g.chr2:170504002G>A	c.182G>A	p.G61D	Missense
MGAM	NM_004668	Br14X	g.chr7:141211268A>G	c.3775A>G	p.I1259V	Missense
MGC16635	CCDS14097.1	Br27P	g.chr22:49277907C>T	c.871C>T	p.P291S	Missense
MGC19764	NM_144975	Br27P	g.chr17:30616547C>T	c.2203C>T	p.P735S	Missense
MGC20419	CCDS562.1	Br27P	g.chr1:52211229G>A	c.226G>A	p.V76I	Missense
MGC20419	CCDS562.1	Br27P	g.chr1:52211110G>A	c.345G>A	p.A115A	Synonymous
MGC20741	CCDS4861.1	Br27P	g.chr6:41882523G>A	c.177G>A	p.E59E	Synonymous
MGC21830	CCDS10463.1	Br27P	g.chr16:2199693G>A	c.454G>A	p.V152I	Missense
MGC24039	NM_144973	Br27P	g.chr12:31468870G>A	c.2149G>A	p.E717K	Missense
MGC2655	CCDS10491.1	BR15X	g.chr16:3016079G>A	c.235G>A	p.V79I	Missense
MGC26598	CCDS9036.1	Br05x	g.chr12:89850557G>A	c.431G>A	p.G144D	Missense
MGC26818	CCDS44.1	Br27P	g.chr1:25525444A>T	c.482A>T	p.H161L	Missense
MGC27016	CCDS3790.1	Br27P	g.chr4:156076585C>T	c.169C>T	p.P57S	Missense
MGC29814	CCDS11742.1	Br27P	g.chr17:71778171G>A	c.485G>A	p.G162D	Missense
MGC29875	CCDS1493.1	Br27P	g.chr1:206398540G>A	IVS5-1G>A	Splice Site	Splice Site
MGC33367	CCDS10738.1	Br11P	g.chr16:47969907A>G	c.296A>G	p.D99G	Missense
MGC33414	CCDS279.1	Br07X	g.chr1:26378279C>T	c.221C>T	p.P74L	Missense

Fig. 10

MGC33486	CCDS8133.1	Br27P	g.chr11:65819120C>T	c.827C>T	p.P276L	Missense
MGC33889	CCDS14216.1	Br14X	g.chrX:25917303C>T	c.544C>T	p.L182F	Missense
MGC34647	CCDS10895.1	Br27P	g.chr16:69251453G>A	c.591G>A	p.Q197Q	Synonymous
MGC35118	CCDS10046.1	Br15X	g.chr15:36016860G>T	c.286G>T	p.V96F	Missense
MGC35194	CCDS147.1	Br03X	g.chr1:12755075G>A	c.510G>A	p.P170P	Synonymous
MGC35366	CCDS9057.1	Br14X	g.chr12:94853185C>A	c.564C>A	p.Y188X	Nonsense
MGC39581	CCDS12149.1	Br12P	g.chr19:5714257G>T	c.1237G>T	p.V413L	Missense
MGC42174	NM_152383	Br27P	g.chr2:232705195G>A	IVS1+1G>A	Splice Site	Splice Site
MGC4251	CCDS11474.1	Br20P	g.chr17:39447383C>T	c.186C>T	p.A62A	Synonymous
MGC4268	CCDS2152.1	Br23X	g.chr2:128343293C>T	c.689C>T	p.T230I	Missense
MGC45562	CCDS11371.1	Br14X	g.chr17:36071741C>T	c.178C>T	p.R60C	Missense
MGC45780	CCDS6064.1	Br27P	g.chr8:27900983C>T	c.69C>T	p.S23S	Synonymous
MGC47869	CCDS8667.1	Br16X	g.chr12:14867397T>A	c.261T>A	p.C87X	Nonsense
MHC2TA	CCDS10544.1	Br02X	g.chr16:10908851G>C	c.2001G>C	p.L667L	Synonymous
MIA3	ENST00000320831	Br27P	g.chr1:219191115G>A	c.682G>A	p.V228I	Missense
MICAL-L2	CCDS5324.1	Br27P	g.chr7:1251179C>T	c.2174C>T	p.T725I	Missense
MINK1	NM_170663	Br27P	g.chr17:4734784C>T	c.1538C>T	p.P513L	Missense
MINK1	NM_170663	Br27P	g.chr17:4735122C>T	c.1661C>T	p.A554V	Missense
MIPEP	CCDS9303.1	Br27P	g.chr13:23232352G>A	c.1853G>A	p.W618X	Nonsense
MIR16	CCDS10578.1	BR27P	g.chr16:19423783C>T	c.769C>T	p.L257F	Missense
MKI67	CCDS7659.1	Br27P	g.chr10:129803650C>T	c.1012C>T	p.P338S	Missense
MLL	NM_005933	Br27P	g.chr11:117877759G>A	c.6473G>A	p.G2158D	Missense
MLL3	CCDS5931.1	Br08X	g.chr7:151238619G>A	c.13041G>A	p.P4347P	Synonymous
MLL4	NM_014727	Br27P	g.chr19:40909940C>T	c.4047C>T	p.D1349D	Synonymous
MLL4	NM_014727	Br27P	g.chr19:40903018G>A	c.929G>A	p.R310K	Missense
MLLT4	CCDS5303.1	Br08X	g.chr6:168130361G>A (homozygous)	c.1746G>A	p.E582E	Synonymous
MLLT7	NM_005938	Br10P	g.chrX:70103911G>A	c.810G>A	p.R270R	Synonymous
MME	CCDS3172.1	Br17X	g.chr3:156342495T>A	c.971T>A	p.L324X	Nonsense
MMP10	CCDS8321.1	Br27P	g.chr11:102146779G>A	c.1386G>A	p.R462R	Synonymous
MMP16	CCDS6246.1	Br27P	g.chr8:89155969G>A	c.1202G>A	p.G401E	Missense
MOCS1	CCDS4845.1	Br27P	g.chr6:39985589C>T	c.1070C>T	p.A357V	Missense
MON2	NM_015026	Br14X	g.chr12:61233048C>T	c.3037C>T	p.H1013Y	Missense
MON2	NM_015026	Br27P	g.chr12:61147262G>A	c.8G>A	p.G3D	Missense
MPDU1	CCDS11115.1	Br17X	g.chr17:7431513C>T	c.664C>T	p.L222F	Missense
MPDZ	NM_003829	Br27P	g.chr9:13182159G>A	c.1939G>A	p.D647N	Missense
MPP1	CCDS14762.1	Br27P	g.chrX:153573680G>A	c.1048G>A	p.E350K	Missense
MPZ	CCDS1229.1	Br23X	g.chr1:158089246A>G	c.560A>G	p.Y187C	Missense
MRC2	CCDS11634.1	Br27P	g.chr17:58121092G>A	c.3679G>A	p.G1227R	Missense
MRGX1	CCDS7846.1	Br13X	g.chr11:18912677C>T	c.231C>T	p.S77S	Synonymous
MRPL13	CCDS6332.1	Br05X	g.chr8:121524697C>G	c.60C>G	p.L20L	Synonymous
MRPL16	CCDS7976.1	Br16X	g.chr11:59330577G>A	c.575G>A	p.R192H	Missense
MRPL37	ENST00000329505	Br07X	g.chr18:54508739C>T	c.160C>T	p.P54S	Missense
MRPL44	CCDS2459.1	Br27P	g.chr2:224654081C>T	c.752C>T	p.S251L	Missense
MRPL46	CCDS10341.1	Br27P	g.chr15:86803844G>A	UTR+4G>A	3'UTR	3'UTR
MRPL55	CCDS1567.1	Br11P	g.chr1:224602692C>T	c.5C>T	p.A2V	Missense
MRPS5	CCDS2010.1	Br27P	g.chr2:95175109C>T	c.1160C>T	p.P387L	Missense
MRPS7	CCDS11718.1	Br27P	g.chr17:70770272G>A	c.183G>A	p.E61E	Synonymous
MRVI1	NM_006069	Br27P	g.chr11:10630214G>A	c.155G>A	p.C52Y	Missense
MS4A7	CCDS7985.1	Br27P	ır11:59916824_59916835delAACAACCCTC	c.637_648delAACAACCCTGGG	p.N213_G216del	INDEL
MSI2	CCDS11596.1	Br27P	g.chr17:52833756G>A	c.330G>A	p.K110K	Synonymous

MSL2L1	NM_018133	Br04X	g.chr3:137353846A>G	c.575A>G	p.N192S	Missense
MSRB3	CCDS8973.1	Br23X	g.chr12:64143316G>A	c.526G>A	p.E176K	Missense
MTA1	NM_004689	Br27P	g.chr14:105001442G>A	c.1105G>A	p.V369I	Missense
MTHFD2L	NM_001004346	Br03X	g.chr4:75430698G>T	c.430G>T	p.G144X	Nonsense
MTNR1B	CCDS8290.1	Br9PT	g.chr11:92354586C>T	c.549C>T	p.Y183Y	Synonymous
MTP	CCDS3651.1	Br02X	g.chr4:100885100G>A	c.1362G>A	p.K454K	Synonymous
MTR	CCDS1614.1	Br27P	g.chr1:233341895C>T	c.1729C>T	p.L577F	Missense
MTX2	CCDS2272.1	Br05X	g.chr2:177019633T>A	c.515T>A	p.I172N	Missense
MUC15	CCDS7859.1	Br15X	g.chr11:26541255C>T	c.828C>T	p.D276D	Synonymous
MUC16	NM_024690	Br27P	g.chr19:8951078G>A	c.1737G>A	p.G579G	Synonymous
MUC16	NM_024690	Br27P	g.chr19:8910153G>A	c.32478G>A	p.T10826T	Synonymous
MUC16	NM_024690	Br15X	g.chr19:8908401T>C	c.34230T>C	p.S11410S	Synonymous
MUC16	NM_024690	Br27P	g.chr19:8948685C>T	c.4130C>T	p.T1377I	Missense
MUC16	NM_024690	Br26X	g.chr19:8947573A>G	c.5242A>G	p.S1748G	Missense
MUC5AC	ENST00000349637	Br27P	g.chr11:1229470C>T	c.14619C>T	p.T4873T	Synonymous
MUC7	CCDS3541.1	Br14X	g.chr4:71527580C>A	c.359C>A	p.S120Y	Missense
MVP	CCDS10656.1	Br27P	g.chr16:29755686C>T	c.815C>T	p.P272L	Missense
MYBPC3	NM_000256	Br27P	g.chr11:47321680G>A	c.1162G>A	p.A388T	Missense
MYBPHL	NM_001010985	Br14X	g.chr1:109549781G>A	c.1048G>A	p.V350M	Missense
MYF6	CCDS9019.1	Br27P	g.chr12:79604235C>T	c.269C>T	p.A90V	Missense
MYH14	NM_024729	Br15X	g.chr19:55475105G>A	IVS27-1G>A	Splice Site	Splice Site
MYH15	ENST00000273353	Br27P	g.chr3:109707262G>A	c.253G>A	p.E85K	Missense
MYH15	ENST00000273353	Br13X	g.chr3:109639116C>T	c.3256C>T	p.R1086X	Nonsense
MYH3	CCDS11157.1	Br27P	g.chr17:10477729T>C	c.4551T>C	p.I1517I	Synonymous
MYH4	CCDS11154.1	Br27P	g.chr17:10291219G>A	c.5005G>A	p.D1669N	Missense
MYO15A	NM_016239	Br27P	g.chr17:17999185C>T	c.8261C>T	p.T2754M	Missense
MYO18B	NM_032608	Br27P	g.chr22:24518509C>T	c.2412C>T	p.A804A	Synonymous
MYO18B	NM_032608	Br27P	g.chr22:24596841C>T	c.4212C>T	p.L1404L	Synonymous
MYO18B	NM_032608	Br27P	g.chr22:24747854C>T	c.7360C>T	p.P2454S	Missense
MYO1B	CCDS2311.1	Br08X	g.chr2:192077579G>A	c.1678G>A	p.A560T	Missense
MYO1B	CCDS2311.1	Br17X	g.chr2:192104887G>A	c.2971G>A	p.V991I	Missense
MYO1D	NM_015194	Br03X	g.chr17:28072304G>A	c.1763G>A	p.R588H	Missense
MYO1E	NM_004998	Br27P	g.chr15:57307050G>C	c.542G>C	p.G181A	Missense
MYO3A	CCDS7148.1	Br14X	g.chr10:26476369delT (homozygous)	c.2510delT	fs	INDEL
MYO3B	NM_138995	Br17X	g.chr2:171074457G>A	c.1736G>A	p.R579K	Missense
MYO5A	NM_000259	Br27P	g.chr15:50439471C>T	c.3409C>T	p.P1137S	Missense
MYO5C	NM_018728	Br27P	g.chr15:50275882A>T	c.4911A>T	p.A1637A	Synonymous
MYO5C	NM_018728	Br27P	g.chr15:50355051G>A	c.606G>A	p.E202E	Synonymous
MYO5C	NM_018728	Br23X	g.chr15:50352205G>T	c.614G>T	p.G205V	Missense
MYO9B	NM_004145	Br27P	g.chr19:17144142C>T	IVS10-4C>T	Splice Site	Splice Site
MYOCD	CCDS11163.1	Br16X	g.chr17:12590006G>A	c.1017G>A	p.T339T	Synonymous
MYOCD	CCDS11163.1	Br27P	g.chr17:12607551C>T	c.2682C>T	p.D894D	Synonymous
MYOM1	NM_003803	Br27P	g.chr18:3178881G>A	c.636G>A	p.R212R	Synonymous
MYOM2	CCDS5957.1	Br27P	g.chr8:1993210G>A	c.465G>A	p.E155E	Synonymous
MYR8	NM_015011	Br04X	g.chr13:108273608C>A	c.1012C>A	p.P338T	Missense
MYRIP	CCDS2689.1	Br17X	g.chr3:40198763C>T	c.922C>T	p.P308S	Missense
MYST3	CCDS6124.1	Br27P	g.chr8:41931994C>T	c.1575C>T	p.S525S	Synonymous
MYT1L	NM_015025	Br27P	g.chr2:1866304C>T	c.2079C>T	p.Y693Y	Synonymous
NAGA	CCDS14030.1	Br27P	g.chr22:40787285C>T	c.526C>T	p.L176L	Synonymous
NALP1	NM_014922	Br27P	g.chr17:5403560C>T	c.1180C>T	p.P394S	Missense

Fig. 10

NALP11	CCDS12935.1	Br27P	g.chr19:61011060G>A	c.1974G>A	p.E658E	Synonymous
NALP7	CCDS12912.1	Br20P	g.chr19:60126916G>A	UTR+4G>A	3'UTR	3'UTR
NAPSB	ENST00000253720	Br13X	g.chr19:55528981G>A (homozygous)	c.1225G>A	p.G409R	Missense
NARG1L	CCDS9379.1	Br27P	g.chr13:40839646C>T	c.1611C>T	p.A537A	Synonymous
NAV1	CCDS1414.1	Br27P	g.chr1:198481871C>T	c.1440C>T	p.A480A	Synonymous
NAV1	CCDS1414.1	Br27P	g.chr1:198350039G>A	c.586G>A	p.D196N	Missense
NCBP1	CCDS6728.1	Br27P	g.chr9:97497920G>A	c.1371G>A	p.M457I	Missense
NCKAP1L	NM_005337	Br27P	g.chr12:53189757G>A	c.544G>A	p.E182K	Missense
NCOA5	CCDS13392.1	Br27P	g.chr20:44132330G>A	c.291G>A	p.R97R	Synonymous
NCOA6	CCDS13241.1	Br27P	g.chr20:32809387G>A	c.825G>A	p.Q275Q	Synonymous
NDUFA11	CCDS12155.1	Br27P	g.chr19:5847519C>T	c.258C>T	p.D86D	Synonymous
NDUFB2	CCDS5862.1	Br17X	g.chr7:139855878C>T	c.127C>T	p.R43W	Missense
NDUFS6	CCDS3866.1	Br04X	g.chr5:1854528C>A	UTR-4C>A	5'UTR	5'UTR
NEB	NM_004543	Br27P	g.chr2:152347499C>T	c.5094C>T	p.S1698S	Synonymous
NEIL3	CCDS3828.1	Br16X	g.chr4:178658657G>T	c.1701G>T	p.K567N	Missense
NEUROG2	CCDS3698.1	BR27P	g.chr4:113793867C>T	c.369C>T	p.N123N	Synonymous
NF1	CCDS11264.1	Br23X	g.chr17:26570198T>G (homozygous)	c.1577T>G	p.I526S	Missense
NF1	CCDS11264.1	Br27P	g.chr17:26677066C>T	c.4875C>T	p.T1625T	Synonymous
NF1	CCDS11264.1	Br16X	g.chr17:26678862C>T	c.5425C>T	p.R1809C	Missense
NF1	CCDS11264.1	Br04X	g.chr17:26707634C>G (homozygous)	c.7583C>G	p.S2528X	Nonsense
NFATC3	CCDS10862.1	Br27P	g.chr16:66749293G>A	c.1422G>A	p.K474K	Synonymous
NFATC4	CCDS9629.1	Br27P	g.chr14:23909514G>A	c.1070G>A	p.G357E	Missense
NGEF	CCDS2500.1	Br20P	g.chr2:233660448C>T	c.364C>T	p.P122S	Missense
NGEF	CCDS2500.1	Br9PT	g.chr2:233610551G>A	c.776G>A	p.R259Q	Missense
NHS	CCDS14181.1	Br29P	g.chrX:17509864C>T	c.4516C>T	p.R1506C	Missense
NIF3L1BP1	CCDS2900.1	Br27P	g.chr3:63799130C>T	c.223C>T	p.L75F	Missense
NIN	NM_182944	Br14X	g.chr14:50309444A>G	c.786A>G	p.R262R	Synonymous
NISCH	NM_007184	Br15X	g.chr3:52497091G>T	c.2543G>T	p.C848F	Missense
NKG7	CCDS12830.1	Br27P	g.chr19:56567585C>T	c.17C>T	p.S6F	Missense
NKRF	NM_017544	Br13X	g.chrX:118506348C>A	c.922C>A	p.P308T	Missense
NKX2-5	CCDS4387.1	Br27P	g.chr5:172594371G>A	c.322G>A	p.A108T	Missense
NLGN1	CCDS3222.1	Br27P	g.chr3:174805443C>T	c.353C>T	p.P118L	Missense
NLGN2	CCDS11103.1	Br02X	g.chr17:7261063G>A (homozygous)	c.1729G>A	p.E577K	Missense
NLN	CCDS3989.1	Br27P	g.chr5:65124210G>A	c.1499G>A	p.G500D	Missense
NM_001080470.1	ENST00000271263	Br27P	g.chr1:119877458G>A	c.605G>A	p.G202D	Missense
NMBR	CCDS5196.1	Br27P	g.chr6:142451323G>A	c.166G>A	p.V56M	Missense
NMUR1	CCDS2486.1	Br20P	g.chr2:232219206C>T	c.31C>T	p.L11F	Missense
NNT	CCDS3949.1	Br27P	g.chr5:43685112G>A	c.1551G>A	p.W517X	Nonsense
NOD3	NM_178844	Br27P	g.chr16:3553329G>A	c.1610G>A	p.G537D	Missense
NOR1	CCDS409.1	Br27P	g.chr1:36573473C>T	c.274C>T	p.L92L	Synonymous
NOS3	CCDS5912.1	Br27P	g.chr7:150141911C>T	c.2011C>T	p.L671L	Synonymous
NOTCH1	NM_017617	Br07X	g.chr9:136679184A>T	c.3149A>T	p.Q1050L	Missense
NOTCH1	NM_017617	Br06X	g.chr9:136673514G>T	c.5127G>T	p.S1709S	Synonymous
NOTCH2	CCDS908.1	Br27P	g.chr1:120218353G>T	c.1801G>T	p.G601C	Missense
NOTCH2	CCDS908.1	Br27P	g.chr1:120176905C>T	c.5209C>T	p.L1737L	Synonymous
NOTCH3	CCDS12326.1	Br27P	g.chr19:15151091G>A	c.3463G>A	p.V1155M	Missense
NOTCH4	NM_004557	Br27P	g.chr6:32298278C>T	c.439C>T	p.P147S	Missense
NOX4	CCDS8285.1	Br27P	g.chr11:88817033C>T	c.365C>T	p.A122V	Missense
NP_001073909.1	ENST00000327928	Br27P	g.chr3:162703860G>A	c.862G>A	p.D288N	Missense
NP_001073931.1	ENST00000341689	Br27P	g.chr15:70486147G>A	IVS3+1G>A	Splice Site	Splice Site

Fig. 10

NP_001073940.1	ENST00000292357	Br07X	g.chr1:153695670C>T	c.2245C>T	p.P749S	Missense
NP_001073948.1	ENST00000296794	Br27P	g.chr5:73108187C>T	c.750C>T	p.T250T	Synonymous
NP_001073961.1	ENST00000219301	Br27P	g.chr16:56872074G>A	c.743G>A	p.C248Y	Missense
NP_001073971.1	ENST00000266524	Br15X	g.chr12:31180262G>A	c.2293G>A	p.V765I	Missense
NP_001074294.1	ENST00000342607	Br27P	g.chr12:120613521C>T	c.96C>T	p.I32I	Synonymous
NPC1L1	CCDS5491.1	Br9PT	g.chr7:44349148C>T	c.1801C>T	p.R601X	Nonsense
NPL	CCDS1350.1	Br27P	g.chr1:179519388G>A	c.513G>A	p.G171G	Synonymous
NPLOC4	NM_017921	Br27P	g.chr17:77186221C>T	c.505C>T	p.R169W	Missense
NPPA	CCDS139.1	Br27P	g.chr1:11841655C>T	c.231C>T	p.L77L	Synonymous
NPR3	NM_000908	Br27P	g.chr5:32774866G>A	c.1032G>A	p.E344E	Synonymous
NPTXR	NM_014293	Br27P	g.chr22:37543669G>A	c.1197G>A	p.G399G	Synonymous
NPTXR	NM_014293	Br27P	g.chr22:37543668G>A	c.1198G>A	p.E400K	Missense
NR_002781.1	ENST00000246203	Br27P	g.chr20:30241272G>A	c.462G>A	p.W154X	Nonsense
NR2E1	CCDS5063.1	Br27P	g.chr6:108604438C>T	c.298C>T	p.R100C	Missense
NRAP	CCDS7578.1	Br12P	g.chr10:115413102G>A	c.166G>A	p.A56T	Missense
NRBP2	NM_178564	Br26X	g.chr8:144992873C>T	c.78C>T	p.R26R	Synonymous
NRK	NM_198465	Br20P	g.chrX:104996069C>T	c.4120C>T	p.R1374X	Nonsense
NRP1	CCDS7177.1	Br27P	g.chr10:33542636G>A	c.1298G>A	p.G433E	Missense
NRP1	CCDS7177.1	Br27P	g.chr10:33592695G>A	c.543G>A	p.K181K	Synonymous
NRP2	CCDS2364.1	Br27P	g.chr2:206418180G>A	c.1050G>A	p.R350R	Synonymous
NRXN2	CCDS8077.1	Br27P	g.chr11:64184928C>T	c.2058C>T	p.C686C	Synonymous
NS3TP2	CCDS4136.1	Br27P	g.chr5:125850557C>T	c.1152C>T	p.T384T	Synonymous
NT5E	CCDS5002.1	Br27P	g.chr6:86251702G>A	c.782G>A	p.G261E	Missense
NTN2L	CCDS10469.1	BR27P	g.chr16:2463320G>A	c.1318G>A	p.D440N	Missense
NTRK3	CCDS10340.1	Br27P	g.chr15:86472961G>A	c.1213G>A	p.D405N	Missense
NUAK1	NM_014840	Br08X	g.chr12:104963998C>T	c.1035C>T	p.T345T	Synonymous
NUP160	NM_015231	Br17X	g.chr11:47776510G>A	c.2977G>A	p.D993N	Missense
NUP188	NM_015354	Br04X	g.chr9:128484667T>A	c.5205T>A	p.P1735P	Synonymous
NUP205	NM_015135	Br27P	g.chr7:134742962G>A	c.2364G>A	p.V788V	Synonymous
NUP210L	NM_207308	Br27P	g.chr1:150885659G>A	c.1025G>A	p.S342N	Missense
NUP98	CCDS7746.1	Br27P	1r11:3701100_3701087delCCATTGTTGCA	c.2009_2022delCCATTGTTGCATTA	fs	INDEL
NURIT	CCDS9399.1	Br27P	g.chr13:45174589G>A	c.63G>A	p.W21X	Nonsense
NXF3	CCDS14503.1	Br27P	g.chrX:102144135C>T	c.633C>T	p.N211N	Synonymous
NXF5	CCDS14491.1	Br15X	g.chrX:100902882G>A (homozygous)	c.149G>A	p.R50Q	Missense
NXPH1	NM_152745	Br23X	g.chr7:8564335C>T	c.512C>T	p.T171I	Missense
OAS3	NM_006187	Br02X	g.chr12:111870246G>A	c.3218G>A	p.R1073Q	Missense
OBSCN	CCDS1570.1	Br27P	g.chr1:224782705G>A	c.10020G>A	p.A3340A	Synonymous
ODZ2	ENST00000314238	Br27P	g.chr5:167559701C>T	c.1554C>T	p.L518L	Synonymous
ODZ2	ENST00000314238	Br27P	g.chr5:167484534G>A	c.220G>A	p.V74I	Missense
ODZ2	ENST00000314238	Br08X	g.chr5:167606953C>A	c.4565C>A	p.T1522N	Missense
ODZ2	ENST00000314238	Br27P	g.chr5:167607933G>C	c.5545G>C	p.D1849H	Missense
OLIG2	CCDS13620.1	Br27P	g.chr21:33321336_33321338dupAGC	c.296_298dupAGC	p.Q100del	INDEL
OPRD1	CCDS329.1	Br20P	g.chr1:29006099C>T	c.245C>T	p.T82M	Missense
OPRL1	CCDS13556.1	Br05X	g.chr20:62200248C>T	c.765C>T	p.D255D	Synonymous
OR10G3	NM_001005465	Br27P	g.chr14:21107895C>T	c.821C>T	p.A274V	Missense
OR10G4	NM_001004462	Br27P	g.chr11:123392034G>A	c.543G>A	p.P181P	Synonymous
OR10H2	CCDS12333.1	Br27P	g.chr19:15700209G>A	c.356G>A	p.G119D	Missense
OR10P1	NM_206899	Br27P	g.chr12:54317845C>T	c.903C>T	p.A301A	Synonymous
OR10T2	NM_001004475	Br25X	g.chr1:155182089C>A	c.241C>A	p.Q81K	Missense
OR13J1	NM_001004487	Br04X	g.chr9:35860164C>T	c.235C>T	p.P79S	Missense

Fig. 10

OR1L8	NM_001004454	Br04X	g.chr9:122410060T>G	c.251T>G	p.M84R	Missense
OR2A12	NM_001004135	Br14X	g.chr7:143230447C>T	c.599C>T	p.A200V	Missense
OR2AG1	NM_001004489	Br02X	g.chr11:6763740G>A	c.896G>A	p.R299Q	Missense
OR2AG2	NM_001004490	Br27P	g.chr11:6746632C>T	c.133C>T	p.L45L	Synonymous
OR2D2	NM_003700	Br26X	g.chr11:6869599G>A	c.709G>A	p.A237T	Missense
OR2G3	NM_001001914	Br05X	g.chr1:244094933G>T	c.5G>T	p.G2V	Missense
OR2L13	CCDS1637.1	Br03x	g.chr1:244589038C>T	c.320C>T	p.A107V	Missense
OR2L13	CCDS1637.1	Br17X	g.chr1:244589283A>G	c.565A>G	p.T189A	Missense
OR2L2	NM_001004686	Br17X	g.chr1:244527924C>A	c.314C>A	p.T105N	Missense
OR2S2	CCDS6596.1	Br27P	g.chr9:35947789G>A	c.277G>A	p.A93T	Missense
OR2T4	NM_001004696	Br20P	g.chr1:244851039C>G	c.116C>G	p.T39S	Missense
OR2V2	CCDS4461.1	Br27P	g.chr5:180514912G>A	c.364G>A	p.D122N	Missense
OR2Y1	NM_001001657	Br27P	g.chr5:180099334G>A	c.331G>A	p.E111K	Missense
OR2Z1	NM_001004699	Br27P	g.chr19:8702563C>T	c.173C>T	p.P58L	Missense
OR3A1	CCDS11023.1	Br17X	g.chr17:3142552G>A	c.75G>A	p.G25G	Synonymous
OR4A5	NM_001005272	Br12P	g.chr11:51268333C>A	c.639C>A	p.I213I	Synonymous
OR4L1	NM_001004717	Br07X	g.chr14:19598334C>T (homozygous)	c.291C>T	p.C97C	Synonymous
OR4N2	NM_001004723	Br27P	g.chr14:19365489C>T	c.42C>T	p.L14L	Synonymous
OR4P4	NM_001004124	Br9PT	g.chr11:55162451delG	c.42delG	fs	INDEL
OR52A5	NM_001005160	Br05x	g.chr11:5109517delT	c.932delT	fs	INDEL
OR52B2	NM_001004052	Br17X	g.chr11:6147331C>T	c.802C>T	p.R268C	Missense
OR52D1	NM_001005163	Br27P	g.chr11:5466584G>A	c.72G>A	p.E24E	Synonymous
OR52E6	NM_001005167	Br27P	g.chr11:5819151G>A	c.553G>A	p.G185S	Missense
OR52I1	NM_001005169	Br27P	g.chr11:4572398A>G	c.554A>G	p.H185R	Missense
OR52N4	NM_001005175	Br12P	g.chr11:5732981G>T	c.435G>T	p.K145N	Missense
OR56A4	NM_001005179	Br13X	g.chr11:5980580C>T	c.375C>T	p.D125D	Synonymous
OR56B1	NM_001005180	Br27P	g.chr11:5714584C>T	c.262C>T	p.P88S	Missense
OR56B4	NM_001005181	Br27P	g.chr11:6086389G>A	c.805G>A	p.A269T	Missense
OR5A1	NM_001004728	Br27P	g.chr11:58967301C>T	c.84C>T	p.A28A	Synonymous
OR5AP2	NM_001002925	Br27P	g.chr11:56166004C>T	c.488C>T	p.A163V	Missense
OR5AU1	NM_001004731	Br27P	g.chr14:20693728G>A	c.297G>A	p.L99L	Synonymous
OR5B17	ENST00000357377	Br27P	g.chr11:57890665G>A	c.148G>A	p.D50N	Missense
OR5BF1	NM_001001918	Br07X	g.chr1:244838450G>A	c.333G>A	p.L111L	Synonymous
OR5D14	NM_001004735	Br26X	g.chr11:55319814T>C	c.207T>C	p.S69S	Synonymous
OR5K4	NM_001005517	Br17X	g.chr3:99556305C>T	c.918C>T	p.N306N	Synonymous
OR5M1	ENST00000303005	Br29P	g.chr11:56006764G>A	c.549G>A	p.P183P	Synonymous
OR5M8	NM_001005282	Br07x	g.chr11:56014968C>T	c.455C>T	p.A152V	Missense
OR5M9	NM_001004743	Br15X	g.chr11:55987439G>A	c.15G>A	p.T5T	Synonymous
OR6C74	NM_001005490	Br17X	g.chr12:53927523G>A	c.185G>A	p.R62Q	Missense
OR6K3	NM_001005327	Br14X	g.chr1:155500526C>T	c.501C>T	p.F167F	Synonymous
OR6W1P	ENST00000340373	Br27P	g.chr7:142276589G>A	c.774G>A	p.R258R	Synonymous
OR7A5	CCDS12318.1	Br27P	g.chr19:14799350A>T	c.704A>T	p.Y235F	Missense
OR7D4	NM_001005191	Br27P	g.chr19:9185711C>T	c.803C>T	p.S268F	Missense
OR8D2	NM_001002918	Br11P	g.chr11:123694585C>G	c.719C>G	p.T240S	Missense
OR8K3	NM_001005202	Br27P	g.chr11:55843094G>A	c.736G>A	p.V246M	Missense
OR9K2	NM_001005243	Br27P	g.chr12:53810025G>A	c.206G>A	p.G69E	Missense
OR9Q2	NM_001005283	Br27P	g.chr11:57714754C>T	c.216C>T	p.C72C	Synonymous
OSAP	NM_032623	Br27P	g.chr4:140545427G>A	c.654G>A	p.E218E	Synonymous
OSBPL2	CCDS13494.1	Br13X	g.chr20:60292518C>T	c.858C>T	p.I286I	Synonymous
OSBPL5	NM_145638	Br20P	g.chr11:30677734C>T	c.2215C>T	p.R739W	Missense

Fig. 10

OSBPL9	CCDS558.1	Br27P	g.chr1:51939596C>T	c.380C>T	p.S127F	Missense
OSR2	NM_053001	Br10P	g.chr8:100030880A>G	c.524A>G	p.K175R	Missense
OSTM1	CCDS5062.1	Br27P	g.chr6:108477150C>T	c.949C>T	p.P317S	Missense
OTOF	CCDS1725.1	Br07X	g.chr2:26629590C>T	c.768C>T	p.V256V	Synonymous
OTOG	ENST00000342528	Br27P	g.chr11:17564682G>A	c.65G>A	p.G22D	Missense
OTOR	CCDS13124.1	Br27P	g.chr20:166786467T>G	c.354T>G	p.V118V	Synonymous
OTUD1	ENST00000298035	Br03X	g.chr10:23769412G>A	c.234G>A	p.R78R	Synonymous
OVCH1	NM_183378	Br27P	g.chr12:29495725C>T	c.2575C>T	p.P859S	Missense
OVCH1	NM_183378	Br20P	g.chr12:29495715G>A	c.2585G>A	p.R862Q	Missense
OVCH1	NM_183378	Br27P	g.chr12:29539614C>T	c.325C>T	p.L109F	Missense
OVOL1	CCDS8112.1	Br27P	g.chr11:65318668C>T	c.402C>T	p.N134N	Synonymous
OXA1L	CCDS9573.1	Br27P	g.chr14:22308982G>A	c.762G>A	p.E254E	Synonymous
p44S10	CCDS2901.1	Br03X	g.chr3:63983090G>A	c.295G>A	p.E99K	Missense
PADI2	CCDS177.1	Br27P	g.chr1:17174839G>A	c.298G>A	p.E100K	Missense
PAPLN	NM_173462	Br27P	g.chr14:72791442G>A	c.1509G>A	p.V503V	Synonymous
PAPOLG	CCDS1863.1	Br15X	g.chr2:60926307G>A	c.1297G>A	p.V433I	Missense
PAPPA2	NM_020318	Br25X	g.chr1:173257746G>A	c.628G>A	p.G210R	Missense
PARC	CCDS4890.1	Br27P	g.chr6:43260574G>A	c.548G>A	p.R183H	Missense
PARP11	CCDS8523.1	Br17X	g.chr12:3801413_3801410delTCAA	c.414_417delTCAA	fs	INDEL
PAX9	CCDS9662.1	Br9PT	g.chr14:36201924C>T	c.76C>T	p.R26W	Missense
PCAF	CCDS2634.1	Br27P	g.chr3:20139274G>A	c.1387G>A	p.D463N	Missense
PCDH11X	CCDS14463.1	BR02X	g.chrX:90944096C>A	UTR+1C>A	3'UTR	3'UTR
PCDHA10	NM_031859	Br26X	g.chr5:140217718G>A (homozygous)	c.1901G>A	p.R634H	Missense
PCDHA13	CCDS4240.1	Br04X	g.chr5:140242246G>C	c.209G>C	p.R70T	Missense
PCDHB7	CCDS4249.1	Br04X	g.chr5:140533518A>G	c.918A>G	p.Q306Q	Synonymous
PCDHGA4	NM_032053	Br27P	g.chr5:140716538G>A	c.1587G>A	p.Q529Q	Synonymous
PCDHGA4	NM_032053	Br27P	g.chr5:140716717C>T	c.1766C>T	p.T589I	Missense
PCDHGA9	NM_032089	Br27P	g.chr5:140764920C>T	c.2217C>T	p.H739H	Synonymous
PCDHGB7	NM_032101	Br23X	g.chr5:140779284C>T	c.1674C>T	p.N558N	Synonymous
PCDHGC4	CCDS4260.1	Br27P	g.chr5:140791568C>T	c.1058C>T	p.A353V	Missense
PCDHGC4	CCDS4261.1	Br27P	g.chr5:140837868C>T	c.2001C>T	p.T667T	Synonymous
PCDHGC4	CCDS4263.1	Br27P	g.chr5:140849287G>A	c.296G>A	p.S99N	Missense
PCGF2	NM_007144	Br08X	g.chr17:34149384C>T	c.190C>T	p.R64W	Missense
PCNXL2	ENST00000344698	Br27P	g.chr1:229428818C>T	c.1951C>T	p.P651S	Missense
PCSK2	CCDS13125.1	Br08X	g.chr20:17382530C>T	c.1029C>T	p.Y343Y	Synonymous
PCSK2	CCDS13125.1	Br02X	g.chr20:17365459A>T	c.816A>T	p.T272T	Synonymous
PCYOX1	CCDS1902.1	Br27P	g.chr2:70397047C>T	c.100C>T	p.P34S	Missense
PDCD10	CCDS3202.1	Br27P	g.chr3:168888183G>A	c.396G>A	p.K132K	Synonymous
PDCD11	NM_014976	Br03X	g.chr10:105194320C>T (homozygous)	c.5335C>T	p.R1779W	Missense
PDE1C	CCDS5437.1	Br02X	g.chr7:31692010T>G	c.264T>G	p.D88E	Missense
PDE4A	CCDS12238.1	Br27P	g.chr19:10439192C>T	c.1839C>T	p.H613H	Synonymous
PDE4B	CCDS632.1	Br27P	g.chr1:66435499C>T	c.516C>T	p.V172V	Synonymous
PDE4C	CCDS12373.1	Br27P	g.chr19:18194052G>A	c.324G>A	p.Q108Q	Synonymous
PDE4D	NM_006203	Br27P	g.chr5:58320177G>A	IVS10-1G>A	Splice Site	Splice Site
PDGFB	CCDS13987.1	Br02X	g.chr22:37946297C>A (homozygous)	c.657C>A	p.P219P	Synonymous
PDGFRA	CCDS3495.1	Br15X	g.chr4:55002246T>C	c.3149T>C	p.I1050T	Missense
PDGFRB	CCDS4303.1	Br27P	g.chr5:149492589C>T	c.1044C>T	p.V348V	Synonymous
PDHA2	CCDS3644.1	Br06X	g.chr4:97119398G>A	c.919G>A	p.E307K	Missense
PDHB	CCDS2890.1	Br27P	g.chr3:58394545C>T	c.32C>T	p.P11L	Missense
PDIA2	NM_006849	Br23X	g.chr16:275424C>T	c.907C>T	p.R303C	Missense

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PDK1	CCDS2250.1	Br27P	g.chr2:173261008C>T	c.894C>T	p.Y298Y	Synonymous
PDLIM4	CCDS4152.1	Br27P	g.chr5:131634592G>A	c.413G>A	p.G138E	Missense
PDZD2	NM_178140	Br27P	g.chr5:32124299C>G	c.4988C>G	p.S1663C	Missense
PDZD2	NM_178140	Br08X	g.chr5:32126540T>G	c.7229T>G	p.L2410R	Missense
PDZD7	NM_024895	Br27P	g.chr10:102773736C>T	c.306C>T	p.R102R	Synonymous
PEG10	ENST00000362013	Br27P	g.chr7:93938352G>A	c.884G>A	p.R295H	Missense
PELP1	NM_014389	Br27P	g.chr17:4523466G>A	c.1673G>A	p.G558D	Missense
PENK	CCDS6168.1	Br27P	g.chr8:57521016G>A	c.51G>A	p.G17G	Synonymous
PERQ1	NM_022574	Br27P	g.chr7:99925593G>A	c.1628G>A	p.C543Y	Missense
PEX1	CCDS5627.1	Br12P	g.chr7:91793015T>C	c.302T>C	p.V101A	Missense
PEX10	CCDS41.1	Br27P	g.chr1:2372259G>A	c.394G>A	p.G132R	Missense
PFAS	CCDS11136.1	Br27P	g.chr17:8107654C>T	c.1604C>T	p.A535V	Missense
PFAS	CCDS11136.1	Br27P	g.chr17:8099715G>A	c.555G>A	p.E185E	Synonymous
PFKFB3	CCDS7078.1	Br27P	g.chr10:6297219G>A	c.232G>A	p.A78T	Missense
PGAP1	CCDS2318.1	Br27P	g.chr2:197603144C>T	c.617C>T	p.A206V	Missense
PGBD5	CCDS1583.1	Br17X	g.chr1:226793553C>T	c.870C>T	p.I290I	Synonymous
PHC3	NM_024947	Br20P	g.chr3:171329309G>A	c.1560G>A	p.Q520Q	Synonymous
PHEMX	CCDS7733.1	Br26X	g.chr11:2294472C>T	c.718C>T	p.R240X	Nonsense
PHF2	ENST00000298216	Br26X	g.chr13:185233210G>A	c.595G>A	p.A199T	Missense
PHF21A	NM_016621	Br27P	g.chr11:45949455C>T	c.400C>T	p.L134L	Synonymous
PHIP	CCDS4987.1	Br04X	g.chr6:79721272C>T (homozygous)	c.4031C>T	p.P1344L	Missense
PHIP	CCDS4987.1	Br9PT	g.chr6:79792464A>G	c.737A>G	p.D246G	Missense
PHKA2	CCDS14190.1	Br27P	g.chrX:18674973G>A	c.3247G>A	p.G1083R	Missense
PHLPP	NM_194449	Br27P	g.chr18:58657123G>A	IVS3+1G>A	Splice Site	Splice Site
PHLPPL	NM_015020	Br04X	g.chr16:70263693G>T	c.1505G>T	p.S502I	Missense
PHOX2B	CCDS3463.1	Br07X	g.chr4:41590408C>T	c.315C>T	p.F105F	Synonymous
PIGN	NM_176787	Br27P	g.chr18:57972836T>C	c.471T>C	p.Y157Y	Synonymous
PIGQ	CCDS10411.1	Br27P	g.chr16:564229G>A	c.154G>A	p.V52M	Missense
PIGR	CCDS1474.1	Br08X	g.chr1:203502259G>A	c.13G>A	p.V5M	Missense
PIK3C2G	NM_004570	Br17X	g.chr12:18415448delA	c.1693delA	fs	INDEL
PIK3CA	NM_006218	Br27P	g.chr3:180404246C>T	c.1026C>T	p.T342T	Synonymous
PIK3CA	NM_006218	Br26X	g.chr3:180429864G>C	c.2598G>C	p.L866F	Missense
PIK3CA	NM_006218	Br05X	g.chr3:180434792G>A	c.3145G>A	p.G1049S	Missense
PIK3CG	CCDS5739.1	Br27P	g.chr7:106103291C>T	c.1334C>T	p.A445V	Missense
PIK3CG	CCDS5739.1	Br08X	g.chr7:106102464C>T	c.507C>T	p.H169H	Synonymous
PIK3R1	CCDS3993.1	Br14X	g.chr5:67624906_67624908delTTA	c.1138_1140delTTA	p.I380del	INDEL
PIK3R1	CCDS3993.1	Br12P	g.chr5:67625341_67625346delCATGAA	c.1348_1350delCATGAA	p.H450_E451del	INDEL
PIK3R1	CCDS3993.1	Br27P	g.chr5:67626876C>T	c.1713C>T	p.I571I	Synonymous
PIK3R4	CCDS3067.1	Br27P	g.chr3:131892162G>A	c.3133G>A	p.V1045I	Missense
PIK3R5	CCDS11147.1	Br17X	g.chr17:8755455C>T	c.82C>T	p.R28C	Missense
PIP5K1A	CCDS990.1	Br27P	g.chr1:148027705G>A	c.1358G>A	p.G453D	Missense
PIP5K3	CCDS2382.1	Br02X	g.chr2:208988927C>A	c.968C>A	p.S323X	Nonsense
PISD	CCDS13899.1	Br27P	g.chr22:30341678G>A	c.600G>A	p.A200A	Synonymous
PITPNM1	NM_004910	Br13X	g.chr11:67023775C>T	c.1166C>T	p.T389M	Missense
PITPNM2	CCDS9242.1	Br27P	g.chr12:122014890G>A	c.729G>A	p.R243R	Synonymous
PITPNM3	CCDS11076.1	Br23X	g.chr17:6382100C>T (homozygous)	c.49C>T	p.P17S	Missense
PITPNM3	CCDS11076.1	Br27P	g.chr17:6322610G>A	c.758G>A	p.G253E	Missense
PIWIL3	NM_001008496	Br27P	g.chr22:23440063C>T	c.2579C>T	p.A860V	Missense
PKD1	NM_000296	Br27P	g.chr16:2083676C>T	c.10883C>T	p.T3628I	Missense
PKD1L2	NM_182740	Br14X	g.chr16:79765857G>T	c.2747G>T	p.G916V	Missense

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PKD1L2	NM_182740	Br27P	g.chr16:79755806C>T	c.3289C>T	p.P1097S	Missense
PKHD1	CCDS4935.1	Br05X	g.chr6:52028414G>A	c.1766G>A	p.R589H	Missense
PKHD1	CCDS4935.1	Br13X	g.chr6:51855963C>T (homozygous)	c.7237C>T	p.R2413C	Missense
PKHD1	CCDS4935.1	Br15X	g.chr6:52038789C>A	c.824C>A	p.T275K	Missense
PKHD1L1	NM_177531	Br10P	g.chr8:110508510C>T	c.2949C>T	p.Y983Y	Synonymous
PKHD1L1	NM_177531	Br13X	g.chr8:110543250C>T	c.7320C>T	p.C2440C	Synonymous
PKIA	CCDS6222.1	Br27P	g.chr8:79676585G>A	c.205G>A	p.G69R	Missense
PLA1A	CCDS2991.1	Br27P	g.chr3:120799463C>T	c.13C>T	p.P5S	Missense
PLCH2	NM_014638	Br27P	g.chr1:2462060G>A	c.1888G>A	p.V630M	Missense
PLCH2	NM_014638	Br27P	g.chr1:2462173G>A	c.2274G>A	p.K758K	Synonymous
PLCH2	NM_014638	Br27P	g.chr1:2443787G>A	c.519G>A	p.W173X	Nonsense
PLCXD3	NM_001005473	Br27P	g.chr5:41546381C>T	c.5C>T	p.A2V	Missense
PLD2	CCDS11057.1	Br27P	g.chr17:4659769C>T	c.573C>T	p.V191V	Synonymous
PLEC1	NM_201378	Br07X	g.chr8:145069023G>A (homozygous)	c.7020G>A	p.A2340A	Synonymous
PLEKHA4	CCDS12737.1	Br02X	g.chr19:54047346G>A	c.1376G>A	p.G459D	Missense
PLEKHH2	CCDS1812.1	Br27P	g.chr2:43838666C>T	c.918C>T	p.L306L	Synonymous
PLIN	CCDS10353.1	Br27P	g.chr15:88011246G>A	c.1134G>A	p.G378G	Synonymous
PLSCR3	NM_020360	Br27P	g.chr17:7234727G>A	c.781G>A	p.D261N	Missense
PLXDC2	CCDS7132.1	Br27P	g.chr10:20397169C>T	c.536C>T	p.T179I	Missense
PLXNA3	CCDS14752.1	Br03X	hrX:153259847_153259848insT (homozygc	c.3619__3620insT	fs	INDEL
PLXNB2	ENST00000359337	Br03X	g.chr22:49026886G>C	c.1976G>C	p.R659P	Missense
PLXNC1	CCDS9049.1	Br27P	g.chr12:93122909C>T	c.1851C>T	p.H617H	Synonymous
PMS1	CCDS2302.1	Br17X	g.chr2:190508255C>A	c.425C>A	p.T142N	Missense
PMS2L4	ENST00000275546	Br27P	g.chr7:66211539G>C	c.11G>C	p.S4T	Missense
PNLIP	CCDS7594.1	Br26X	g.chr10:118308785C>T (homozygous)	c.1060C>T	p.R354C	Missense
PNOC	CCDS6066.1	Br27P	g.chr8:28252730G>A	c.381G>A	p.Q127Q	Synonymous
PODXL2	CCDS3044.1	Br14X	g.chr3:128862487G>A (homozygous)	c.918G>A	p.L306L	Synonymous
POLD1	CCDS12795.1	Br27P	g.chr19:55610809C>T	c.2734C>T	p.P912S	Missense
POLE	CCDS9278.1	Br03X	g.chr12:131829493G>A	c.4901G>A	p.R1634H	Missense
POLG2	NM_007215	Br27P	g.chr17:59923448C>T	c.101C>T	p.T34M	Missense
POLM	NM_013284	Br23X	g.chr7:43887015G>T	c.1026G>T	p.Q342H	Missense
POLR3B	CCDS9105.1	Br17X	g.chr12:105393000G>A	c.2821G>A	p.G941R	Missense
POLR3E	CCDS10605.1	Br27P	g.chr16:22250989G>A	c.2052G>A	p.E684E	Synonymous
POPDC2	CCDS2992.1	Br27P	g.chr3:120861955C>T	c.6C>T	p.S2S	Synonymous
POR	CCDS5579.1	Br07X	g.chr7:75259971G>A	c.1749G>A	p.A583A	Synonymous
PORCN	CCDS14296.1	Br27P	g.chrX:48135017G>A	c.1252G>A	p.G418S	Missense
POT1	CCDS5793.1	Br20P	g.chr7:124086991G>A	c.855G>A	p.V285V	Synonymous
POU1F1	CCDS2919.1	Br27P	g.chr3:87394002C>T	c.513C>T	p.C171C	Synonymous
POU2F1	CCDS1259.1	Br27P	g.chr1:164112867C>T	c.1500C>T	p.T500T	Synonymous
POU6F2	NM_007252	Br15X	g.chr7:39277017C>T	IVS8-4C>T	Splice Site	Splice Site
PPAP2C	CCDS12023.1	Br27P	g.chr19:233754G>A	c.538G>A	p.A180T	Missense
PPARA	NM_001001930	Br27P	g.chr22:44948569A>G	c.1073A>G	p.K358R	Missense
PPBP	CCDS3563.1	Br27P	g.chr4:75218279G>A	c.274G>A	p.V92I	Missense
PPEF2	NM_006239	Br27P	g.chr4:77139251delG	c.2010delG	fs	INDEL
PPIG	CCDS2235.1	Br27P	g.chr2:170315217C>T	c.970C>T	p.L324F	Missense
PPL	CCDS10526.1	BR27P	g.chr16:4889085G>A	c.806G>A	p.R269K	Missense
PPM2C	CCDS6259.1	Br27P	g.chr8:95003531C>T	c.68C>T	p.T23I	Missense
PPP1CC	CCDS9150.1	Br27P	g.chr12:109631287C>T	IVS2-3C>T	Splice Site	Splice Site
PPP1R12A	NM_002480	Br27P	g.chr12:78769096C>T	c.328C>T	p.L110L	Synonymous
PPP1R12C	CCDS12916.1	Br23X	g.chr19:60298771G>A	c.1240G>A	p.A414T	Missense

Fig. 10

PPP2CZ	CCDS855.1	Br27P	g.chr1:112965510G>A	c.498G>A	p.R166R	Synonymous
PPP2R2C	CCDS3387.1	Br15X	g.chr4:6495627G>A	c.438G>A	p.T146T	Synonymous
PPRC1	CCDS7529.1	Br27P	g.chr10:103896443C>T	c.3704C>T	p.P1235L	Missense
PRCC	CCDS1157.1	Br27P	g.chr1:153580163G>A	c.1346G>A	p.G449D	Missense
PRCC	CCDS1157.1	Br27P	g.chr1:153550879C>T	c.243C>T	p.P81P	Synonymous
PRDM16	NM_199454	Br10P	g.chr1:3324915A>G	c.481A>G	p.N161D	Missense
PRDM5	CCDS3716.1	Br27P	g.chr4:122063793C>T	c.1247C>T	p.P416L	Missense
PRELP	CCDS1438.1	Br27P	g.chr1:200187622G>A	c.1105G>A	p.D369N	Missense
PRIC285	CCDS13527.1	Br27P	g.chr20:61664927C>T	c.3985C>T	p.P1329S	Missense
PRIC285	CCDS13527.1	Br04X	g.chr20:61661854A>G	c.5989A>G	p.T1997A	Missense
PRKCBP1	CCDS13404.1	Br17X	g.chr20:45308281T>G	c.2162T>G	p.V721G	Missense
PRKCBP1	CCDS13404.1	Br27P	g.chr20:45308267G>A	c.2176G>A	p.D726N	Missense
PRKCZ	CCDS37.1	Br27P	g.chr1:2114391G>A	c.688G>A	p.D230N	Missense
PRKDC	NM_006904	Br27P	g.chr8:48934868C>T	c.6064C>T	p.P2022S	Missense
PRKDC	NM_006904	Br04X	g.chr8:49009077G>A	IVS15+1G>A	Splice Site	Splice Site
PRKG2	CCDS3589.1	Br27P	g.chr4:82422614G>A	c.1204G>A	p.E402K	Missense
PRKG2	CCDS3589.1	Br15X	g.chr4:82482975C>A	c.406C>A	p.L136M	Missense
PRKRA	CCDS2279.1	Br27P	g.chr2:179133564G>A	c.451G>A	p.G151R	Missense
PRO1853	CCDS1788.1	Br25X	g.chr2:37380406G>C	c.443G>C	p.C148S	Missense
PRO1855	CCDS11566.1	Br27P	g.chr17:45817595C>T	c.559C>T	p.L187L	Synonymous
PROM1	NM_006017	Br15X	g.chr4:15669171C>A	c.1926C>A	p.P642P	Synonymous
PROSC	CCDS6096.1	Br27P	g.chr8:37743032G>A	IVS4+1G>A	Splice Site	Splice Site
PRPF18	CCDS7100.1	Br04X	g.chr10:13692110C>T	c.429C>T	p.V143V	Synonymous
PRR12	ENST00000246798	Br14X	g.chr19:54794996A>G	c.1874A>G	p.N625S	Missense
PRSS16	CCDS4623.1	Br27P	g.chr6:27330561G>A	c.1261G>A	p.A421T	Missense
PRSS16	CCDS4623.1	Br27P	g.chr6:27327000C>T	c.695C>T	p.T232I	Missense
PRSS22	CCDS10481.1	Br02X	g.chr16:2846838C>T	c.95C>T	p.A32V	Missense
PSF1	NM_021067	Br27P	g.chr20:25345836C>T	c.237C>T	p.Y79Y	Synonymous
PSIP1	CCDS6479.1	Br27P	g.chr9:15456783G>A	c.1495G>A	p.D499N	Missense
PSMD8	CCDS12515.1	Br26X	g.chr19:43558671C>T	c.113C>T	p.T38I	Missense
PSRC2	NM_144982	Br27P	g.chr12:70327821G>A	c.1055G>A	p.S352N	Missense
PTAR1	ENST00000340434	Br16X	g.chr9:69595384G>T	c.123G>T	p.R41S	Missense
PTCH2	CCDS516.1	Br27P	g.chr1:44962636C>T	c.2030C>T	p.A677V	Missense
PTCH2	CCDS516.1	Br04X	g.chr1:44976628A>G	c.249A>G	p.E83E	Synonymous
PTEN	NM_000314	Br07X	g.chr10:89682890G>A (homozygous)	c.394G>A	p.G132S	Missense
PTEN	NM_000314	Br04X	g.chr10:89710832C>T (homozygous)	c.1003C>T	p.R335X	Nonsense
PTEN	NM_000314	Br17X	10:89715128_89715131delTAGA (homozyg	c.1131_1134delTAGA fs		INDEL
PTEN	NM_000314	Br03X	g.chr10:89710630G>A (homozygous)	IVS7-1G>A	Splice Site	Splice Site
PTEN	NM_000314	Br25X	g.chr10:89710857T>G (homozygous)	IVS8+2T>G	Splice Site	Splice Site
PTGDR	CCDS9707.1	Br27P	g.chr14:51804540C>T	c.258C>T	p.A86A	Synonymous
PTGFR	CCDS686.1	Br07X	g.chr1:78714146A>T	c.833A>T	p.H278L	Missense
PTGS2	CCDS1371.1	Br27P	g.chr1:183376164C>T	c.1279C>T	p.P427S	Missense
PTPLA	CCDS7121.1	Br27P	g.chr10:17681411G>A	c.489G>A	p.Q163Q	Synonymous
PTPN23	CCDS2754.1	Br11P	chr3:47428149_47428159delTCATGCTGG	c.3854_3864delTCATGCTGGTT fs		INDEL
PTPRF	CCDS489.1	Br27P	g.chr1:43732747G>A	c.2019G>A	p.W673X	Nonsense
PTPRK	CCDS5137.1	Br27P	g.chr6:128368056C>T	c.2360C>T	p.A787V	Missense
PTPRM	CCDS11840.1	Br15X	g.chr18:8369249A>G	c.3658A>G	p.M1220V	Missense
PTPRS	CCDS12139.1	Br27P	g.chr19:5165667C>T	c.3058C>T	p.P1020S	Missense
PTPRU	CCDS334.1	Br03X	g.chr1:29402467C>T	c.138C>T	p.Y46Y	Synonymous
PTX3	CCDS3180.1	Br27P	g.chr3:158637474C>T	c.50C>T	p.A17V	Missense

Fig. 10

PUM1	CCDS338.1	Br27P	g.chr1:31147821G>A	c.692G>A	p.G231D	Missense
PYGB	CCDS13171.1	Br27P	g.chr20:25209674C>T	c.1329C>T	p.A443A	Synonymous
Q13034_HUMAN	ENST00000225928	Br27P	g.chr17:37953829C>T	c.620C>T	p.T207I	Missense
Q4VXG5_HUMAN	ENST00000327794	Br27P	g.chr1:221618015G>A	c.1065G>A	p.W355X	Nonsense
Q4VXG5_HUMAN	ENST00000331811	Br27P	g.chr1:221761194A>T	c.3732A>T	p.K1244N	Missense
Q5JX50_HUMAN	ENST00000325076	Br27P	g.chr20:33651159G>A	c.1566G>A	p.E522E	Synonymous
Q5JYU7_HUMAN	ENST00000333418	Br27P	g.chr22:36707744C>T	c.776C>T	p.P259L	Missense
Q5T740_HUMAN	ENST00000343319	BR02X	g.chr10:44750111C>T	c.351C>T	p.G117G	Synonymous
Q5W0A0_HUMAN	ENST00000298738	Br17X	g.chr13:45022091G>T	c.1584G>T	p.R528S	Missense
Q68CJ6_HUMAN	ENST00000341513	Br25X	g.chr8:27943827G>T	c.139G>T	p.D47Y	Missense
Q6IEE8_HUMAN	ENST00000354872	Br27P	g.chr17:30908947delC	c.242delC	fs	INDEL
Q6PK04_HUMAN	ENST00000329214	Br27P	g.chr17:77245281G>A	c.252G>A	p.K84K	Synonymous
Q6RGF6_HUMAN	ENST00000359144	Br27P	g.chr4:18168367G>A	c.102G>A	p.W34X	Nonsense
Q6ZRB0_HUMAN	ENST00000297487	Br27P	g.chr7:1311692G>A	c.1175G>A	p.C392Y	Missense
Q6ZSY1_HUMAN	ENST00000320930	Br27P	g.chr15:31232700A>G	c.1708A>G	p.T570A	Missense
Q6ZT40_HUMAN	ENST00000296564	Br27P	g.chr5:5514743C>T	c.463C>T	p.P155S	Missense
Q6ZUG5_HUMAN	ENST00000344062	Br16X	g.chr3:130134493G>A	c.1137G>A	p.T379T	Synonymous
Q6ZV46_HUMAN	ENST00000341696	Br27P	g.chr7:1347402G>A	c.219G>A	p.T73T	Synonymous
Q76B61_HUMAN	ENST00000360022	Br27P	g.chr7:148919650C>T	c.797C>T	p.P266L	Missense
Q86U37_HUMAN	ENST00000335192	Br27P	g.chr14:28311812G>A	c.57G>A	p.R19R	Synonymous
Q86XQ1_HUMAN	ENST00000261673	Br27P	g.chr12:131770009C>T	c.1299C>T	p.G433G	Synonymous
Q86XQ1_HUMAN	ENST00000261673	Br27P	g.chr12:131761336G>A	c.532G>A	p.G178R	Missense
Q86YU6_HUMAN	ENST00000330768	Br27P	g.chr16:69256483G>A	c.291G>A	p.E97E	Synonymous
Q8IUR1_HUMAN	ENST00000327506	Br03X	g.chr2:234522856T>C	c.730T>C	p.L244L	Synonymous
Q8N1R6_HUMAN	ENST00000331014	Br27P	g.chr13:110066133C>T	c.495C>T	p.S165S	Synonymous
Q8N646_HUMAN	ENST00000359720	Br08X	g.chr9:86854631C>T	c.164C>T	p.T55M	Missense
Q8N800_HUMAN	ENST00000322516	Br03X	g.chr13:102185000G>A (homozygous)	c.2161G>A	p.V721I	Missense
Q8N822_HUMAN	ENST00000317280	Br27P	g.chr1:209187813C>T	c.295C>T	p.L99F	Missense
Q8N8C3_HUMAN	ENST00000319889	Br20P	g.chr7:70042362G>T	c.422G>T	p.C141F	Missense
Q8N8K0_HUMAN	ENST00000301807	Br08X	g.chr3:36855185A>G	c.3801A>G	p.G1267G	Synonymous
Q8N9H1_HUMAN	ENST00000359503	Br27P	g.chr22:16818069G>A	c.281G>A	p.G94E	Missense
Q8NBE0_HUMAN	ENST00000297801	Br04X	g.chr7:128108555G>A	c.670G>A	p.E224K	Missense
Q8NDH2_HUMAN	ENST00000322527	Br11P	chr13:102180027_102180020delTGAAAG/	c.1104_1111delTGAAAGAA	fs	INDEL
Q8NDH2_HUMAN	ENST00000322527	Br11P	g.chr13:102181079_102181078delAA	c.52_53delAA	fs	INDEL
Q8NGK8_HUMAN	ENST00000334020	Br9PT	g.chr11:55380131C>A	c.83C>A	p.T28N	Missense
Q8NGL5_HUMAN	ENST00000328673	Br9PT	g.chr11:55279853C>A	c.798C>A	p.N266K	Missense
Q8NH06_HUMAN	ENST00000324144	Br16X	g.chr17:3004187G>T	c.659G>T	p.R220M	Missense
Q8NHB0_HUMAN	ENST00000315712	Br9PT	g.chr5:180052803G>A	c.460G>A	p.V154M	Missense
Q8TBR1_HUMAN	ENST00000354206	Br10P	g.chr7:23303688G>A	c.134G>A	p.R45H	Missense
Q96CH6_HUMAN	ENST00000329920	Br27P	g.chr22:28967205G>A	c.458G>A	p.G153E	Missense
Q96CK5_HUMAN	ENST00000273582	Br02X	g.chr3:19891974 7C>T	c.550C>T	p.Q184X	Nonsense
Q96DR3_HUMAN	ENST00000324748	Br27P	g.chr1:25831361C>T	c.36C>T	p.A12A	Synonymous
Q96FF7_HUMAN	ENST00000269720	Br27P	g.chr19:14046199C>T	IVS1-3C>T	Splice Site	Splice Site
Q96NE0_HUMAN	ENST00000329922	Br27P	g.chr4:7649826>A	c.72G>A	p.R24R	Synonymous
Q96NL2_HUMAN	ENST00000272907	Br25X	g.chr2:226099141G>A	c.115G>A	p.D39N	Missense
Q96PS2_HUMAN	ENST00000326978	Br03X	g.chr4:37690920A>T	c.85A>T	p.R29X	Nonsense
Q9H030_HUMAN	ENST00000237449	Br27P	g.chr2:84954843G>A	c.3939G>A	p.R1313R	Synonymous
Q9H6A9_HUMAN	ENST00000309024	Br27P	g.chr11:65142913C>T	c.1147C>T	p.R383C	Missense
Q9H800_HUMAN	ENST00000357106	Br27P	g.chr20:51620384G>A	c.402G>A	p.L134L	Synonymous
Q9H8D1_HUMAN	ENST00000360549	Br11P	g.chr6:80076998G>A	c.487G>A	p.A163T	Missense

Fig. 10

Q9HAC4_HUMAN	ENST00000206466	Br27P	g.chr14:23954179G>A	c.3147G>A	p.W1049X	Nonsense
Q9P1M5_HUMAN	ENST00000303007	Br20P	g.chr16:77143863C>T	c.207C>T	p.D69D	Synonymous
Q9ULE4_HUMAN	ENST00000265018	Br27P	g.chr4:17325528G>A	IVS12+1G>A	Splice Site	Splice Site
Q9Y6V0-3	ENST00000333891	Br23X	g.chr7:82240015A>T	c.3584A>T	p.K1195M	Missense
QPCT	CCDS1790.1	Br27P	g.chr2:37506022C>T	IVS3-4C>T	Splice Site	Splice Site
QRICH2	NM_032134	Br27P	g.chr17:71789568C>T	c.3737C>T	p.P1246L	Missense
QSCN6	CCDS1337.1	Br27P	g.chr1:176897466G>A	c.1881G>A	p.E627E	Synonymous
QSER1	NM_024774	Br27P	g.chr11:32912116G>A	c.1632G>A	p.Q544Q	Synonymous
QSER1	NM_024774	Br27P	g.chr11:32913184G>A	c.2700G>A	p.E900E	Synonymous
QTRTD1	NM_024638	Br27P	g.chr3:115266805G>A	c.11G>A	p.S4N	Missense
RAB36	CCDS13805.1	Br27P	g.chr22:21819859C>T	c.511C>T	p.P171S	Missense
RAB3C	CCDS3976.1	Br16X	g.chr5:57949348G>A (homozygous)	c.146G>A	p.R49H	Missense
RAB3GAP2	NM_012414	Br14X	g.chr1:216732842T>C	c.2593T>C	p.L865L	Synonymous
RAB3IL1	CCDS8014.1	Br27P	g.chr11:61422371G>A	c.1104G>A	p.K368K	Synonymous
RAC2	CCDS13945.1	Br08X	g.chr22:35953427G>T	c.139G>T	p.D47Y	Missense
RAD23A	CCDS12289.1	Br27P	g.chr19:12920370G>A	IVS4+4G>A	Splice Site	Splice Site
RAD51L3	CCDS11287.1	Br16X	g.chr17:30452129G>T	c.943G>T	p.G315W	Missense
RAD52	CCDS8507.1	Br04X	g.chr12:910696G>A	c.137G>A	p.R46K	Missense
RAFTLIN	NM_015150	Br04X	g.chr3:16386690G>A	c.927G>A	p.Q309Q	Synonymous
RAI1	CCDS11188.1	Br27P	g.chr17:17640870C>T	c.3883C>T	p.P1295S	Missense
RALBP1	CCDS11845.1	Br08X	g.chr18:9525789G>A	c.1822G>A	p.D608N	Missense
RANBP17	NM_022897	Br23X	g.chr5:170559307C>T	c.2067C>T	p.F689F	Synonymous
RANP1	ENST00000333828	Br27P	g.chr13:20220032C>T	c.157C>T	p.P53S	Missense
RAP140	CCDS2877.1	Br27P	g.chr3:56669816C>T	c.163C>T	p.L55L	Synonymous
RAPGEF4	NM_007023	Br27P	g.chr2:173681090G>A	c.1420G>A	p.V474I	Missense
RAPGEF6	NM_016340	Br9PT	g.chr5:130868963A>T	c.1094A>T	p.D365V	Missense
RAPGEFL1	CCDS11363.1	Br15X	g.chr17:35603492C>T	c.1297C>T	p.R433C	Missense
RAPH1	CCDS2359.1	Br27P	g.chr2:204130462G>A	c.2957G>A	p.G986D	Missense
RAPH1	CCDS2359.1	Br27P	g.chr2:204179828G>A	c.717G>A	p.G239G	Synonymous
RARSL	CCDS5011.1	Br27P	g.chr6:88312065G>A	c.523G>A	p.G175S	Missense
RASGRF1	CCDS10309.1	Br20P	g.chr15.77097236G>A	c.1674G>A	p.P558P	Synonymous
RASGRF2	CCDS4052.1	Br25X	g.chr5:80445480C>T	c.2455C>T	p.R819X	Nonsense
RASL11B	CCDS3490.1	Br27P	g.chr4:53572619C>T	c.466C>T	p.L156L	Synonymous
RAX	CCDS11972.1	Br17X	g.chr18:55091191G>A	c.228G>A	p.A76A	Synonymous
RB1	NM_000321	Br04X	g.chr13:47853551C>T (homozygous)	c.1666C>T	p.R556X	Nonsense
RB1	NM_000321	Br15X	g.chr13:47937481delC (homozygous)	c.2465delC	fs	INDEL
RBM14	CCDS8147.1	Br04X	g.chr11:66149438G>A	c.1515G>A	p.G505G	Synonymous
RBM19	CCDS9172.1	Br27P	g.chr12:112846399C>T	c.1580C>T	p.A527V	Missense
RBM21	CCDS8021.1	Br27P	g.chr11:62099535G>A	c.2232G>A	p.E744E	Synonymous
RBM25	NM_021239	Br27P	g.chr14:72645842G>A	c.1581G>A	p.K527K	Synonymous
RBM25	NM_021239	Br29P	g.chr14:72633565T>G	IVS6+4T>G	Splice Site	Splice Site
RBM27	ENST00000265271	Br04X	g.chr5:145644445C>A	c.3056C>A	p.P1019Q	Missense
RBM27	ENST00000265271	Br04X	g.chr5:145644453T>G	c.3064T>G	p.S1022A	Missense
RBM34	ENST00000362051	Br27P	g.chr1:231627288C>T	c.794C>T	p.A265V	Missense
RBMS3	NM_001003792	Br25X	g.chr3:29756314A>G	c.496A>G	p.I166V	Missense
RBP3	CCDS7218.1	Br08X	g.chr10:48009668G>A (homozygous)	c.1216G>A	p.E406K	Missense
RBPSUH	CCDS3436.1	Br27P	g.chr4:26084098G>A	c.86G>A	p.G29E	Missense
RC74	NM_018250	Br08X	g.chr8:28684457G>A	c.1623G>A	p.S541S	Synonymous
RCD-8	CCDS10849.1	Br27P	g.chr16:66471294G>A	c.1862G>A	p.S621N	Missense
RCD-8	CCDS10849.1	Br13X	g.chr16:66473355C>T	IVS22-3C>T	Splice Site	Splice Site

Fig. 10

RDHE2	CCDS6167.1	Br27P	g.chr8:57391284G>A	c.177G>A	p.Q59Q	Synonymous
RDS	CCDS4871.1	Br20P	g.chr6:42797544C>T	c.507C>T	p.N169N	Synonymous
REG1B	CCDS1963.1	Br20P	g.chr2:79225679C>T	c.97C>T	p.R33X	Nonsense
REN	NM_000537	Br20P	g.chr1:200862821G>A	c.226G>A	p.V76M	Missense
REPS2	CCDS14180.1	Br27P	g.chrX:16855059C>T	c.971C>T	p.S324F	Missense
RET	CCDS7200.1	Br16X	g.chr10:42921950C>T (homozygous)	c.988C>T	p.R330W	Missense
RFC2	CCDS5567.1	Br25X	g.chr7:73113319C>T	c.46C>T	p.Q16X	Nonsense
RFNG	NM_002917	Br27P	g.chr17:77600984C>T	c.686C>T	p.A229V	Missense
RFX3	CCDS6450.1	Br27P	g.chr9:3237930C>T	c.2070C>T	p.N690N	Synonymous
RGS22	NM_015668	Br27P	g.chr8:101063523C>T	IVS21-3C>T	Splice Site	Splice Site
RGSL1	CCDS1346.1	Br03X	g.chr1:179249594G>A	c.1183G>A	p.V395I	Missense
RHOT1	NM_001033568	Br03X	g.chr17:27552098T>A	c.1111T>A	p.Y371N	Missense
RICTOR	NM_152756	Br27P	g.chr5:38998885C>T	c.1416C>T	p.A472A	Synonymous
RIMBP2	NM_015347	Br17X	g.chr12:129452013G>A	c.713G>A	p.R238Q	Missense
RIMBP2	NM_015347	Br27P	g.chr12:129423546C>T	IVS12+4C>T	Splice Site	Splice Site
RIMS2	NM_014677	Br27P	g.chr8:104967454G>A	c.875G>A	p.S292N	Missense
RIMS4	CCDS13338.1	Br04X	g.chr20:42818210G>T	c.789G>T	p.G263G	Synonymous
RIPK4	CCDS13675.1	Br05X	g.chr21:42042391C>A	c.665C>A	p.P222Q	Missense
RLBP1	NM_000326	Br27P	g.chr15:87554535G>A	c.939G>A	p.E313E	Synonymous
RLTPR	NM_001013838	Br05X	g.chr16:66245596G>A	c.3164G>A	p.R1055H	Missense
RNASEH2A	CCDS12282.1	Br27P	g.chr19:12778824C>T	c.130C>T	p.P44S	Missense
RNF103	NM_005667	Br27P	g.chr2:86761663G>A	c.5G>A	p.W2X	Nonsense
RNF127	CCDS14575.1	Br29P	g.chrX:117890725G>A	c.100G>A	p.D34N	Missense
RNF128	CCDS14521.1	Br27P	g.chrX:105776494G>A	c.206G>A	p.G69D	Missense
RNF19	CCDS6286.1	Br27P	g.chr8:101369110G>A	c.469G>A	p.D157N	Missense
RNF25	CCDS2420.1	Br27P	g.chr2:219354326G>A	c.1239G>A	p.R413R	Synonymous
RNF40	CCDS10691.1	Br27P	g.chr16:30685339G>A	c.1252G>A	p.A418T	Missense
RNPC2	CCDS13265.1	Br25X	g.chr20:33776054G>A	c.539G>A	p.R180Q	Missense
ROBO3	NM_022370	Br27P	g.chr11:124252678C>T	c.2900C>T	p.P967L	Missense
ROCK1	CCDS11870.1	Br03X	8:16825270_16825265delGAGATA (homoz	c.2008_2013delGAGATA	p.E670_I671del	INDEL
ROM1	CCDS8024.1	Br27P	g.chr11:62138672C>T	c.841C>T	p.L281L	Synonymous
ROS1	CCDS5116.1	Br27P	g.chr6:117772120A>G	IVS26-2A>G	Splice Site	Splice Site
RoXaN	CCDS14013.1	Br27P	g.chr22:40061588C>T	IVS9-4C>T	Splice Site	Splice Site
RP1L1	NM_178857	Br02X	g.chr8:10517973G>A	c.149G>A	p.R50H	Missense
RPL11	CCDS238.1	Br15X	g.chr1:23765668C>T	c.223C>T	p.R75X	Nonsense
RPS14	CCDS4307.1	Br27P	g.chr5:149806617G>A	c.252G>A	p.R84R	Synonymous
RPS6KA2	CCDS5294.1	Br27P	g.chr6:166802208C>T	c.1854C>T	p.T618T	Synonymous
RPS6KB2	NM_003952	Br27P	g.chr11:66953040C>T	c.90C>T	p.P30P	Synonymous
RPUSD3	CCDS2586.1	Br10P	g.chr3:9857404C>T	c.469C>T	p.Q157X	Nonsense
RRAGD	CCDS5022.1	Br27P	g.chr6:90178409C>T	c.23C>T	p.P8L	Missense
RSHL1	CCDS12675.1	Br27P	g.chr19:51009812G>A	c.463G>A	p.D155N	Missense
RSU1	CCDS7112.1	Br27P	g.chr10:16834645A>G	c.497A>G	p.D166G	Missense
RTN1	CCDS9740.1	Br23X	g.chr14:59263427C>T (homozygous)	c.1728C>T	p.G576G	Synonymous
RTTN	NM_173630	Br27P	g.chr18:66015864C>T	c.669C>T	p.F223F	Synonymous
RUNX1	CCDS13639.1	Br27P	g.chr21:35086533C>T	c.1212C>T	p.H404H	Synonymous
RUNX1T1	CCDS6256.1	Br27P	g.chr8:93086672C>T	c.588C>T	p.L196L	Synonymous
RWDD1	NM_001007464	Br27P	g.chr6:117018748A>G	c.264A>G	p.K88K	Synonymous
RYR2	NM_001035	Br27P	g.chr1:234250313C>T	c.11420C>T	p.A3807V	Missense
RYR2	NM_001035	Br23X	g.chr1:234273164C>T	c.12111C>T	p.P4037P	Synonymous
RYR2	NM_001035	Br27P	g.chr1:233992712C>T	c.2479C>T	p.L827L	Synonymous

Fig. 10

RYR2	NM_001035	Br10P	g.chr1:233820306G>A	c.256G>A	p.V86M	Missense
RYR2	NM_001035	Br17X	g.chr1:233858830G>A	c.365G>A	p.R122H	Missense
RYR2	NM_001035	Br05X	g.chr1:234132736A>G	c.7290A>G	p.G2430G	Synonymous
RYR3	NM_001036	Br9PT	g.chr15:31893017C>T	c.10447C>T	p.R3483W	Missense
RYR3	NM_001036	Br27P	g.chr15:31837073A>G	c.8689A>G	p.K2897E	Missense
SALL3	CCDS12013.1	BR27P	g.chr18:74854681C>T	c.1702C>T	p.P568S	Missense
SAMD11	ENST00000294573	Br25X	g.chr2:132034808C>T	c.1361C>T	p.T454M	Missense
SAMD9	NM_017654	Br05X	g.chr7:92379086C>T	c.976C>T	p.Q326X	Nonsense
SAPS2	NM_014678	Br27P	g.chr22:49172490G>A	c.2550G>A	p.K850K	Synonymous
SARG	CCDS1475.1	Br27P	g.chr1:203584228C>T	c.1276C>T	p.P426S	Missense
SARS	CCDS795.1	Br27P	g.chr1:109468784G>A	c.128G>A	p.W43X	Nonsense
SASH1	CCDS5212.1	Br27P	g.chr6:148906777G>A	c.2478G>A	p.E826E	Synonymous
SCHIP1	CCDS3186.1	Br27P	g.chr3:161097235G>A	c.1434G>A	p.K478K	Synonymous
SCN1B	CCDS12441.1	BR02X	g.chr19:40213563C>T	UTR-2C>T	5'UTR	5'UTR
SCN3A	NM_006922	Br03x	g.chr2:165772558G>A	c.5612G>A	p.R1871Q	Missense
SCN3B	CCDS8442.1	Br16X	g.chr11:123018465_123018464delCT	c.344_345delCT	fs	INDEL
SCN5A	NM_000335	Br20P	g.chr3:38579032G>T	c.3838G>T	p.V1280F	Missense
SCN9A	NM_002977	Br07X	g.chr2:166881761C>T	c.4862C>T	p.T1621M	Missense
SCN9A	NM_002977	Br9PT	g.chr2:166987822G>A	c.583G>A	p.V195I	Missense
SCRIB	CCDS6411.1	Br27P	g.chr8:144958235G>A	c.3089G>A	p.G1030D	Missense
SCUBE1	CCDS14048.1	Br02X	g.chr22:41959439C>T (homozygous)	c.747C>T	p.N249N	Synonymous
SCUBE1	CCDS14048.1	Br17X	g.chr22:41959381G>A	c.805G>A	p.V269I	Missense
SDC3	NM_014654	Br13X	g.chr1:31019055G>A	c.307G>A	p.V103I	Missense
SDR-O	CCDS8926.1	Br25X	g.chr12:55603976A>G	c.850A>G	p.K284E	Missense
SEC24C	CCDS7332.1	Br13X	g.chr10:75176601A>G (homozygous)	c.5A>G	p.N2S	Missense
SELO	NM_031454	Br27P	g.chr22:48958001G>A	c.1832G>A	p.G611E	Missense
SEMA5A	CCDS3875.1	Br27P	g.chr5:9433001G>A	c.58G>A	p.A20T	Missense
SEMA5B	CCDS3019.1	Br26X	g.chr3:124125250C>G	c.1176C>G	p.L392L	Synonymous
SEMA7A	CCDS10262.1	Br27P	g.chr15:72496781C>T	c.609C>T	p.F203F	Synonymous
SEN2L	CCDS2611.1	Br27P	g.chr3:125331340>A	c.934G>A	p.G312R	Missense
SENP3	NM_015670	Br27P	g.chr17:7409481G>A	c.1068G>A	p.R356R	Synonymous
SEPT2	CCDS2548.1	Br27P	g.chr2:241997158C>T	c.557C>T	p.T186I	Missense
SERPINA12	CCDS9926.1	Br08X	g.chr14:94034334A>G	c.154A>G	p.N52D	Missense
SERPINA12	CCDS9926.1	Br17X	g.chr14:94034441C>T	c.47C>T	p.T16M	Missense
SERPINA9	NM_175739	Br26X	g.chr14:94005784C>T	c.201C>T	p.T67T	Synonymous
SERPINB3	CCDS11987.1	Br27P	475118_59475107delTGGAAATACCAT (ho	c.695_706delTGGAAATACCAT	indel	INDEL
SERPINB7	CCDS11988.1	Br06X	g.chr18:59622650G>A	c.944G>A	p.R315H	Missense
SERPINE2	CCDS2460.1	Br27P	g.chr2:224692077C>T	c.46C>T	p.P16S	Missense
SERPING1	CCDS7962.1	Br14X	g.chr11:57124012G>A	c.136G>A	p.A46T	Missense
SET7	CCDS3748.1	Br27P	g.chr4:140796648G>A	c.916G>A	p.D306N	Missense
SETDB2	CCDS9417.1	Br27P	g.chr13:48952406C>T	c.956C>T	p.P319L	Missense
SEZ6	NM_178860	Br23X	g.chr17:24308535G>T (homozygous)	c.2451G>T	p.Q817H	Missense
SEZ6L	CCDS13833.1	Br07X	g.chr22:25071613C>T	c.2449C>T	p.R817C	Missense
SFI1	NM_001007467	Br27P	g.chr22:30293732C>T	c.900C>T	p.R300R	Synonymous
SFMBT2	NM_001029880	Br27P	g.chr10:7245754C>T	c.2669C>T	p.A890V	Missense
SFRP2	NM_003013	Br27P	g.chr4:155060321G>A	c.775G>A	p.V259I	Missense
SFTPB	CCDS1983.1	Br04X	g.chr2:85804437C>T	c.532C>T	p.L178F	Missense
SG223_HUMAN	ENST00000330777	Br27P	g.chr8:8271455G>A	c.1874G>A	p.R625K	Missense
SG223_HUMAN	ENST00000330777	Br27P	g.chr8:8272807C>T	c.522C>T	p.N174N	Synonymous
SGCZ	CCDS5992.1	Br16X	g.chr8:144566651C>G	c.156C>G	p.A52A	Synonymous

Fig. 10

SGK2	CCDS13320.1	Br14X	g.chr20:41631484C>G	c.454C>G	p.R152G	Missense
SGPP1	CCDS9760.1	Br27P	g.chr14:63222958C>T	c.944C>T	p.S315F	Missense
SGPP2	CCDS2453.1	Br03X	g.chr2:223212118C>T	c.506C>T	p.A169V	Missense
SGSH	CCDS11770.1	Br27P	g.chr17:75799257C>T	c.1098C>T	p.S366S	Synonymous
SH3BP1	CCDS13952.1	Br27P	g.chr22:36367399C>T	c.759C>T	p.S253S	Synonymous
SH3BP2	NM_003023	Br27P	g.chr4:2863884G>A	c.384G>A	p.E128E	Synonymous
SH3GL3	CCDS10325.1	Br27P	g.chr15:81950638C>T	c.49C>T	p.L17F	Missense
SHANK2	CCDS8198.1	Br27P	g.chr11:70183653G>A	c.225G>A	p.Q75Q	Synonymous
SHANK3	ENST00000262795	Br26X	g.chr22:49449774G>A (homozygous)	c.567G>A	p.A189A	Synonymous
SHB	NM_003028	Br27P	g.chr9:38058254C>T	c.389C>T	p.A130V	Missense
SHB	NM_003028	Br27P	g.chr9:37964796G>A	c.877G>A	p.G293S	Missense
SHE	NM_001010846	Br27P	g.chr1:151287205G>A	c.371G>A	p.R124Q	Missense
SHMT2	CCDS8934.1	Br16X	g.chr12:55914414G>A	UTR+3G>A	3'UTR	3'UTR
SIGLEC11	CCDS12790.1	Br16X	g.chr19:55153383C>T	c.1584C>T	p.A528A	Synonymous
SIGLEC11	CCDS12790.1	Br27P	g.chr19:55145101C>T	c.1999C>T	p.L667L	Synonymous
SIGLEC5	NM_003830	Br04X	g.chr19:56822806C>T	c.1003C>T	p.P335S	Missense
SIGLEC8	NM_014442	Br27P	g.chr19:56652596C>T	c.664C>T	p.L222F	Missense
SIM2	CCDS13646.1	Br27P	g.chr21:37003376C>T	c.214C>T	p.P72S	Missense
SIPA1L2	NM_020808	Br27P	g.chr1:228933357G>A	c.1132G>A	p.G378R	Missense
SIPA1L2	NM_020808	Br27P	g.chr1:228888104C>T	c.2587C>T	p.P863S	Missense
SIPA1L3	NM_015073	Br27P	g.chr19:43346959G>A	c.3781G>A	p.G1261R	Missense
SKIV2L	CCDS4731.1	Br27P	g.chr6:32043101G>A	c.2551G>A	p.E851K	Missense
SKP2	CCDS3915.1	Br06X	g.chr5:36202389C>T	c.404C>T	p.S135F	Missense
SKP2	CCDS3915.1	Br06X	g.chr5:36202488C>T	c.503C>T	p.S168L	Missense
SLC10A4	CCDS3482.1	Br27P	g.chr4:48326769C>T	c.263C>T	p.P88L	Missense
SLC11A1	CCDS2415.1	Br25X	g.chr2:219077407G>A	c.520G>A	p.V174I	Missense
SLC12A1	CCDS10129.1	Br27P	g.chr15:46287430C>T	c.222C>T	p.L74L	Synonymous
SLC12A5	CCDS13391.1	Br14X	g.chr20:44097883G>A	c.340G>A	p.V114I	Missense
SLC14A1	CCDS11925.1	Br07X	g.chr18:41568248C>T	c.353C>T	p.A118V	Missense
SLC14A2	CCDS11924.1	Br23X	g.chr18:41477955G>A	c.1183G>A	p.V395M	Missense
SLC16A5	CCDS11713.1	Br04X	g.chr17:70611797G>T	c.1291G>T	p.A431S	Missense
SLC1A2	NM_004171	Br03X	g.chr11:35239082_35239081delCT	c.1660_1661delCT	fs	INDEL
SLC22A11	CCDS8074.1	Br27P	nr11:64080137_64080148delGATACCTTCC	c.90_101delGATACCTTCCCA	p.I31_Q34del	INDEL
SLC22A18	CCDS7740.1	Br27P	g.chr11:2902956G>A	c.1228G>A	p.V410I	Missense
SLC22A18	CCDS7740.1	Br27P	g.chr11:2887492G>A	c.512G>A	p.G171D	Missense
SLC22A3	CCDS5277.1	Br25X	g.chr6:160828440G>T	c.1074G>T	p.W358C	Missense
SLC24A6	NM_024959	Br27P	g.chr12:112208284G>A	c.1343G>A	p.G448D	Missense
SLC25A13	CCDS5645.1	Br17X	g.chr7:95444083C>T	c.1236C>T	p.N412N	Synonymous
SLC26A4	CCDS5746.1	Br27P	g.chr7:106923522G>A	c.1075G>A	p.V359M	Missense
SLC26A4	CCDS5746.1	Br27P	g.chr7:106928845C>T	c.1310C>T	p.A437V	Missense
SLC2A1	CCDS477.1	Br27P	g.chr1:43062548C>T	c.1099C>T	p.L367L	Synonymous
SLC2A1	CCDS477.1	Br27P	g.chr1:43065861G>A	c.224G>A	p.G75E	Missense
SLC30A1	CCDS1499.1	Br27P	g.chr1:208140283G>A	c.67G>A	p.V23M	Missense
SLC30A5	CCDS3996.1	Br27P	g.chr5:68448005G>A	c.1101G>A	p.K367K	Synonymous
SLC30A9	CCDS3465.1	Br27P	g.chr4:41833643C>T	c.47C>T	p.S16F	Missense
SLC30A9	CCDS3465.1	Br20P	g.chr4:41905996G>A	c.962G>A	p.G321D	Missense
SLC35B2	NM_178148	Br27P	g.chr6:44330964G>A	c.756G>A	p.M252I	Missense
SLC35D3	NM_001008783	Br27P	g.chr6:137287138G>A	c.862G>A	p.V288M	Missense
SLC35F2	NM_017515	Br20P	g.chr11:107181384_107181381delTTGT	c.642_645delTTGT	fs	INDEL
SLC38A1	NM_030674	Br27P	g.chr12:44877977G>A	c.1256G>A	p.G419E	Missense

Fig. 10

SLC38A4	CCDS8750.1	Br03X	g.chr12:45458758A>T	c.786A>T	p.S262S	Synonymous
SLC38A6	CCDS9751.1	Br27P	g.chr14:60517766G>A	c.18G>A	p.G6G	Synonymous
SLC39A2	CCDS9563.1	Br27P	g.chr14:20538978C>T	c.330C>T	p.S110S	Synonymous
SLC43A3	CCDS7956.1	Br27P	g.chr11:56950108G>A	c.114G>A	p.K38K	Synonymous
SLC4A1	CCDS11481.1	Br25X	g.chr17:39695604T>C	c.32T>C	p.M11T	Missense
SLC4A5	CCDS1936.1	Br27P	g.chr2:74380808G>A	c.2086G>A	p.A696T	Missense
SLC4A7	NM_003615	Br27P	g.chr3:27411600C>T	c.2687C>T	p.P896L	Missense
SLC5A5	CCDS12368.1	Br15X	g.chr19:17855697G>A	c.1368G>A	p.S456S	Synonymous
SLC5A7	CCDS2074.1	Br15X	g.chr2:108067164C>A	c.263C>A	p.P88Q	Missense
SLC7A10	CCDS12431.1	Br27P	g.chr19:38395111C>A	c.715C>A	p.L239I	Missense
SLC7A13	NM_138817	Br12P	g.chr8:87298891C>T	c.1103C>T	p.S368L	Missense
SLC7A14	NM_020949	Br27P	g.chr3:171667699G>A	c.2162G>A	p.G721D	Missense
SLC7A6	NM_003983	Br13X	g.chr16:66883037C>T	c.994C>T	p.L332F	Missense
SLC8A1	CCDS1806.1	Br07X	g.chr2:40568624C>G	c.448C>G	p.L150V	Missense
SLC9A1	CCDS295.1	Br07X	g.chr1:27120218C>T	c.1006C>T	p.L336F	Missense
SLC9A2	CCDS2062.1	Br27P	g.chr2:102758380G>A	c.1147G>A	p.V383M	Missense
SLC9A2	CCDS2062.1	Br27P	g.chr2:102732565C>T	c.314C>T	p.P105L	Missense
SLC9A2	CCDS2062.1	Br23X	g.chr2:102732730G>A	c.479G>A	p.R160H	Missense
SLC9A3R2	NM_004785	Br27P	g.chr16:2026853C>T	c.718C>T	p.R240W	Missense
SLC9A4	NM_001011552	Br9PT	g.chr2:102583058G>A	c.1201G>A	p.V401I	Missense
SLCO1B1	CCDS8685.1	Br20P	g.chr12:21244773G>A	c.1035G>A	p.T345T	Synonymous
SLCO2A1	CCDS3084.1	Br27P	g.chr3:135144251C>T	c.1521C>T	p.C507C	Synonymous
SLCO4C1	NM_180991	Br27P	g.chr5:101654959G>A	c.606G>A	p.G202G	Synonymous
SLCO6A1	NM_173488	Br20P	g.chr5:101752341G>A	c.1967G>A	p.R656H	Missense
SLIT2	CCDS3426.1	Br11P	g.chr4:20188405A>C	c.933A>C	p.T311T	Synonymous
SLITRK1	CCDS9464.1	Br27P	g.chr13:83352763G>A	c.881G>A	p.G294E	Missense
SLITRK5	CCDS9465.1	Br05x	g.chr13:87126216G>A	c.572G>A	p.S191N	Missense
SLITRK6	ENST00000313206	Br27P	g.chr13:85268389G>A	c.256G>A	p.G86R	Missense
SMARCA2	NM_003070	Br29P	g.chr9:2046831C>T	c.1333C>T	p.R445C	Missense
SMARCA4	CCDS12253.1	Br27P	g.chr19:10955957G>A	c.130G>A	p.G44R	Missense
SMARCC2	CCDS8907.1	Br27P	g.chr12:54845445G>A	c.3063G>A	p.G1021G	Synonymous
SMARCC2	CCDS8907.1	Br03X	g.chr12:54861124C>T	c.985C>T	p.R329C	Missense
SMC5L1	CCDS6632.1	Br27P	g.chr9:70159251G>A	c.1618G>A	p.A540T	Missense
SMCR8	CCDS11195.1	Br20P	g.chr17:18162194T>A	UTR+2T>A	3'UTR	3'UTR
SMF_HUMAN SN	ENST00000261804 CCDS13060.1	Br27P Br15X	g.chr5:149407502G>A g.chr20:3635219G>T	c.3520G>A c.184G>T	p.E1177K p.D62Y	Missense Missense
SNED1	ENST00000310397	Br27P	g.chr2:241741088C>T	c.3218C>T	p.P1073L	Missense
SNRPA	CCDS12565.1	Br23X	g.chr19:45957225G>A	c.296G>A	p.G99D	Missense
SNX13	NM_015132	Br27P	g.chr7:17611574C>T	c.2492C>T	p.A831V	Missense
SNX27	CCDS1001.1	Br27P	g.chr1:148443903G>A	c.663G>A	p.G221G	Synonymous
SNX4	CCDS3032.1	Br15X	g.chr3:126721635C>T	c.72C>T	p.D24D	Synonymous
SOCS5	CCDS1830.1	Br27P	g.chr2:46897685G>A	c.365G>A	p.G122E	Missense
SOHLH1	NM_001012415	Br20P	g.chr9:135814487G>A	c.577G>A	p.A193T	Missense
SORCS2	NM_020777	Br27P	g.chr4:7787006C>T	c.706C>T	p.P236S	Missense
SORCS3	CCDS7558.1	Br27P	g.chr10:106949819G>A	c.2082G>A	p.R694R	Synonymous
SORL1	CCDS8436.1	Br08X	g.chr11:120995788C>T	c.5841C>T	p.S1947S	Synonymous
SOS1	CCDS1802.1	Br17X	g.chr2:39161923G>A	c.1297G>A	p.E433K	Missense
SOSTDC1	CCDS5360.1	Br17X	g.chr7:16275425C>T	c.609C>T	p.H203H	Synonymous
SOX13	NM_005686	Br27P	g.chr1:200813919G>A	c.219G>A	p.W73X	Nonsense
SOX30	CCDS4339.1	Br27P	g.chr5:156998029G>A	c.1667G>A	p.R556K	Missense

Fig. 10

SOX8	CCDS10428.1	Br27P	g.chr16:973886C>T	c.580C>T	p.P194S	Missense
SP100	CCDS2477.1	Br25X	g.chr2:231194445A>T	c.1805A>T	p.Q602L	Missense
SPACA4	CCDS12725.1	Br13X	g.chr19:53802290C>T	c.243C>T	p.G81G	Synonymous
SPAG1	NM_003114	Br27P	g.chr8:101306708G>A	c.1820G>A	p.G607E	Missense
SPAG5	NM_006461	Br27P	g.chr17:23943830G>A	c.559G>A	p.A187T	Missense
SPAG7	NM_004890	Br27P	g.chr17:4804840G>A	c.117G>A	p.E39E	Synonymous
SPATA1	CCDS697.1	Br27P	g.chr1:84710633G>A	c.680G>A	p.G227E	Missense
SPATA2	CCDS13422.1	Br27P	g.chr20:47958148G>A	c.287G>A	p.G96D	Missense
SPATC1	CCDS6413.1	Br27P	g.chr8:145167826C>T	c.863C>T	p.P288L	Missense
Spc25	CCDS2229.1	Br27P	g.chr2:169559318G>A	c.283G>A	p.E95K	Missense
SPEG	ENST00000265327	Br27P	g.chr2:220170269G>A	c.5244G>A	p.L1748L	Synonymous
SPEN	CCDS164.1	Br27P	g.chr1:15944675G>A	c.142G>A	p.A48T	Missense
SPG3A	CCDS9700.1	Br27P	g.chr14:50157167C>T	c.963C>T	p.T321T	Synonymous
SPI1	CCDS7933.1	Br27P	g.chr11:47333534C>T	c.615C>T	p.H205H	Synonymous
SPIN3	NM_001010862	Br20P	g.chrX:56904355C>T	c.47C>T	p.T16M	Missense
SPIRE2	NM_032451	Br27P	g.chr16:88463485C>T	c.1816C>T	p.P606S	Missense
SPN	CCDS10650.1	Br27P	g.chr16:29583027G>A	c.477G>A	p.E159E	Synonymous
SPOCK3	NM_016950	Br27P	g.chr4:168050575T>A	c.754T>A	p.S252T	Missense
SPON2	CCDS3347.1	Br27P	g.chr4:1154911G>A	c.414G>A	p.A138A	Synonymous
SPRED2	NM_181784	Br25X	5452553insCGACTCCCTGAGAACTTGCATI990insCGACTCCCTGAGAACTTGCATCCGCCGC		indel	INDEL
SPTB	NM_001024858	Br27P	g.chr14:64311795C>T	c.4643C>T	p.A1548V	Missense
SPTBN1	NM_178313	Br27P	g.chr2:54767929C>T	c.1968C>T	p.D656D	Synonymous
SPTBN1	NM_178313	Br27P	g.chr2:54770045C>T	c.3171C>T	p.D1057D	Synonymous
SPTBN2	CCDS8150.1	Br27P	g.chr11:66231778C>T	c.1438C>T	p.R480W	Missense
SPTBN4	CCDS12559.1	Br13X	g.chr19:45670480G>A (homozygous)	c.112G>A	p.A38T	Missense
SPTBN5	NM_016642	Br15X	g.chr15:39936447G>A	c.8704G>A	p.A2902T	Missense
SREBF2	CCDS14023.1	Br27P	g.chr22:40596166G>A	c.1324G>A	p.A442T	Missense
SRGAP1	CCDS8967.1	Br14X	g.chr12:62777286A>T	IVS14-2A>T	Splice Site	Splice Site
SRPK2	CCDS5735.1	Br27P	g.chr7:104377559G>A	c.950G>A	p.G317D	Missense
SRRM2	NM_016333	Br27P	g.chr16:2751609G>A	c.1079G>A	p.G360D	Missense
SSFA2	CCDS2284.1	Br27P	g.chr2:182591112A>G	c.687A>G	p.V229V	Synonymous
ST14	CCDS8487.1	Br9PT	g.chr11:129565700C>G	c.776C>G	p.T259S	Missense
ST8SIA4	CCDS4091.1	Br25X	g.chr5:100219999G>T	c.504G>T	p.R168S	Missense
STAB1	NM_015136	Br20P	g.chr3:52516997C>G	c.2063C>G	p.P688R	Missense
STAP2	CCDS12128.1	Br02X	g.chr19:4279780A>C	c.482A>C	p.E161A	Missense
STIM2	CCDS3440.1	Br02X	g.chr4:26686687G>T	c.1544G>T	p.R515L	Missense
STK33	CCDS7789.1	Br27P	g.chr11:8391759G>A	c.1203G>A	p.W401X	Nonsense
STK39	NM_013233	Br10P	g.chr2:168843809T>C	c.623T>C	p.I208T	Missense
STRA6	CCDS10261.1	Br08X	g.chr15:72274725C>T	c.568C>T	p.Q190X	Nonsense
STS	CCDS14127.1	Br27P	g.chrX:7035338G>A	c.370G>A	p.D124N	Missense
STS-1	NM_032873	Br15X	g.chr11:122177146C>T	c.1491C>T	p.P497P	Synonymous
STX11	CCDS5205.1	Br25X	g.chr6:144550027C>T (homozygous)	c.570C>T	p.S190S	Synonymous
STX12	CCDS310.1	Br27P	g.chr1:27830323G>A	c.670G>A	p.E224K	Missense
STXBP2	CCDS12181.1	Br9PT	g.chr19:7613394C>T	c.874C>T	p.R292C	Missense
STXBP3	CCDS790.1	Br27P	g.chr1:109037111G>A	c.835G>A	p.E279K	Missense
STYK1	CCDS8629.1	Br27P	g.chr12:106665525C>T	c.946C>T	p.L316F	Missense
SUCLA2	CCDS9406.1	Br27P	g.chr13:47440869C>T	c.664C>T	p.L222F	Missense
SUCLG2	NM_003848	Br27P	g.chr3:67628971G>A	c.859G>A	p.G287S	Missense
SULT6B1	NM_001032377	Br03X	g.chr2:37310339T>A	c.556T>A	p.F186I	Missense
SUNC1	NM_152782	Br27P	g.chr7:47820016C>T	c.478C>T	p.P160S	Missense

Fig. 10

SUSD5	ENST00000309558	Br27P	g.chr3:33230444G>A	c.687G>A	p.W229X	Nonsense
SV2B	CCDS10370.1	Br23X	g.chr15:89633801dupT	c.1755dupT	fs	INDEL
SWAP70	NM_015055	Br27P	g.chr11:9710759G>A	c.1006G>A	p.E336K	Missense
SYDE2	ENST00000234668	Br06X	g.chr1:85360243C>T	c.1620C>T	p.D540D	Synonymous
SYN2	NM_133625	Br27P	g.chr3:12186278C>T	c.1180C>T	p.L394L	Synonymous
SYNE1	CCDS5236.1	Br27P	g.chr6:152744768C>T	c.13166C>T	p.A4389V	Missense
SYNE1	CCDS5236.1	Br27P	g.chr6:152723692C>T	c.16972C>T	p.P5658S	Missense
SYNE1	CCDS5237.1	Br07X	g.chr6:152655536_152655534delATC	c.3418_3420delATC	p.I1140del	INDEL
SYNE1	CCDS5236.1	Br27P	g.chr6:152780625G>A	c.9814G>A	p.V3272M	Missense
SYNE1	CCDS5236.1	Br27P	g.chr6:152775573G>A	IVS61-1G>A	Splice Site	Splice Site
SYNE2	CCDS9761.1	Br27P	g.chr14:63698738G>A	c.5445G>A	p.Q1815Q	Synonymous
SYT15	NM_181519	Br27P	g.chr10:46385078C>T	c.873C>T	p.Y291Y	Synonymous
SYT16	NM_031914	Br27P	g.chr14:61617332C>T	c.961C>T	p.P321S	Missense
SYT6	CCDS8871.1	Br27P	g.chr1:114358340C>T	c.862C>T	p.P288S	Missense
TAAR9	ENST00000340640	Br27P	g.chr6:132901206C>T	c.85C>T	p.P29S	Missense
TACC2	CCDS7626.1	Br20P	g.chr10:123836918G>A	c.4913G>A	p.R1638K	Missense
TACC3	CCDS3352.1	Br23X	g.chr4:1708936G>A	c.2038G>A	p.E680K	Missense
TAF1L	NM_153809	Br27P	g.chr9:32622684G>A	c.2894G>A	p.C965Y	Missense
TAF4B	ENST00000269142	Br08X	g.chr18:22169166G>T	c.2298G>T	p.Q766H	Missense
TAF6	CCDS5686.1	Br04X	g.chr7:99350752G>A	c.1347G>A	p.R449R	Synonymous
TANC1	NM_033394	Br27P	g.chr2:159912250C>T	c.4806C>T	p.G1602G	Synonymous
TAOK1	NM_020791	Br17X	g.chr17:24873431A>G	c.1916A>G	p.N639S	Missense
TARBP2	CCDS8861.1	Br27P	g.chr12:52183775C>T	c.338C>T	p.P113L	Missense
TAS1R2	CCDS187.1	Br17X	g.chr1:189263667C>T	c.903C>T	p.S301S	Synonymous
TAS2R3	CCDS5867.1	Br27P	g.chr7:140917650C>T	c.508C>T	p.H170Y	Missense
TBC1D20	CCDS13002.1	Br13X	g.chr20:367925C>T	c.783C>T	p.R261R	Synonymous
TBC1D4	NM_014832	Br27P	g.chr13:74759159G>A	c.3670G>A	p.A1224T	Missense
TBCD	NM_001033052	Br27P	g.chr17:78303503G>A	c.145G>A	p.G49S	Missense
TBX20	CCDS5445.1	Br26X	g.chr7:35044358G>C	c.888G>C	p.E296D	Missense
TBX22	CCDS14445.1	Br9PT	g.chrX:79083947G>A	c.34G>A	p.V12M	Missense
TBX22	CCDS14445.1	Br13X	g.chrX:79089707C>T	c.936C>T	p.G312G	Synonymous
TCF7L1	CCDS1971.1	Br27P	g.chr2:85444157C>T	c.962C>T	p.P321L	Missense
TCF8	CCDS7169.1	Br27P	g.chr10:31850182C>T	c.1913C>T	p.S638L	Missense
TCHH	ENST00000290532	Br13X	g.chr1:148898499C>T	c.267C>T	p.L89L	Synonymous
TCN2	CCDS13881.1	Br27P	g.chr22:29336279C>T	c.891C>T	p.N297N	Synonymous
TDRD5	CCDS1332.1	Br05X	g.chr1:176391563G>A	c.2774G>A	p.R925H	Missense
TDRD9	CCDS9987.1	Br03X	g.chr14:103558360C>T	c.1691C>T	p.S564F	Missense
TEAD2	CCDS12761.1	Br27P	g.chr19:54537527G>A	c.1210G>A	p.E404K	Missense
TEAD2	CCDS12761.1	Br27P	g.chr19:54552343G>A	c.338G>A	p.R113K	Missense
TEPP	CCDS10790.1	Br15X	g.chr16:56575722G>A	c.403G>A	p.A135T	Missense
TERF2IP	NM_018975	Br27P	g.chr16:74239592C>T	c.311C>T	p.A104V	Missense
TFE3	CCDS14315.1	Br27P	g.chrX:48653042G>A	c.373G>A	p.A125T	Missense
TGFBRAP1	CCDS2067.1	Br27P	g.chr2:105347941C>T	c.1861C>T	p.L621L	Synonymous
TGM1	CCDS9622.1	Br27P	g.chr14:23799722G>A	c.531G>A	p.K177K	Synonymous
TGM1	CCDS9622.1	Br04X	chr14:23798998_23798990delGAACTACG	c.864_872delGAACTACGG	indel	INDEL
TGM5	NM_004245	Br29P	g.chr15:41332273G>A	c.592G>A	p.V198I	Missense
THAP9	CCDS3598.1	Br03X	4:84195390_84195404delAAGTATGCCTC*	c.846_860delAAGTATGCCTCTCAA	indel	INDEL
THBS1	NM_003246	Br02X	g.chr15:37666845G>A	c.1126G>A	p.D376N	Missense
THEA	CCDS592.1	Br27P	g.chr1:54762516G>A	c.201G>A	p.G67G	Synonymous
THOP1	CCDS12095.1	Br27P	g.chr19:2756027G>A	c.603G>A	p.E201E	Synonymous

Fig. 10

THRAP3	ENST00000354618	Br08x	g.chr3:31471061C>T	c.1453C>T	p.R485X	Nonsense
THSD7B	ENST00000272643	Br27P	g.chr2:137706467C>T	c.1241C>T	p.S414F	Missense
THSD7B	ENST00000272643	Br16X	g.chr2:137824412C>T	c.2127C>T	p.H709H	Synonymous
TIMP2	CCDS11758.1	Br27P	g.chr17:74381568G>A	c.159G>A	p.K53K	Synonymous
TINAG	CCDS4955.1	Br17X	g.chr6:54294093A>T	c.459A>T	p.V153V	Synonymous
TJP3	NM_014428	Br27P	g.chr19:3691579C>T	c.1760C>T	p.A587V	Missense
TLL1	CCDS3811.1	Br9PT	g.chr4:167293224C>T	c.949C>T	p.R317C	Missense
TLN1	NM_006289	Br14X	g.chr9:35707211G>A	c.2390G>A	p.R797H	Missense
TLX3	NM_021025	Br25X	g.chr5:170669954C>G	c.617C>G	p.T206R	Missense
TM4SF14	CCDS7369.1	Br27P	g.chr10:82259144C>T	c.387C>T	p.S129S	Synonymous
TM4SF3	CCDS8999.1	Br27P	g.chr12:69824205C>T	c.116C>T	p.S39F	Missense
TM9SF4	CCDS13196.1	Br29P	g.chr20:30206600A>G	c.1228A>G	p.I410V	Missense
TMED1	CCDS12249.1	Br27P	g.chr19:10806724G>A	c.351G>A	p.K117K	Synonymous
TMEM131	ENST00000186436	Br27P	g.chr2:97889046C>T	c.1181C>T	p.S394F	Missense
TMEM131	ENST00000186436	Br17X	g.chr2:97835650G>A	c.4690G>A	p.V1564I	Missense
TMEM132C	ENST00000315208	Br02X	g.chr12:127715233C>A	c.1688C>A	p.T563N	Missense
TMEM16B	NM_020373	Br08X	g.chr12:5592348G>A	c.1969G>A	p.D657N	Missense
TMEM16C	NM_031418	Br9PT	g.chr11:26515535G>A	c.983G>A	p.R328H	Missense
TMEM16E	NM_213599	Br27P	g.chr11:22233570G>A	c.1258G>A	p.E420K	Missense
TMEM16G	NM_001001891	Br27P	g.chr2:241864319G>A	c.1101G>A	p.V367V	Synonymous
TMEM16J	NM_001012302	Br27P	g.chr11:423872G>A	c.147G>A	p.R49R	Synonymous
TMEM16J	NM_001012302	Br23X	g.chr11:410714C>T	IVS18+4C>T	Splice Site	Splice Site
TMEM38A	CCDS12349.1	Br27P	g.chr19:16651821C>T	c.151C>T	p.P51S	Missense
TMEM38A	CCDS12349.1	Br27P	g.chr19:16652313G>A	c.387G>A	p.K129K	Synonymous
TMEM46	NM_001007538	Br27P	g.chr13:25518984C>T	c.555C>T	p.A185A	Synonymous
TMEM63B	NM_018426	Br27P	g.chr6:44215211G>A	c.437G>A	p.G146D	Missense
TMEM8	CCDS10407.1	Br27P	g.chr16:365425G>A	c.1236G>A	p.R412R	Synonymous
TMEM8	CCDS10407.1	Br27P	g.chr16:366366G>A	c.995G>A	p.S332N	Missense
TMPRSS2	NM_005656	Br27P	g.chr21:41762253C>T	c.1254C>T	p.N418N	Synonymous
TMPRSS4	NM_019894	Br26X	g.chr11:117489205A>T	c.755A>T	p.D252V	Missense
TNC	CCDS6811.1	Br27P	g.chr9:114924560G>A	c.2212G>A	p.A738T	Missense
TNFAIP2	CCDS9979.1	Br17X	g.chr14:102662727G>A	c.180G>A	p.A60A	Synonymous
TNFSF18	CCDS1305.1	Br9PT	g.chr1:169742463G>A	c.235G>A	p.V79M	Missense
TNFSF4	CCDS1306.1	Br27P	g.chr1:169887356C>T	c.508C>T	p.L170L	Synonymous
TNFSF9	CCDS12169.1	Br9PT	g.chr19:6486005C>T	c.693C>T	p.G231G	Synonymous
TNIP1	NM_006058	Br27P	g.chr5:150398977C>T	c.1137C>T	p.T379T	Synonymous
TNIP2	CCDS3362.1	Br15X	g.chr4:2786718C>T	c.437C>T	p.S146F	Missense
TNK1	NM_003985	Br27P	g.chr17:7228135C>T	c.705C>T	p.Y235Y	Synonymous
TNMD	CCDS14469.1	Br23X	g.chrX:99658721G>T	c.499G>T	p.D167Y	Missense
TNN	NM_022093	Br27P	g.chr1:171778440G>A	c.229G>A	p.E77K	Missense
TNPO1	CCDS4016.1	Br27P	g.chr5:72221442G>A	c.1579G>A	p.V527I	Missense
TNR	CCDS1318.1	Br27P	g.chr1:172107441G>A	c.67G>A	p.G23S	Missense
TNRC15	NM_015575	Br27P	g.chr2:233530088C>T	c.2791C>T	p.Q931X	Nonsense
TNRC15	NM_015575	Br27P	g.chr2:233534273C>T	c.2902C>T	p.Q968X	Nonsense
TNRC4	CCDS1002.1	Br13X	g.chr1:148493426G>A	c.545G>A	p.R182H	Missense
TNRC6C	NM_018996	Br27P	g.chr17:73599140T>C	c.3827T>C	p.V1276A	Missense
TOE1	CCDS521.1	Br27P	g.chr1:45478074C>T	c.1140C>T	p.T380T	Synonymous
TOP2A	NM_001067	Br11P	g.chr17:35820923A>G	c.1167A>G	p.G389G	Synonymous
TOR1A	CCDS6930.1	Br03X	g.chr9:129660704C>A	c.494C>A	p.S165Y	Missense
TOSO	CCDS1473.1	Br27P	g.chr1:203471565C>T	c.885C>T	p.A295A	Synonymous

Fig. 10

TP53	CCDS11118.1	Br9PT	g.chr17:7520254G>A	c.158G>A	p.W53X	Nonsense
TP53	CCDS11118.1	Br23X	g.chr17:7519128G>T (homozygous)	c.527G>T	p.C176F	Missense
TP53	CCDS11118.1	Br29P	g.chr17:7518988C>T	c.586C>T	p.R196X	Nonsense
TP53	CCDS11118.1	Br13X	g.chr17:7518984T>A	c.590T>A	p.V197E	Missense
TP53	CCDS11118.1	Br27P	g.chr17:7518957delT	c.617delT	fs	INDEL
TP53	CCDS11118.1	Br9PT	g.chr17:7518948_7518947delGA	c.626_627delGA	fs	INDEL
TP53	CCDS11118.1	Br04X	g.chr17:7518273G>A (homozygous)	c.733G>A	p.G245S	Missense
TP53	CCDS11118.1	Br12P	g.chr17:7518272G>A	c.734G>A	p.G245D	Missense
TP53	CCDS11118.1	Br07X	g.chr17:7518264C>T	c.742C>T	p.R248W	Missense
TP53	CCDS11118.1	Br10P	g.chr17:7517846C>T	c.817C>T	p.R273C	Missense
TP53	CCDS11118.1	Br11P	g.chr17:7517845G>A	c.818G>A	p.R273H	Missense
TP53	CCDS11118.1	Br03X	g.chr17:7517819C>T (homozygous)	c.844C>T	p.R282W	Missense
TP53	CCDS11118.1	Br11P	g.chr17:7625707delG	c.1045delG	fs	INDEL
TPH2	NM_173353	Br13X	g.chr12:70702490G>A	c.1113G>A	p.G371G	Synonymous
TPR	NM_003292	Br27P	g.chr1:183064235G>A	IVS4-1G>A	Splice Site	Splice Site
TPST2	CCDS13839.1	Br02X	g.chr22:25261698G>A (homozygous)	c.453G>A	p.P151P	Synonymous
TRAM1L1	CCDS3707.1	Br08X	g.chr4:118363316G>A	c.837G>A	p.S279S	Synonymous
TRAPPC3	CCDS404.1	Br07X	g.chr1:36272641C>G	c.272C>G	p.P91R	Missense
TREML2	CCDS4853.1	Br03x	g.chr6:41276676G>A	c.226G>A	p.V76I	Missense
TREML3	ENST00000332842	Br9PT	g.chr6:41292883G>A	c.306G>A	p.T102T	Synonymous
TRIM14	CCDS6734.1	Br27P	g.chr9:97936784C>T	c.620C>T	p.P207L	Missense
TRIM42	CCDS3113.1	Br26X	g.chr3:141884298G>A	c.638G>A	p.R213H	Missense
TRIM45	CCDS893.1	Br15X	g.chr1:117370353C>G	c.1353C>G	p.S451R	Missense
TRIM46	CCDS1097.1	Br27P	g.chr1:151969718G>A	c.2259G>A	p.G753G	Synonymous
TRIM55	CCDS6186.1	Br15X	g.chr8:67249339G>A	c.683G>A	p.R228H	Missense
TRIM56	NM_030961	Br27P	g.chr7:100325094C>T	c.1066C>T	p.P356S	Missense
TRIM58	CCDS1636.1	Br11P	g.chr1:244365813T>C	c.1442T>C	p.V481A	Missense
TRIO	CCDS3883.1	Br04X	g.chr5:14340101_14340102insCCC	c.469__470insCCC	p.A156_L157insP	INDEL
TRIOBP	NM_007032	Br27P	g.chr22:36479751C>T	c.1165C>T	p.P389S	Missense
TRIP12	NM_004238	Br07x	g.chr2:230549372A>G	c.522A>G	p.K174K	Synonymous
TRIP6	CCDS5708.1	Br27P	g.chr7:100115547C>T	c.1402C>T	p.L468F	Missense
TRMT5	NM_020810	Br27P	g.chr14:60512237G>A	c.1153G>A	p.V385I	Missense
TRMT5	NM_020810	Br27P	g.chr14:60512083G>A	c.1307G>A	p.G436E	Missense
TRPC4AP	CCDS13246.1	Br27P	g.chr20:33095976C>A	c.858C>A	p.I286I	Synonymous
TRPC6	CCDS8311.1	Br27P	g.chr11:100880259C>T	c.651C>T	p.S217S	Synonymous
TRPM2	CCDS13710.1	Br27P	g.chr21:44635733C>T	c.1591C>T	p.L531L	Synonymous
TRPM3	CCDS6634.1	Br10P	g.chr9:70447878G>C	c.2271G>C	p.W757C	Missense
TRPM4	NM_017636	Br03X	g.chr19:54363651C>T (homozygous)	c.642C>T	p.R214R	Synonymous
TRPM5	NM_014555	Br29P	g.chr11:2382782G>A	c.3459G>A	p.W1153X	Nonsense
TRPM6	CCDS6647.1	Br27P	g.chr9:74607488C>T	c.3653C>T	p.T1218I	Missense
TRPM7	NM_017672	Br27P	g.chr15:48662577G>A	c.4555G>A	p.V1519I	Missense
TRPV5	CCDS5875.1	Br15X	g.chr7:142139519G>A	c.1064G>A	p.R355H	Missense
TRPV5	CCDS5875.1	Br14X	g.chr7:142139507G>A	c.1076G>A	p.R359H	Missense
TRRAP	CCDS5659.1	Br27P	g.chr7:98232807C>T	c.9595C>T	p.P3199S	Missense
TSAP6	CCDS2125.1	Br27P	g.chr2:119728523G>A	c.1054G>A	p.E352K	Missense
TSAP6	CCDS2125.1	Br20P	g.chr2:119736998G>A	c.1321G>A	p.V441I	Missense
TSC2	CCDS10458.1	BR27P	g.chr16:2046664G>A	c.667G>A	p.D223N	Missense
TSCOT	CCDS6786.1	Br27P	g.chr9:112732030G>A	c.487G>A	p.G163S	Missense
TSGA10	CCDS2037.1	Br27P	g.chr2:99110332A>C	c.1493A>C	p.Q498P	Missense
TTC12	CCDS8360.1	Br27P	g.chr11:112720256C>T	c.1038C>T	p.A346A	Synonymous

Fig. 10

TTC18	CCDS7324.1	Br27P	g.chr10:74739980G>A	c.1408G>A	p.E470K	Missense
TTC6	NM_001007795	Br15X	g.chr14:37335842G>T	c.161G>T	p.R54I	Missense
TTLL2	CCDS5301.1	Br27P	g.chr6:167724715G>A	c.916G>A	p.G306R	Missense
TTLL5	NM_015072	Br16X	g.chr14:75199303G>A	c.58G>A	p.E20K	Missense
TTN	NM_133378	Br15X	g.chr2:179417362G>A	c.16504G>A	p.A5502T	Missense
TTN	NM_133378	Br27P	g.chr2:179413114G>A	c.18286G>A	p.V6096I	Missense
TTN	NM_133378	Br27P	g.chr2:179314846G>A	c.36963G>A	p.G12321G	Synonymous
TTN	NM_133432	Br07x	g.chr2:179259759G>T	c.49787G>T	p.G16596V	Missense
TTN	NM_133432	Br27P	g.chr2:179258095C>T	c.51451C>T	p.P17151S	Missense
TUBGCP3	CCDS9525.1	Br05X	g.chr13:112248141A>G	c.1208A>G	p.Y403C	Missense
TUBGCP6	CCDS14087.1	Br27P	g.chr22:48959592C>A	c.4818C>A	p.Y1606X	Nonsense
TUBGCP6	CCDS14087.1	Br27P	g.chr22:48959587T>G	IVS21+2T>G	Splice Site	Splice Site
TULP1	CCDS4807.1	Br27P	g.chr6:35586617G>A	c.498G>A	p.R166R	Synonymous
TXNDC3	CCDS5452.1	Br20P	g.chr7:37674978C>T	c.379C>T	p.R127X	Nonsense
TYR	CCDS8284.1	Br03X	g.chr11:88551006G>A	c.237G>A	p.S79S	Synonymous
UBAP2L	CCDS1063.1	Br27P	g.chr1:151020282G>A	c.422G>A	p.G141E	Missense
UBE2G2	CCDS13714.1	Br27P	g.chr21:45032421C>T	c.61C>T	p.P21S	Missense
UCHL1	CCDS3462.1	Br27P	g.chr4:41103715G>A	c.298G>A	p.A100T	Missense
UGCGL2	CCDS9480.1	Br27P	g.chr13:95473926C>T	c.330C>T	p.F110F	Synonymous
UGDH	CCDS3455.1	Br23X	g.chr4:39328607T>C	c.1259T>C	p.F420S	Missense
UGT1A6	CCDS2510.1	Br02X	g.chr2:234451438G>T	c.505G>T	p.V169L	Missense
ULK1	CCDS9274.1	Br27P	g.chr12:131058307G>A	IVS5+1G>A	Splice Site	Splice Site
UNQ2446	CCDS10850.1	Br04X	g.chr16:66477589C>T	c.424C>T	p.L142F	Missense
UNQ3030	CCDS3319.1	Br17X	g.chr3:197875921C>T	c.1097C>T	p.T366M	Missense
UNQ689	CCDS3542.1	Br13X	g.chr4:71571406G>T	c.262G>T	p.G88W	Missense
UPK3B	CCDS5588.1	Br12P	g.chr7:75784626delG	c.6delG	fs	INDEL
URB1	ENST00000270201	Br13X	g.chr21:32660798C>T	c.1266C>T	p.N422N	Synonymous
USH2A	CCDS1516.1	Br20P	g.chr1:212761551G>T	c.3624G>T	p.W1208C	Missense
USP11	CCDS14277.1	Br27P	g.chrX:46860526G>A	c.2164G>A	p.V722M	Missense
USP26	CCDS14635.1	Br27P	g.chrX:131886308dupT	c.1461dupT	fs	INDEL
USP8	CCDS10137.1	Br27P	g.chr15:48520970C>T	c.237C>T	p.F79F	Synonymous
VANGL1	CCDS883.1	Br27P	g.chr1:115918753C>T	c.634C>T	p.R212W	Missense
VCAM1	CCDS773.1	Br27P	g.chr1:100906938G>A	c.1183G>A	p.G395R	Missense
VCIP135	CCDS6192.1	Br27P	g.chr8:67709358G>A	c.3601G>A	p.E1201K	Missense
VCL	CCDS7340.1	Br27P	g.chr10:75524051C>T	c.1369C>T	p.P457S	Missense
VDP	NM_003715	Br27P	g.chr4:77065503C>T	c.965C>T	p.A322V	Missense
VDR	CCDS8757.1	Br27P	g.chr12:46524945C>T	c.1135C>T	p.L379F	Missense
VGCNL1	CCDS9498.1	Br27P	g.chr13:100557861G>A	c.2557G>A	p.V853M	Missense
VGLL2	CCDS5115.1	Br17X	8780delGGCGCCCGGCCCGCCTCGCAA	6_773delGGCGCCCGGCCCGCCTCGCAACCGC	fs	INDEL
VIPR2	CCDS5950.1	Br27P	g.chr7:158329069G>A	c.598G>A	p.V200M	Missense
VMD2	NM_004183	Br27P	g.chr11:61482304C>T	c.825C>T	p.V275V	Synonymous
VN2R1P	ENST00000312652	Br27P	g.chr3:157237662C>T	c.1753C>T	p.P585S	Missense
VPS11	NM_021729	Br02X	g.chr11:118445239A>C	c.310A>C	p.K104Q	Missense
VPS13A	CCDS6655.1	Br27P	g.chr9:77195897G>A	c.7400G>A	p.G2467D	Missense
VPS24	NM_001005753	Br27P	g.chr2:86644694C>T	c.362C>T	p.A121V	Missense
VPS41	CCDS5457.1	Br27P	g.chr7:38565112G>A	c.1830G>A	p.Q610Q	Synonymous
VPS45A	CCDS944.1	Br27P	g.chr1:146862067G>A	c.370G>A	p.E124K	Missense
VSIG2	CCDS8452.1	Br27P	chr11:124124879_124124873delAGCCAG	c.521_527delAGCCAGT	fs	INDEL
VWF	CCDS8539.1	Br26X	g.chr12:5929291C>T	c.8175C>T	p.N2725N	Synonymous
WBSCR17	CCDS5540.1	Br27P	g.chr7:70480944C>T	c.986C>T	p.S329L	Missense

Fig. 10

WBSCR27	CCDS5561.1	Br27P	g.chr7:72700151C>T	c.152C>T	p.P51L	Missense
WDFY3	CCDS3609.1	Br27P	g.chr4:86099881C>T	c.1126C>T	p.H376Y	Missense
WDR21	CCDS9809.1	Br27P	g.chr14:72490871C>T	c.932C>T	p.T311I	Missense
WDR22	NM_003861	Br04X	g.chr14:68689345G>A	c.104G>A	p.R35K	Missense
WDR24	CCDS10420.1	Br06x	g.chr16:677287C>T	c.790C>T	p.R264C	Missense
WDR27	NM_182552	Br27P	g.chr6:169675358G>A	c.2649G>A	p.L883L	Synonymous
WDR32	CCDS6613.1	Br27P	g.chr9:37851206C>T	c.940C>T	p.L314L	Synonymous
WDR34	CCDS6906.1	Br27P	g.chr9:128475704C>T	c.1133C>T	p.T378I	Missense
WDR34	CCDS6906.1	Br27P	g.chr9:128478821G>A	c.124G>A	p.A42T	Missense
WDR42B	ENST00000329763	Br14X	g.chrX:27525350T>A (homozygous)	c.552T>A	p.H184Q	Missense
WDR52	CCDS2972.1	Br27P	g.chr3:114580980G>A	c.2161G>A	p.E721K	Missense
WDR6	CCDS2782.1	Br27P	g.chr3:49025141C>T	c.1170C>T	p.F390F	Synonymous
WDR70	NM_018034	Br27P	g.chr5:37432400G>A	c.463G>A	p.E155K	Missense
WDTC1	CCDS296.1	Br27P	g.chr1:27308633C>T	c.1118C>T	p.A373V	Missense
WEE1	CCDS7800.1	Br27P	g.chr11:9554199G>A	c.765G>A	p.K255K	Synonymous
WFS1	CCDS3386.1	Br27P	g.chr4:6403941G>A	c.282G>A	p.R94R	Synonymous
WFS1	CCDS3386.1	Br27P	g.chr4:6411108G>A	c.573G>A	p.K191K	Synonymous
WNK1	CCDS8506.1	Br27P	g.chr12:866660G>A	c.5293G>A	p.G1765S	Missense
WNK2	CCDS6704.1	Br06X	g.chr9:93109685G>A	c.3799G>A	p.A1267T	Missense
WNT9A	NM_003395	Br27P	g.chr1:224419937C>T	c.114C>T	p.P38P	Synonymous
XAB2	NM_020196	Br04X	g.chr19:7595305C>A	c.849C>A	p.I283I	Synonymous
XDH	CCDS1775.1	Br04X	g.chr2:31535799C>A	c.244C>A	p.H82N	Missense
XPO1	NM_003400	Br27P	g.chr2:61632778G>A	c.1147G>A	p.E383K	Missense
XPO7	NM_015024	Br23X	g.chr8:21896149G>A	c.1157G>A	p.R386Q	Missense
XR_016172.1	ENST00000355015	Br17X	g.chr11:1145657C>T	c.345C>T	p.Y115Y	Synonymous
XR_017335.1	ENST00000314295	Br03X	g.chr5:79663421C>T	c.627C>T	p.Y209Y	Synonymous
YN004_HUMAN	ENST00000281581	Br27P	g.chr14:59104832C>T	c.375C>T	p.R125R	Synonymous
YTHDC2	CCDS4113.1	Br27P	g.chr5:112896581C>T	c.782C>T	p.A261V	Missense
YWHAH	CCDS13901.1	Br14X	g.chr22:30676761C>T	c.169C>T	p.R57X	Nonsense
ZAN	NM_173059	Br27P	g.chr7:100010258T>A	c.5014T>A	p.Y1672N	Missense
ZAN	NM_173059	Br27P	g.chr7:100034691G>A	c.7725G>A	p.W2575X	Nonsense
ZBTB16	CCDS8367.1	Br27P	g.chr11:113439645C>T	c.413C>T	p.A138V	Missense
ZBTB24	NM_014797	Br27P	g.chr6:109893955C>T	c.1886C>T	p.P629L	Missense
ZBTB4	CCDS11107.1	Br27P	g.chr17:7306183C>T	c.2842C>T	p.L948F	Missense
ZBTB9	NM_006772	Br27P	g.chr6:33513799G>A	c.1094G>A	p.G365E	Missense
ZC3H6	NM_198581	Br11P	g.chr2:112804980G>T	c.2254G>T	p.G752X	Nonsense
ZFPM1	NM_153813	Br05X	g.chr16:87079931G>T	c.124G>T	p.A42S	Missense
ZFYVE9	CCDS563.1	Br20P	g.chr1:52415353C>T	c.243C>T	p.T81T	Synonymous
ZFYVE9	CCDS563.1	Br27P	g.chr1:52416058G>A	c.948G>A	p.G316G	Synonymous
ZIC1	CCDS3136.1	Br08x	g.chr3:148610654G>A	c.57G>A	p.A19A	Synonymous
ZIK1	NM_001010879	Br20P	g.chr19:62794168A>G	c.1177A>G	p.T393A	Missense
ZMAT4	NM_024645	Br26X	g.chr8:40802277G>A	c.76G>A	p.E26K	Missense
ZNF10	CCDS9283.1	Br27P	g.chr12:132343082G>A	c.900G>A	p.K300K	Synonymous
ZNF160	CCDS12859.1	Br07X	g.chr19:58265291C>T	c.308C>T	p.P103L	Missense
ZNF17	NM_006959	Br27P	g.chr19:62623041G>A	c.369G>A	p.E123E	Synonymous
ZNF18	NM_144680	Br27P	g.chr17:11822490C>T	c.1159C>T	p.L387F	Missense
ZNF183L1	CCDS9486.1	Br27P	g.chr13:97626966C>T	c.526C>T	p.P176S	Missense
ZNF189	CCDS6754.1	Br27P	g.chr9:101251158G>A	c.1553G>A	p.G518E	Missense
ZNF25	CCDS7195.1	Br03X	g.chr10:38285976A>G	c.216A>G	p.E72E	Synonymous
ZNF286	CCDS11172.1	Br27P	g.chr17:15552269C>T	c.317C>T	p.P106L	Missense

Fig. 10

ZNF294	NM_015565	Br27P	g.chr21:29238660C>T	c.3898C>T	p.P1300S	Missense
ZNF295	CCDS13678.1	Br26X	g.chr21:42286277G>A	c.997G>A	p.G333S	Missense
ZNF30	NM_194325	Br27P	g.chr19:40126094C>T	c.141C>T	p.T47T	Synonymous
ZNF31	NM_145238	Br27P	g.chr1:33629817G>A	c.2582G>A	p.G861E	Missense
ZNF313	NM_018683	Br27P	g.chr20:47986403G>A	c.47G>A	p.G16E	Missense
ZNF318	CCDS4895.1	Br27P	g.chr6:43413696_43413694delAAA	c.5478_5480delAAA	p.K1827del	INDEL
ZNF333	CCDS12316.1	Br27P	g.chr19:14688011G>A	c.688G>A	p.D230N	Missense
ZNF339	CCDS13132.1	Br29P	g.chr20:17953443C>T	c.665C>T	p.T222M	Missense
ZNF343	CCDS13028.1	Br27P	g.chr20:2412002C>T	c.1605C>T	p.T535T	Synonymous
ZNF358	NM_018083	Br27P	g.chr19:7491396G>A	c.1007G>A	p.G336D	Missense
ZNF366	CCDS4015.1	Br05X	g.chr5:71792658G>A	c.422G>A	p.S141N	Missense
ZNF406	NM_001029939	Br27P	g.chr8:135684102G>A	c.1006G>A	p.V336M	Missense
ZNF440L	NM_001012753	Br14X	g.chr19:11950903G>A (homozygous)	c.1173G>A	p.A391A	Synonymous
ZNF473	NM_015428	Br27P	g.chr19:55234262C>T	c.42C>T	p.D14D	Synonymous
ZNF487	ENST00000315429	Br05x	g.chr7:4939760G>A	c.171G>A	p.L57L	Synonymous
ZNF496	CCDS1631.1	Br27P	g.chr1:243790270G>A	c.1356G>A	p.G452G	Synonymous
ZNF497	CCDS12977.1	Br03x	g.chr19:63559516A>T	c.1298A>T	p.Q433L	Missense
ZNF497	CCDS12977.1	BR02X	g.chr19:63559982G>A	c.832G>A	p.D278N	Missense
ZNF507	NM_014910	Br03X	g.chr19:37537093G>C	c.1517G>C	p.R506T	Missense
ZNF545	CCDS12493.1	Br04X	g.chr19:41575660C>T	c.1422C>T	p.G474G	Synonymous
ZNF547	NM_173631	Br27P	g.chr19:62580926C>T	c.770C>T	p.T257I	Missense
ZNF558	CCDS12208.1	Br27P	g.chr19:8783719G>A	c.447G>A	p.V149V	Synonymous
ZNF585A	CCDS12499.1	Br27P	g.chr19:42335256G>A	c.1220G>A	p.G407E	Missense
ZNF628	NM_033113	Br27P	g.chr19:60687304C>T	c.2899C>T	p.R967C	Missense
ZNF67	ENST00000323012	Br20P	g.chrX:66377878T>G	c.1111T>G	p.Y371D	Missense
ZNF79	CCDS6871.1	Br27P	g.chr9:127287027G>A	c.1494G>A	p.E498E	Synonymous
ZP2	CCDS10596.1	Br27P	g.chr16:21118396G>A	c.1923G>A	p.R641R	Synonymous
ZSCAN2	CCDS10329.1	Br15X	g.chr15:82966044C>G	c.1611C>G	p.S537R	Missense
ZSWIM4	NM_023072	Br04X	g.chr19:13797479C>T	c.1980C>T	p.A660A	Synonymous
ZSWIM4	NM_023072	Br27P	g.chr19:13771646C>T	c.266C>T	p.P89L	Missense
ZW10	CCDS8363.1	Br27P	g.chr11:113112631C>T	c.2140C>T	p.P714S	Missense

*Genomic positions are coordinates in the May 2004, hg17 35.1 UCSC Santa Cruz release of the human genome. Genomic coordinates and sequences of mutations are on the coding strand. are heterozygous unless marked as homozygous. g., genomic sequence; c., cDNA sequence; p., protein sequence; del, deletion; dup, duplication; ins, insertion.

Fig. 10

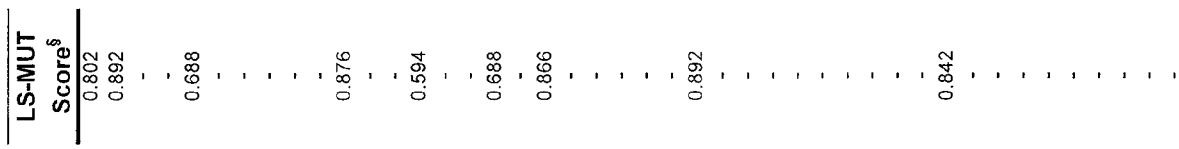

Fig. 10

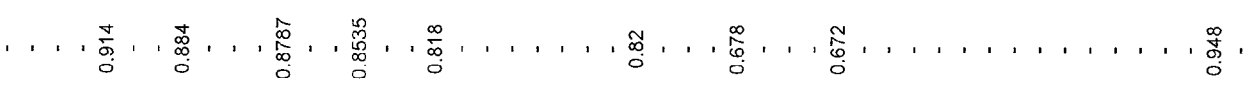

Fig. 10

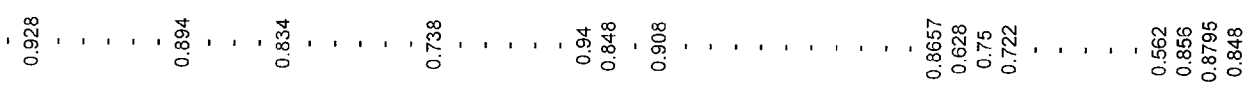
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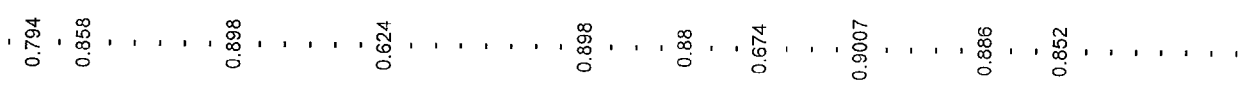
Fig. 10



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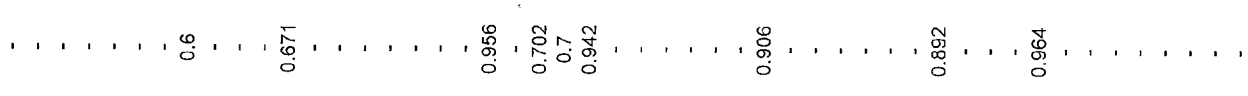

Fig. 10


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0.954
0.624
0.692
0.736
0.6581
0.946
0.722
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0.95
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0.72
0.96
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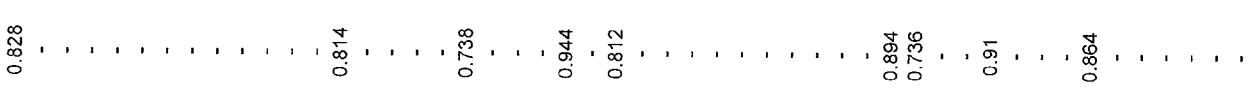
0.842
0.936
0.846

Fig. 10



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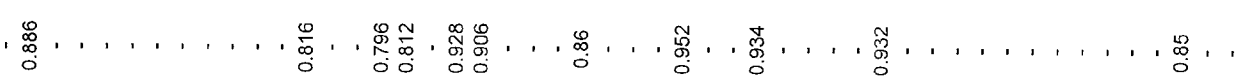


Fig. 10

Fig. 10

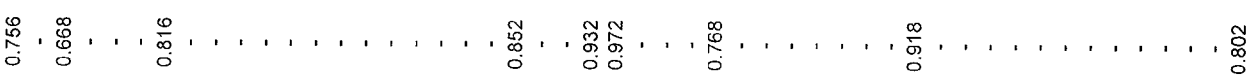
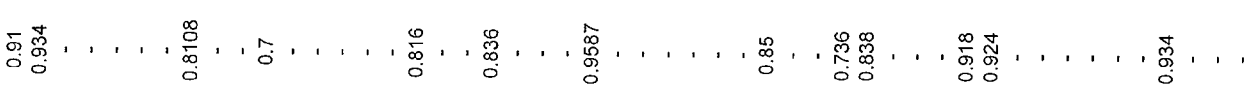


Fig. 10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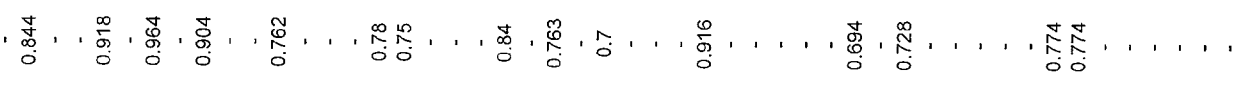
0.934
0.8108
0.7
0.816
0.836
0.9587
0.85
0.736
0.838
0.918
0.924
0.934

Fig. 10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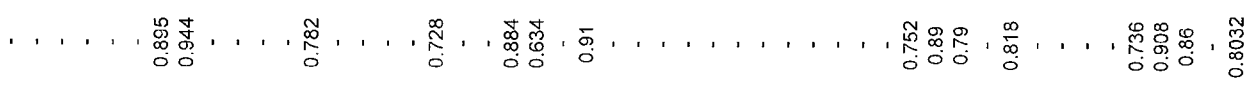
0.84
0.763
0.7
0.916
0.694
0.728
0.774
0.774

Fig. 10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0.782
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0.752
0.89
0.79
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0.736
0.908
0.86
0.8032

Fig. 10

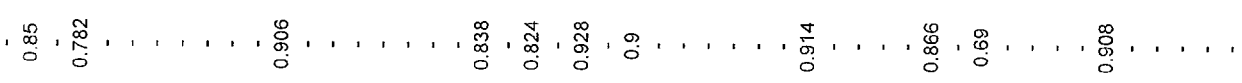
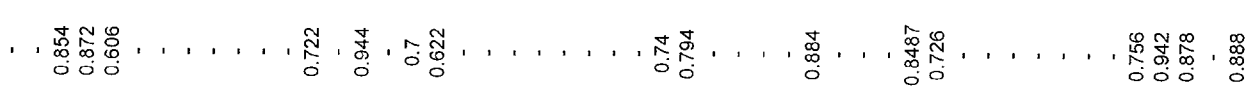


Fig. 10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0.872
0.606
0.722
0.944
0.7
0.622
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0.794
0.884
0.8487
0.726
0.756
0.942
0.878
0.888

Fig. 10

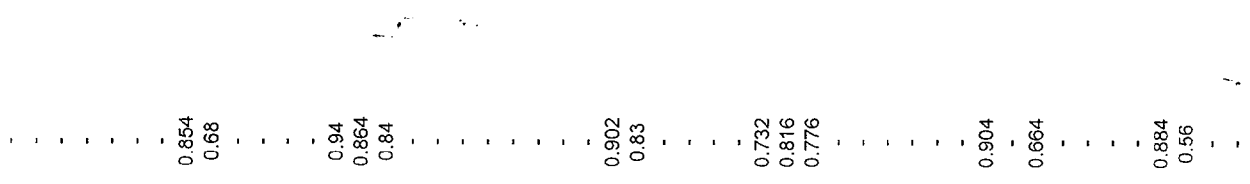
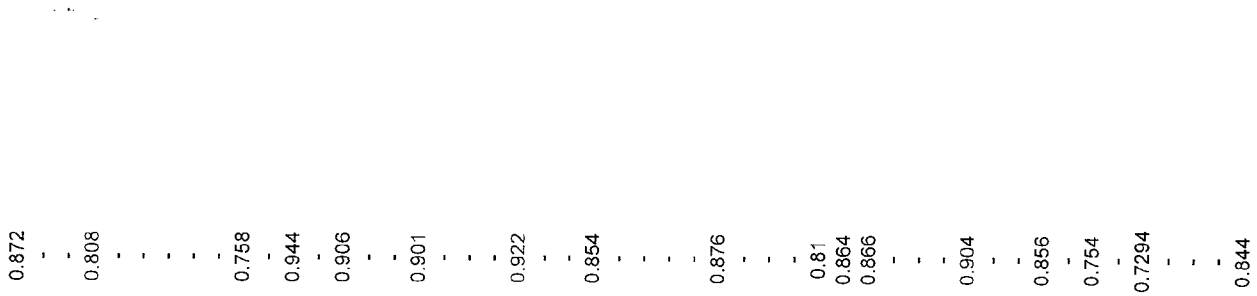

0.854
0.68
0.94
0.864
0.84
0.902
0.83
0.732
0.816
0.776
0.904
0.664
0.884
0.56

Fig. 10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0.944
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0.901
0.922
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0.754
0.7294
0.844

Fig. 10

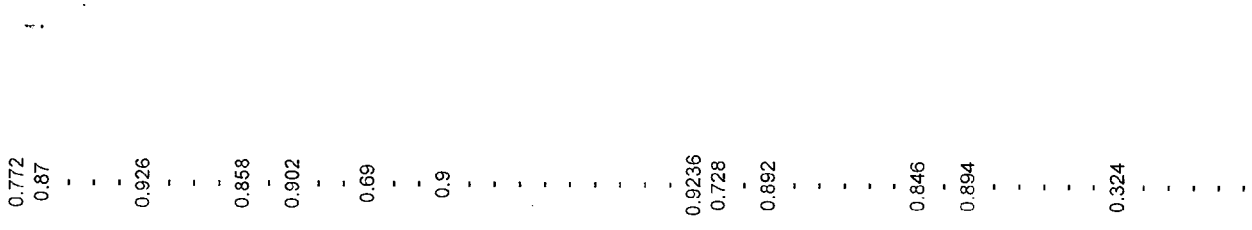
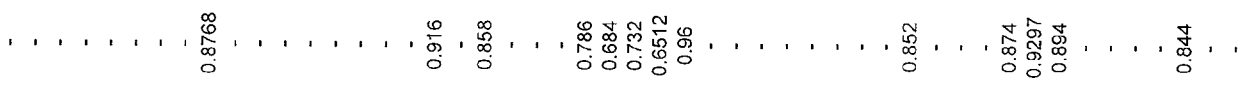


Fig. 10


- 0.944 0.83 - 0.916 - - 0.674 - 0.65 0.65 0.65 0.65 0.65 - - 0.904 - - - - 0.82 0.966 - - - - 0.822 - - - - 0.742 0.814 0.9 - - - - - - - - 0.576 0.96 0.6829 - - - 0.748

Fig. 10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0.786
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0.9297
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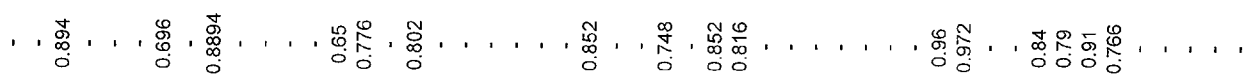
0.844

Fig. 10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0.696
0.8894
0.65
0.776
0.802
0.852
0.748
0.852
0.816
0.96
0.972
0.84
0.79
0.91
0.766

Fig. 10

0.714 0.846 0.776 0.944 0.956 0.908 0.97 0.858 0.94 0.774 0.8 0.862 0.836 0.912 0.894 0.9716 0.64 0.694 0.796

Fig. 10

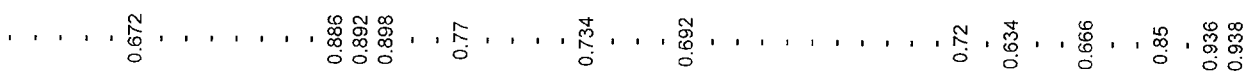
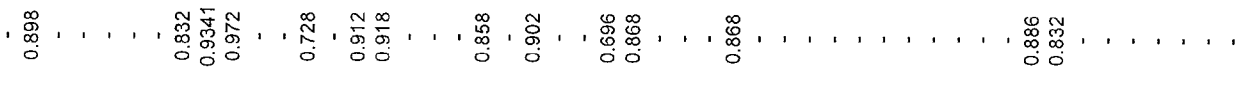


Fig. 10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0.972
0.728
0.912
0.918
0.858
0.902
0.696
0.868
0.868
0.886
0.832

81/131

Fig. 10

Fig. 10

Fig. 10

Fig. 10

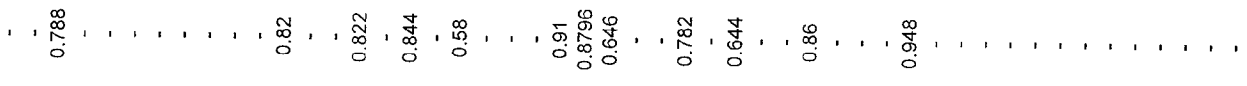


Fig. 10

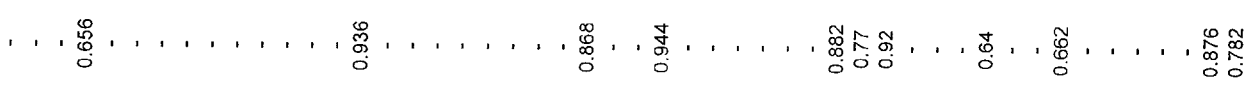
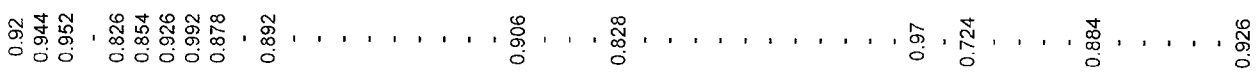


Fig. 10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0.892
0.906
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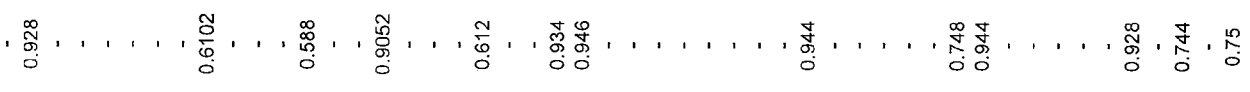
0.724
0.884
0.926

Fig. 10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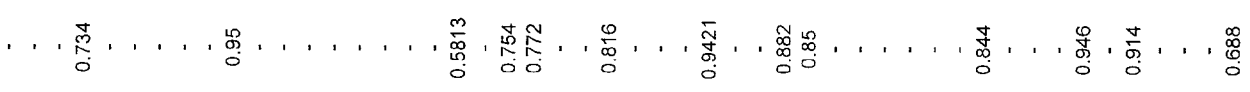
0.75

Fig. 10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0.9421
0.882
0.85
0.844
0.946
0.914
0.688

Fig. 10

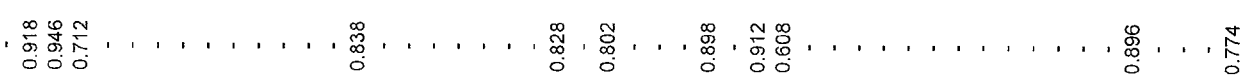


Fig. 10

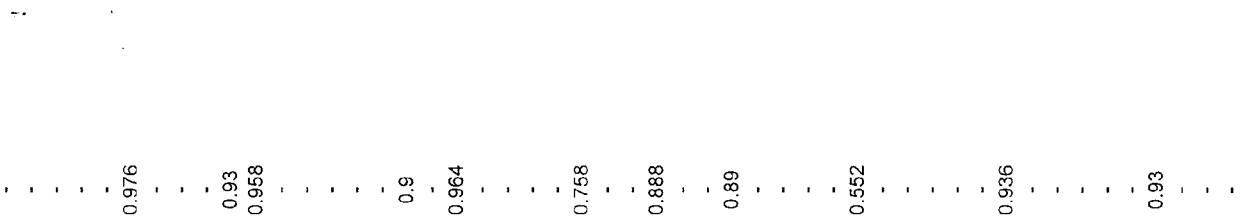
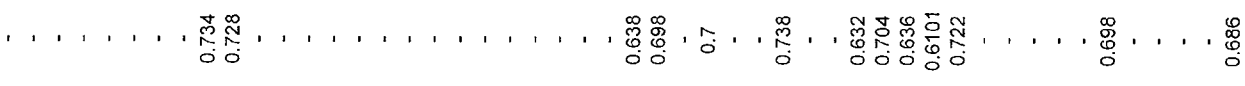


Fig. 10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0.728
0.638
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0.738
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0.704
0.636
0.6101
0.722
0.698
0.686

Fig. 10

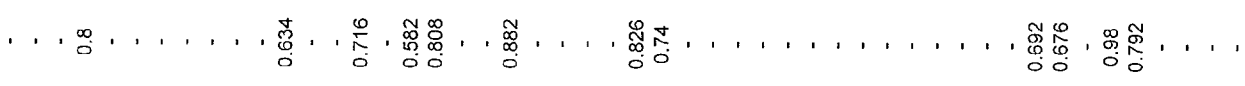
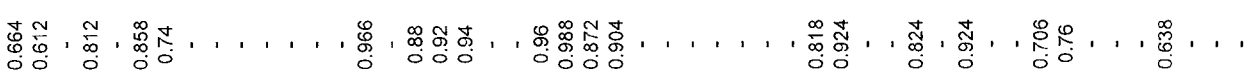


Fig. 10

Fig. 10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0.638

Fig. 10

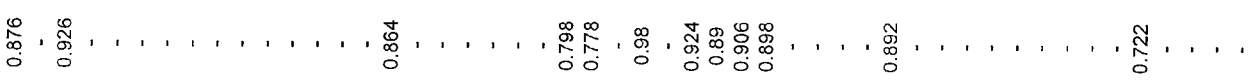

Fig. 10

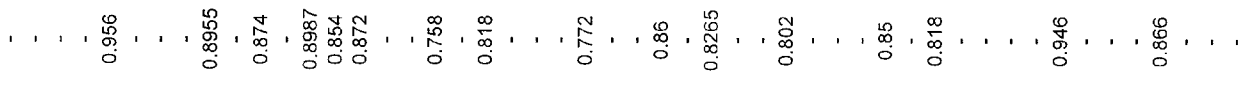
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Fig. 10

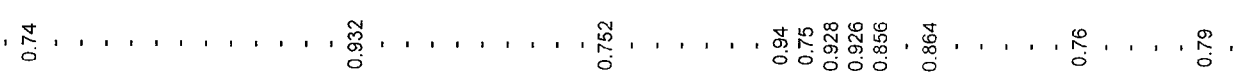

Fig. 10

Fig. 10


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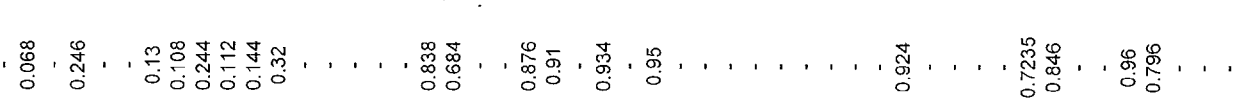
0.858
0.898

Fig. 10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-
0.876
0.91
-
0.934
-
0.95
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-
-
-
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0.96
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Fig. 10

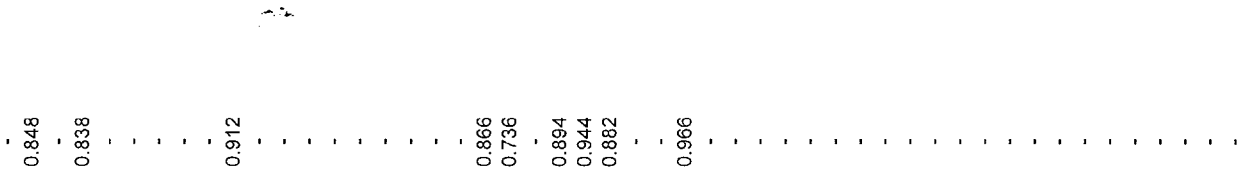

Fig. 10

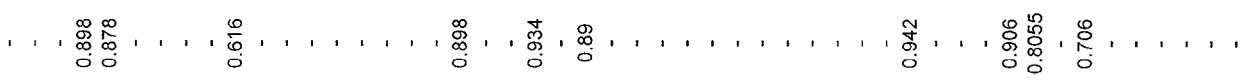

Fig. 10

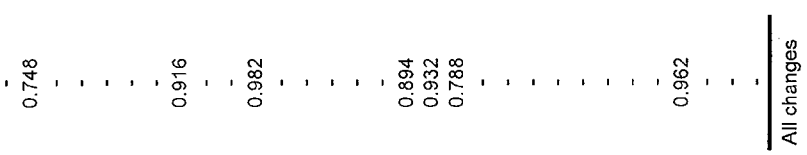

Fig. 10

table S4. Somatic mutations identified in GBM Prevalence Screen

Gene	Transcript Accession ID	Tumor	Nucleotide (genomic)[#]	Nucleotide (cDNA)[§]	Amino acid (protein)[¶]	Mutation Type
ARNT2	NM_014862	Br132X	g.chr15:78642607T>A	c.1288T>A	p.Y430N	Missense
C21orf29	CCDS13712.1	Br248T	g.chr21:44812132G>A	c.268G>A	p.V90I	Missense
DSG4	CCDS11897.1	Br148X	g.chr18:27237386G>T	c.1427G>T	p.G476V	Missense
DSG4	CCDS11897.1	Br148X	g.chr18:27237484C>T	c.1525C>T	p.P509S	Missense
DSG4	CCDS11897.1	Br116X	g.chr18:27237526G>A	c.1569G>A	p.P523P	Synonymous
EGFR	CCDS5514.1	Br112X	g.chr7:54994483C>T	c.664C>T	p.R222C	Missense
EGFR	CCDS5514.1	Br124X	g.chr7:54996031C>T	c.866C>T	p.A289V	Missense
EGFR	CCDS5514.1	Br140X	g.chr7:54996031C>T	c.866C>T	p.A289V	Missense
EGFR	CCDS5514.1	Br306T	g.chr7:54996031C>T	c.866C>T	p.A289V	Missense
EGFR	CCDS5514.1	Br116X	g.chr7:54997745G>A	c.903G>A	p.V301V	Synonymous
EGFR	CCDS5514.1	Br229T	g.chr7:54997773T>A	c.931T>A	p.C311S	Missense
EGFR	CCDS5514.1	Br215T	g.chr7:54997813G>T	c.971G>T	p.R324L	Missense
EGFR	CCDS5514.1	Br213T	g.chr7:55007252G>T	c.1793G>T	p.G598V	Missense
EGFR	CCDS5514.1	Br230T	g.chr7:55007252G>T	c.1793G>T	p.G598V	Missense
EGFR	CCDS5514.1	Br001X	g.chr7:55007263G>C (homozygous)	c.1804G>C	p.E602Q	Missense
EGFR	CCDS5515.1	Br143X	g.chr7:55012285A>T	c.1957A>T	p.S653C	Missense
EGFR	CCDS5515.1	Br143X	g.chr7:55012293C>T	c.1965C>T	p.S655S	Synonymous
EGFR	CCDS5514.1	Br247T	g.chr7:55013103G>A	c.1907G>A	p.C636Y	Missense
EGFR	CCDS5514.1	Br302T	g.chr7:55042273C>G	c.2904C>G	p.F968L	Missense
FRMPD4	NM_014728	Br230T	g.chrX:12276556C>T (homozygous)	c.142C>T	p.R48X	Nonsense
FRMPD4	NM_014728	Br148X	g.chrX:12461363G>A	c.573G>A	p.S191S	Synonymous
FRMPD4	NM_014728	Br104X	g.chrX:12472154G>A	c.857G>A	p.R286Q	Missense
IDH1	CCDS2381.1	Br104X	g.chr2:208938610C>A	c.394C>A	p.R132S	Missense
IDH1	CCDS2381.1	Br129X	g.chr2:208938619C>A	c.394C>A	p.R132S	Missense
IDH1	CCDS2381.1	Br106X	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br122X	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br123X	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br211T	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IDH1	CCDS2381.1	Br237T	g.chr2:208938618G>A	c.395G>A	p.R132H	Missense
IRX6	NM_024335	Br112X	g.chr16:53918999G>C	c.414G>C	p.R138R	Synonymous
IRX6	NM_024335	Br306T	g.chr16:53920595G>C	c.1204G>C	p.E402Q	Missense
MYO1B	CCDS2311.1	Br103X	g.chr2:192071732C>T	c.1224C>T	p.N408N	Synonymous
MYO1B	CCDS2311.1	Br118X	g.chr2:192082380G>A	c.2023G>A	p.V675M	Missense
MYO1B	CCDS2311.1	Br232T	g.chr2:192099396C>T	c.2581C>T	p.H861Y	Missense
NF1	CCDS11264.1	Br132X	g.chr17:26532606G>T	c.627G>T	p.Q209H	Missense
NF1	CCDS11264.1	Br132X	g.chr17:26532608T>A	c.629T>A	p.L210X	Nonsense
NF1	CCDS11264.1	Br232T	g.chr17:26532635T>C	IVS6+2T>C	Splice Site	Splice Site
NF1	CCDS11264.1	Br018X	g.chr17:26583315A>T (homozygous)	c.3296A>T	p.K1099I	Missense
NF1	CCDS11264.1	Br149X	g.chr17:26583948C>A (homozygous)	c.3419C>A	p.S1140X	Nonsense
NF1	CCDS11264.1	Br21PT	g.chr17:26678832delCACCAGGAGTGTGAAGCCA	c.5377_5395delCACCAGGAGTGTGAAGCCA	fs	INDEL
NF1	CCDS11264.1	Br139X	g.chr17:26678895C>T	c.5458C>T	p.Q1820X	Nonsense
NF1	CCDS11264.1	Br21PT	g.chr17:26681564_26681567delAGTA	c.5671_5674delAGTA	fs	INDEL
NF1	CCDS11264.1	Br303T	g.chr17:26686071C>T	c.5839C>T	p.R1947X	Nonsense
NF1	CCDS11264.1	Br232T	g.chr17:26688661_26688662delGA	c.6514_6515delGA	fs	INDEL
NF1	CCDS11264.1	Br113X	g.chr17:26689880_26689883delTTAC	6789_6792delTTAC	fs	INDEL
NF1	CCDS11264.1	Br121X	g.chr17:26689880_26689883delTTAC	6789_6792delTTAC	fs	INDEL
NF1	CCDS11264.1	Br22PT	g.chr17:26689880_26689883delTTAC	6789_6792delTTAC	fs	INDEL
NF1	CCDS11264.1	Br227T	g.chr17:26691648G>C	IVS45-1G>C	Splice Site	Splice Site
NF1	CCDS11264.1	Br107X	g.chr17:26708187_26708188insT	7759__7760insT	fs	INDEL
NF1	CCDS11264.1	Br141X	g.chr17:26709710_26709711delAG	7994__7995delAG	fs	INDEL
NGEF	CCDS2500.1	Br232T	g.chr2:239665017T>C	c.89T>C	p.V30A	Missense
PIK3CA	NM_006218	Br130X	ir3:180399339_180399371delTGAACTGTGGGGCATCCACTTGATGCCCCCA4_56delTGAACTGTGGGGCATCCACTTGATGCCCCCA		indel	INDEL
PIK3CA	NM_006218	Br118X	g.chr3:180399427C>G	c.112C>G	p.R38G	Missense
PIK3CA	NM_006218	Br238T	g.chr3:180399538C>G	c.223C>G	p.Q75E	Missense
PIK3CA	NM_006218	Br001X	g.chr3:180399638G>A	c.323G>A	p.R108H	Missense
PIK3CA	NM_006218	Br401X	g.chr3:180405065T>C	c.1132T>C	p.C378R	Missense
PIK3CA	NM_006218	Br21PT	g.chr3:180434775T>C	c.3128T>C	p.M1043T	Missense
PIK3CA	NM_006218	Br122X	g.chr3:180434781A>G	c.3140A>G	p.H1047R	Missense
PIK3CA	NM_006218	Br129X	g.chr3:180434787A>G	c.3140A>G	p.H1047R	Missense
PIK3R1	CCDS3993.1	Br140X	g.chr5:67624894G>A	c.1126G>A	p.G376R	Missense
PIK3R1	CCDS3993.1	Br223T	g.chr5:67624894G>A	c.1126G>A	p.G376R	Missense
PIK3R1	CCDS3993.1	Br102X	g.chr5:67625368A>G	c.1375A>G	p.K459E	Missense
PIK3R1	CCDS3993.1	Br103X	g.chr5:67625383G>C	c.1390G>C	p.D464H	Missense
PIK3R1	CCDS3993.1	Br019X	g.chr5:67626872T>C	c.1709T>C	p.L570P	Missense

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PIK3R1	CCDS3993.1	Br107X	g.chr5:67627003G>C	IVS12-1G>C	Splice Site	Splice Site
PTEN	NM_000314	Br128X	g.chr10:89614223A>T	c.17A>T	p.K6I	Missense
PTEN	NM_000314	Br141X	g.chr10:89614260_89614261delGG	54_55delGG	fs	INDEL
PTEN	NM_000314	Br301T	g.chr10:89614281G>C	c.75G>C	p.L25F	Missense
PTEN	NM_000314	Br243T	g.chr10:89643840_89643842delTAG	c.158_160delTAG	fs	INDEL
PTEN	NM_000314	Br223T	g.chr10:89643847G>T	IVS2+1G>T	Splice Site	Splice Site
PTEN	NM_000314	Br248T	g.chr10:89643847delG	IVS2+1delG	Splice Site	INDEL
PTEN	NM_000314	Br215T	g.chr10:89675298A>T	IVS3+4A>T	Splice Site	Splice Site
PTEN	NM_000314	Br148X	g.chr10:89680827G>A	IVS4+1G>A	Splice Site	Splice Site
PTEN	NM_000314	Br117X	g.chr10:89682759A>G	c.263A>G	p.Y88C	Missense
PTEN	NM_000314	Br227T	g.chr10:89682767G>T	c.271G>T	p.E91X	Nonsense
PTEN	NM_000314	Br111X	g.chr10:89682783C>T	c.287C>T	p.P96L	Missense
PTEN	NM_000314	Br245T	g.chr10:89682851G>T	c.355G>T	p.V119F	Missense
PTEN	NM_000314	Br136X	g.chr10:89682881G>T	c.385G>T	p.G129X	Nonsense
PTEN	NM_000314	Br217T	g.chr10:89682884C>G	c.388C>G	p.R130G	Missense
PTEN	NM_000314	Br203T	g.chr10:89682885G>C	c.389G>C	p.R130P	Missense
PTEN	NM_000314	Br134X	g.chr10:89682957delT	457delT	fs	INDEL
PTEN	NM_000314	Br22PT	g.chr10:89682957delT	461delT	fs	INDEL
PTEN	NM_000314	Br302T	g.chr10:89710779_89710782delTACT	c.950_953delTACT	fs	INDEL
PTEN	NM_000314	Br138X	g.chr10:89710780_89710783delACTT	951_954delACTT	fs	INDEL
PTEN	NM_000314	Br018X	g.chr10:89710832C>T (homozygous)	c.1003C>T	p.R335X	Nonsense
PTEN	NM_000314	Br145X	g.chr10:89715023G>A	IVS8-1G>A	Splice Site	Splice Site
PTEN	NM_000314	Br101X	g.chr10:89715130_89715133delGATA	c.1133_1136delGATA	fs	INDEL
RB1	NM_000321	Br121X	g.chr13:47779504G>A	c.225G>A	p.W75X	Nonsense
RB1	NM_000321	Br111X	g.chr13:47814735G>A	IVS2-1G>A	Splice Site	Splice Site
RB1	NM_000321	Br126X	g.chr13:47849164delG	1325delG	fs	INDEL
RB1	NM_000321	Br149X	g.chr13:47851744delG	1346delG	fs	INDEL
RB1	NM_000321	Br019X	g.chr13:47935944A>G (homozygous)	c.2168A>G	p.Y728C	Missense
RB1	NM_000321	Br131X	g.chr13:47937134G>A	IVS21-1G>A	Splice Site	Splice Site
SCN9A	NM_002977	Br232T	g.chr2:166987916T>C	c.489T>C	p.Y163Y	Synonymous
SCN9A	NM_002977	Br115X	g.chr2:166988303C>T	c.640C>T	p.R214X	Nonsense
SCN9A	NM_002977	Br238T	g.chr2:166915404A>G	c.3644A>G	p.R1282G	Missense
TP53	CCDS11118.1	Br403P	g.chr17:7520317A>G	IVS2-2A>G	Splice Site	Splice Site
TP53	CCDS11118.1	Br133X	g.chr17:7520234C>G (homozygous)	c.178C>G	p.P60A	Missense
TP53	CCDS11118.1	Br148X	g.chr17:7520233C>G	c.179C>G	p.P60R	Missense
TP53	CCDS11118.1	Br211T	g.chr17:7520207delG (homozygous)	c.205delG	fs	INDEL
TP53	CCDS11118.1	Br237T	g.chr17:7520080T>C	c.332T>C	p.L111P	Missense
TP53	CCDS11118.1	Br403P	g.chr17:7520037G>A	c.375G>A	p.T125T	Synonymous
TP53	CCDS11118.1	Br203T	g.chr17:7519275C>T	c.380C>T	p.S127F	Missense
TP53	CCDS11118.1	Br237T	g.chr17:7519200C>T	c.455C>T	p.P152L	Missense
TP53	CCDS11118.1	Br246T	g.chr17:7519200C>T	c.455C>T	p.P152L	Missense
TP53	CCDS11118.1	Br232T	g.chr17:7519182G>A	c.473G>A	p.R158H	Missense
TP53	CCDS11118.1	Br141X	g.chr17:7519147_7519141delACGGAGG	c.508_514delACGGAGG	fs	INDEL
TP53	CCDS11118.1	Br241T	g.chr17:7519131G>A	c.524G>A	p.R175H	Missense
TP53	CCDS11118.1	Br123X	g.chr17:7519005delC	569delC	fs	INDEL
TP53	CCDS11118.1	Br131X	g.chr17:7518988C>T	c.586C>T	p.R196X	Nonsense
TP53	CCDS11118.1	Br113X	g.chr17:7518948_7518947delGA	626_627delGA	fs	INDEL
TP53	CCDS11118.1	Br104X	g.chr17:7518305A>G (homozygous)	c.701A>G	p.Y234C	Missense
TP53	CCDS11118.1	Br018X	g.chr17:7518273G>A	c.733G>A	p.G245S	Missense
TP53	CCDS11118.1	Br143X	g.chr17:7518273G>A	c.733G>A	p.G245S	Missense
TP53	CCDS11118.1	Br240T	g.chr17:7518273G>A	c.733G>A	p.G245S	Missense
TP53	CCDS11118.1	Br303T	g.chr17:7518273G>A	c.733G>A	p.G245S	Missense
TP53	CCDS11118.1	Br223T	g.chr17:7518264C>T	c.742C>T	p.R248W	Missense
TP53	CCDS11118.1	Br232T	g.chr17:7518264C>T	c.742C>T	p.R248W	Missense
TP53	CCDS11118.1	Br105X	g.chr17:7518263G>A	c.743G>A	p.R248Q	Missense
TP53	CCDS11118.1	Br146X	g.chr17:7517864C>T	c.799C>T	p.R267W	Missense
TP53	CCDS11118.1	Br109X	g.chr17:7517846C>T (homozygous)	c.817C>T	p.R273C	Missense
TP53	CCDS11118.1	Br146X	g.chr17:7517845G>A	c.818G>A	p.R273H	Missense
TP53	CCDS11118.1	Br115X	g.chr17:7517819C>T	c.844C>T	p.R282W	Missense
TP53	CCDS11118.1	Br106X	g.chr17:7514737G>T (homozygous)	c.1015G>T	p.E339X	Nonsense

*Genomic positions are coordinates of the May 2004, hg17 35.1 UCSC Santa Cruz release of the human genome. Genomic coordinates and sequences of mutations are on the coding strand. All changes are heterozygous unless marked as homozygous. g., genomic sequence; c., cDNA sequence; p., protein sequence; del, deletion; dup, duplication; ins, insertion. [$]Mutations in non-coding sequences are annotated by intron number preceded by "IVS", with positive numbers starting from the G of the GT splice donor site and negative numbers starting from the G of the AG splice acceptor site. [#]fs, frameshift mutation; UTR, mutation in 5' or 3' untranslated region; indel, in frame insertion, deletion or duplication change affecting more than a single codon. No mutations were identified in 5 genes that were analyzed in the Prevalence screen (ASTN, KIAA0774, SERPINA12, TRPV5).

Fig. 10

table S5. Amplifications detected by Illumina arrays

Sample	Chromosome	Left Boundary (bp)	Right Boundary (bp)	Candidate target of amplification	Candidate evidence*	Other genes†
Br02X	1	6,553,906	6,618,080	PHF13	1	KLHL21, THAP3, ZBTB48
Br02X	1	6,637,977	6,652,336	Unknown		
Br02X	1	6,850,339	6,914,512	Unknown		
Br02X	1	7,159,397	7,164,110	Unknown		
Br02X	1	7,356,659	7,456,825	Unknown		
Br02X	1	7,475,206	7,578,989	Unknown		
Br02X	1	8,121,850	8,123,277	Unknown		
Br02X	1	37,961,327	37,961,374	Unknown		
Br03X	1	87,579,388	87,580,940	Unknown		
Br02X	1	94,246,433	94,246,484	Unknown		
Br02X	1	156,991,818	156,992,011	Unknown		
Br07X	1	199,264,981	199,292,305	Unknown		
Br07X	1	199,313,698	199,318,935	Unknown		
Br05X	1	202,698,859	203,429,680	MDM4	1	CNTN2, LRRN2, NFASC, RBBP5, TMEM81
Br06X	1	242,284,342	242,287,212	Unknown		
Br07X	2	14,851,412	15,181,861	Unknown		
Br07X	2	15,198,595	16,235,845	MYCN	1	DDX1, MYCNOS, NAG
Br02X	2	20,688,139	20,688,189	Unknown		
Br20P	2	36,263,684	36,263,904	Unknown		
Br20P	2	118,777,060	118,778,863	Unknown		
Br06X	2	162,858,374	162,860,597	Unknown		
Br25X	2	166,230,991	166,231,208	Unknown		
Br03X	2	203,469,116	203,474,001	Unknown		
Br02X	2	219,141,517	219,141,633	Unknown		
Br13X	2	228,948,389	228,949,477	Unknown		
Br03X	3	101,817,778	101,926,422	Unknown		
Br03X	3	102,096,686	102,100,370	Unknown		
Br03X	3	124,127,994	124,129,518	Unknown		
Br03X	3	125,527,639	125,531,454	Unknown		
Br07X	3	127,461,108	127,470,614	Unknown		
Br03X	3	150,242,015	150,250,820	Unknown		
Br03X	3	198,254,194	198,255,951	Unknown		
Br06X	4	1,769,100	1,774,465	Unknown		
Br08X	4	19,130,834	19,131,054	Unknown		
Br20P	4	58,417,022	58,418,102	Unknown		
Br20P	4	84,789,971	84,790,081	Unknown		
Br05X	4	134,352,228	134,352,498	Unknown		
Br02X	4	189,567,179	189,597,490	Unknown		
Br02X	4	189,938,594	190,111,703	Unknown		
Br02X	4	190,132,589	190,276,106	Unknown		
Br02X	4	190,308,979	190,759,195	Unknown		
Br06X	5	276,117	286,572	Unknown		
Br06X	5	1,187,166	1,188,834	Unknown		
Br06X	5	11,227,960	11,230,291	Unknown		
Br06X	5	16,954,752	16,957,555	Unknown		
Br03X	5	67,625,312	67,630,080	Unknown		
Br02X	5	122,710,233	122,710,267	Unknown		
Br02X	5	162,857,364	162,890,889	Unknown		MAT2B
Br02X	5	163,030,420	163,036,004	Unknown		
Br02X	5	165,817,804	165,911,472	Unknown		
Br02X	5	166,443,764	166,599,221	Unknown		
Br02X	5	166,982,050	167,030,901	Unknown		
Br03X	6	44,463,433	44,468,511	Unknown		
Br02X	6	122,814,813	122,814,850	Unknown		
Br15X	6	167,659,759	167,664,399	Unknown		
Br05X	7	11,817,948	11,819,533	Unknown		
Br05X	7	12,990,992	12,997,659	Unknown		
Br20P	7	13,405,074	13,412,371	Unknown		
Br03X	7	14,153,728	14,155,893	Unknown		
Br25X	7	28,036,836	28,042,110	Unknown		
Br03X	7	29,097,237	29,097,478	Unknown		
Br20P	7	33,031,627	33,036,700	Unknown		
Br20P	7	48,557,329	48,623,217	Unknown		

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Br20P	7	50,058,516	50,114,484	Unknown		
Br20P	7	50,332,228	50,741,036	GRB10	3	DDC, FIGNL1
Br04X	7	50,693,179	50,701,856	Unknown		
Br25X	7	54,222,123	58,113,498	EGFR	2	CCT6A, ECOP, GBAS, LANCL2, MRPS17, PSPH, SEC61G, VSTM2A, ZNF713
Br25X	7	54,602,061	55,501,341	EGFR	2	LANCL2, SEC61G
Br05X	7	54,619,020	55,276,919	EGFR	2	SEC61G
Br20P	7	54,760,596	55,358,484	EGFR	2	SEC61G
Br09P	7	54,830,325	55,413,112	EGFR	2	
Br26X	7	56,325,293	56,337,310	Unknown		
Br13X	7	73,272,823	73,288,679	Unknown		
Br03X	7	75,457,586	75,459,458	Unknown		
Br05X	7	78,936,881	78,951,653	Unknown		
Br03X	7	101,704,241	101,708,009	Unknown		
Br13X	7	156,031,360	156,063,977	Unknown		
Br06X	8	49,118,225	49,125,050	Unknown		
Br02X	8	49,125,003	49,125,041	Unknown		
Br03X	8	49,125,012	49,125,050	Unknown		
Br26X	8	141,189,636	141,189,652	Unknown		
Br27P	8	145,056,944	145,064,850	Unknown		
Br03X	9	105,936,630	105,941,327	Unknown		
Br11P	10	18,437,571	18,448,955	Unknown		
Br11P	10	19,494,186	19,507,088	Unknown		
Br11P	10	25,061,733	25,077,869	Unknown		
Br08X	10	45,010,196	45,071,698	Unknown		
Br02X	11	1,737,423	45,350,649	Unknown		MARCH8
Br06X	11	113,673,352	1,739,140	Unknown		
Br11P	11	125,123,118	113,673,398	Unknown		
Br27P	12	43,353,545	125,124,437	Unknown		
Br16X	12	56,170,088	43,859,887	Unknown		DBX2, PLEKHA9
			57,559,240	CDK4	1	MARCH9, AVIL, B4GALNT1, CENTG1, CTDSP2, CYP27B1, DCTN2, DDIT3, DTX3, FAM119B, GEFT, KIF5A, MBD6, METTL1, OS9, PIP4K2C, Q8WYW9_HUMAN, SLC26A10, TSFM, TSPAN31, XR_016180.1, XRCC6BP1
Br27P	12	56,313,053	56,731,426	CDK4	3	MARCH9, AVIL, CENTG1, CTDSP2, CYP27B1, FAM119B, METTL1, OS9, Q8WYW9_HUMAN, TSFM, TSPAN31, XRCC6BP1
Br09P	12	56,354,655	56,496,029	CDK4	1	MARCH9, CENTG1, CYP27B1, FAM119B, METTL1, OS9, TSFM, TSPAN31
Br09P	12	56,505,948	56,745,675	Unknown		XRCC6BP1
Br16X	12	61,104,748	61,250,710	Unknown		
Br27P	12	64,707,303	64,915,539	Unknown		C12orf31, TMBIM4
Br16X	12	67,312,082	68,049,905	RAP1B	1	CPM, CPSF6, LOC643752, LYZ, MDM2, ENST00000361329, NUP107, Q9P175_HUMAN, SLC35E3
Br27P	12	123,395,187	123,955,485	Unknown		SCARB1
Br23X	13	82,550,369	82,574,861	Unknown		
Br23X	13	92,450,749	92,478,066	Unknown		
Br23X	13	93,183,362	93,187,994	Unknown		
Br23X	13	103,367,246	103,381,478	Unknown		
Br23X	13	106,948,221	106,960,600	Unknown		
Br23X	13	107,217,139	107,223,985	Unknown		
Br23X	13	108,100,521	108,117,560	Unknown		
Br02X	16	13,948,459	13,949,578	Unknown		
Br02X	16	55,574,780	55,574,820	Unknown		
Br02X	16	79,740,930	79,740,969	Unknown		
Br06X	17	38,497,326	38,497,366	Unknown		
Br03X	17	43,724,291	43,728,670	Unknown		
Br02X	17	55,042,776	55,042,809	Unknown		
Br03X	17	59,927,132	59,929,108	Unknown		
Br02X	17	75,525,527	75,531,516	Unknown		
Br20P	18	44,290,789	44,291,672	Unknown		
Br07X	18	51,886,633	51,894,189	Unknown		
Br03X	19	642,025	647,905	Unknown		
Br03X	19	703,878	707,985	Unknown		
Br03X	19	858,673	870,656	Unknown		
Br06X	19	3,928,486	3,933,967	Unknown		
Br29P	19	7,600,021	7,600,538	Unknown		
Br06X	19	15,455,019	15,467,228	Unknown		
Br02X	19	50,139,876	50,139,910	Unknown		
Br02X	19	55,220,045	55,236,882	Unknown		
Br06X	20	24,877,913	24,886,121	Unknown		
Br06X	20	34,606,940	34,609,955	Unknown		
Br20P	X	3,575,814	3,582,435	Unknown		

Fig. 10

Br04X	X	12,827,708	12,831,972	Unknown		
Br20P	X	16,305,623	16,306,395	Unknown		
Br04X	X	17,413,003	17,437,823	Unknown		
Br06X	X	20,187,346	20,187,385	Unknown		
Br03X	X	21,576,928	21,576,953	Unknown		
Br04X	X	38,365,465	38,400,112	Unknown		
Br29P	X	53,927,466	53,940,364	Unknown		
Br29P	X	58,276,219	58,292,688	Unknown		
Br29P	X	61,660,428	61,683,946	Unknown		
Br16X	X	63,988,007	63,988,941	Unknown		
Br02X	X	66,859,466	66,859,511	Unknown		
Br03X	X	68,752,130	68,752,682	Unknown		
Br20P	X	124,915,709	124,932,598	Unknown		
Br20P	X	130,099,706	130,113,107	Unknown		
Br29P	X	133,674,808	133,694,475	Unknown		
Br29P	X	144,110,845	144,113,003	Unknown		
Br20P	X	150,561,266	150,564,832	Unknown		
Br02X	X	150,642,155	150,645,024	Unknown		
Br16X	X	154,429,838	154,431,317	Unknown		

[1]Classes of evidence for candidate targets of amplification: 1, compared to normal tissue, candidate was ≥2 fold overexpressed in the tumor in which it was amplified as well as in other tumors; 2, candidate was mutated in a tumor in which it was not amplified and ≥2 fold overexpressed in other tumors; 3, candidate was ≥2 fold overexpressed in other tumors. [2]Indicates genes within the amplicon in addition to the presumptive target gene

table S6. Homozygous deletions detected by Illumina arrays

Sample	Chromosome	Left Boundary (bp)	Right Boundary (bp)	Candidate target of deletion	Candidate evidence*	Other genes†
Br04X	1	3,500,493	4,562,392	MEGF6	1	C1orf174, CCDC27, DFFB, KIAA0495, KIAA0562, LRRC47, TP73
Br17X	1	86,174,832	86,176,913	Unknown		
Br16X	1	108,535,014	108,538,635	Unknown		SLC25A24
Br08X	1	147,305,744	147,448,972	Unknown		
Br13X	1	167,493,525	167,507,362	Unknown		
Br25X	1	173,064,490	173,068,262	Unknown		
Br27P	2	36,263,684	36,263,904	Unknown		
Br06X	2	52,614,242	52,637,176	Unknown		
Br25X	2	123,197,294	123,198,771	Unknown		
Br25X	2	141,180,655	141,267,820	LRP1B	1	
Br03X	2	141,432,018	141,610,364	LRP1B	1	
Br03X	2	141,735,396	141,751,756	Unknown		
Br15X	2	159,667,833	159,669,697	Unknown		
Br25X	2	208,061,364	208,066,083	Unknown		
Br05X	3	26,407,350	26,414,475	Unknown		
Br02X	3	133,194,645	133,195,707	Unknown		
Br23X	3	191,220,845	191,221,750	Unknown		
Br16X	4	42,392,310	42,404,178	Unknown		
Br07X	4	64,378,106	64,392,223	Unknown		
Br14X	4	64,380,191	64,386,602	Unknown		
Br13X	4	69,129,446	69,153,720	Unknown		
Br20P	4	115,398,433	115,401,739	Unknown		
Br23X	4	115,398,433	115,401,739	Unknown		
Br03X	4	122,504,713	122,508,095	Unknown		
Br07X	4	153,010,030	153,012,241	Unknown		
Br07X	4	157,183,142	157,186,835	Unknown		
Br07X	4	181,751,048	181,969,740	Unknown		
Br11P	5	15,772,769	15,773,478	Unknown		
Br07X	5	101,503,405	101,550,575	Unknown		
Br03X	5	155,410,444	155,421,495	Unknown		
Br02X	5	167,925,074	167,933,033	Unknown		PANK3
Br04X	5	170,062,869	170,063,768	Unknown		
Br08X	6	19,151,979	19,156,771	Unknown		
Br14X	6	29,967,496	30,007,126	Unknown		
Br08X	6	31,373,715	31,385,967	Unknown		
Br06X	6	32,061,446	32,096,483	Unknown		
Br27P	6	32,563,460	32,567,928	Unknown		
Br06X	6	32,592,346	32,628,250	HLA-DRB5	1	
Br29P	6	32,643,872	32,650,112	Unknown		
Br14X	6	58,714,934	58,715,776	Unknown		
Br04X	6	100,422,887	100,630,860	Unknown		MCHR2
Br06X	6	139,645,437	139,648,424	Unknown		
Br04X	6	159,236,418	159,237,500	Unknown		
Br12P	7	141,412,174	141,439,888	Unknown		
Br07X	8	15,828,545	15,831,260	Unknown		
Br08X	8	72,378,104	72,380,244	Unknown		
Br14X	8	115,703,454	115,711,712	Unknown		
Br07X	8	142,830,192	143,494,054	TSNARE1	1	
Br07X	8	143,897,019	143,916,095	Unknown		GML
Br07X	8	144,236,804	144,246,305	Unknown		
Br07X	9	1,437,011	1,440,428	Unknown		
Br17X	9	6,691,130	6,695,824	Unknown		
Br27P	9	6,691,130	6,695,824	Unknown		
Br14X	9	14,964,080	15,013,765	Unknown		
Br25X	9	15,539,731	15,761,541	Unknown		C9orf93
Br17X	9	19,409,446	19,540,684	Unknown		ASAH3L, SLC24A2
Br05X	9	19,507,795	19,540,684	Unknown		SLC24A2
Br13X	9	19,660,630	20,836,444	Unknown		SLC24A2, KIAA1797, MLLT3
Br17X	9	19,702,170	20,892,081	Unknown		SLC24A2, KIAA1797, MLLT3
Br05X	9	19,702,170	21,186,356	Unknown		MLLT3, KIAA1797, IFNA21, IFNB1, SLC24A2, IFNA4, IFNW1, PTPLAD2
Br26X	9	19,892,822	20,015,247	Unknown		
Br26X	9	20,134,936	22,206,506	CDKN2A	1	KIAA1797, C9orf53, CDKN2B, IFNA1, IFNA10, IFNA13, IFNA14, IFNA16, IFNA2, IFNA21, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNB1, IFNE1, IFNW1, KLHL9, MTAP, PTPLAD2, Q8WTY6_HUMAN, MLLT3, KIAA1797
Br02X	9	20,830,838	26,141,961	CDKN2A	1	IFNB1, KIAA1797, PTPLAD2, IFNA1, C9orf53, IFNA8, CDKN2B, IFNA2, IFNE1, MTAP, Q8WTY6_HUMAN, DMRTA1, ELAVL2, TUSC1
Br15X	9	21,088,843	22,356,889	CDKN2A	1	IFNA21, IFNA1, IFNW1, IFNA2, IFNA8, KLHL9, IFNA4, IFNA13, IFNA6, IFNA5, IFNE1, Q8WTY6_HUMAN, CDKN2B
Br13X	9	21,337,828	21,993,367	CDKN2A	1	IFNA1, IFNA13, IFNA2, IFNA6, IFNA8, IFNE1, Q8WTY6_HUMAN, C9orf53, CDKN2B
Br17X	9	21,337,828	21,995,330	CDKN2A	1	IFNA1, IFNA13, IFNA2, IFNA6, IFNA8, IFNE1, Q8WTY6_HUMAN, CDKN2B
Br05X	9	21,360,864	22,421,172	CDKN2A	1	IFNA2, IFNA1, C9orf53, IFNA8, IFNE1, MTAP, Q8WTY6_HUMAN
Br20P	9	21,391,106	21,398,857	Unknown		
Br14X	9	21,523,610	21,993,367	CDKN2A	1	Q8WTY6_HUMAN, C9orf53, CDKN2B
Br25X	9	21,762,064	22,663,444	CDKN2A	1	MTAP, CDKN2B

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Fig. 10

Br06X	9	21,792,469	21,981,016	CDKN2A	1	MTAP, C9orf63	
Br20P	9	21,851,557	21,917,327	Unknown	1	MTAP	
Br08X	9	21,965,561	23,315,027	CDKN2A	1	CDKN2B, DMRTA1	
Br20P	9	22,019,547	22,206,506	Unknown			
Br13X	9	22,122,076	22,326,954	Unknown			
Br17X	9	22,122,076	22,436,828	Unknown			
Br14X	9	22,148,598	22,998,119	Unknown			
Br06X	9	22,318,194	22,336,105	Unknown			
Br26X	9	22,596,575	22,598,275	Unknown			
Br05X	9	22,824,703	22,956,660	Unknown			
Br17X	9	22,824,703	24,123,677	Unknown		ELAVL2	
Br26X	9	22,862,406	22,954,237	Unknown			
Br14X	9	23,102,598	23,297,377	Unknown			
Br06X	9	23,469,588	23,507,989	Unknown			
Br08X	9	23,628,686	23,727,408	Unknown		ELAVL2	
Br14X	9	23,628,686	23,813,399	Unknown		ELAVL2	
Br06X	9	23,722,000	23,765,449	Unknown			
Br08X	9	23,958,172	24,282,583	Unknown			
Br14X	9	23,958,172	25,277,180	Unknown			
Br13X	9	24,492,737	24,505,111	Unknown			
Br15X	9	25,145,167	25,277,180	Unknown			
Br14X	9	25,386,115	25,417,205	Unknown		TUSC1	
Br15X	9	25,386,115	26,570,067	Unknown		LINGO2	
Br25X	9	27,988,125	28,151,218	Unknown			
Br25X	9	31,973,460	32,281,795	Unknown			
Br06X	9	113,693,260	113,693,505	Unknown			
Br25X	9	128,560,616	128,561,879	Unknown			
Br02X	9	134,941,052	134,944,131	Unknown			
Br13X	10	56,280,721	56,361,311	Unknown			
Br04X	10	58,567,923	58,606,559	Unknown			
Br15X	10	58,880,806	58,881,704	Unknown	2	PAPSS2, ATAD1, KILLIN	
Br23X	10	89,468,496	86,627,047	PTEN			
Br10P	11	5,741,589	5,765,246	Unknown			
Br04X	11	41,774,842	41,775,435	Unknown			
Br07X	12	38,161,618	38,162,250	Unknown			
Br05X	12	38,161,862	38,162,250	Unknown			
Br27P	12	98,319,260	98,326,639	Unknown			
Br07X	12	124,316,922	124,641,085	TMEM132B	1		
Br07X	13	47,884,077	47,862,826	RB1	2	ITM2B	
Br04X	13	57,491,658	57,497,032	Unknown			
Br04X	13	82,763,946	82,812,014	Unknown			
Br04X	13	86,013,322	86,241,525	Unknown			
Br20P	13	99,378,354	99,379,711	Unknown			
Br17X	14	40,679,974	40,698,108	Unknown			
Br13X	14	98,574,125	98,574,712	Unknown			
Br03X	15	27,688,508	27,690,054	Unknown			
Br04X	15	32,509,617	32,595,161	Unknown			
Br03X	15	54,328,515	55,246,412	ZNF280D	1	MNS1, TEX9, TCF12	
Br17X	15	54,579,805	54,582,930	Unknown			
Br03X	16	6,612,412	6,757,376	A2BP1	1	Q8WZ91_HUMAN	
Br03X	16	27,246,560	27,268,188	IL4R	1		
Br02X	17	7,470,627	7,598,047	TP53	2	ATP1B2, DNAH2, SHBG, SAT2, EFNB3, WDR79	
Br06X	18	36,514,524	36,518,476	Unknown			
Br07X	20	40,694,858	40,702,735	Unknown			
Br03X	21	22,576,805	22,583,018	Unknown			
Br04X	21	22,576,805	22,583,706	Unknown			
Br04X	22	21,806,695	21,809,273	Unknown			
Br13X	22	36,076,340	36,079,559	Unknown		Q8N7Q6_HUMAN	
Br04X	22	37,693,776	37,708,598	Unknown		APOBEC3B	
Br25X	22	45,878,213	46,554,514	Unknown		TBC1D22A, U6126_HUMAN	
Br02X	X	33,964,391	33,978,251	Unknown			
Br12P	X	76,774,818	76,824,354	Unknown		ATRX	
Br16X	X	84,750,960	84,753,048	Unknown			
Br25X	X	154,049,748	154,070,582	Unknown			

[1]Classes of evidence for candidate targets of homozygous deletion: 1, compared to normal tissue, candidate was not expressed in the tumor in which it was deleted and was expressed at >5 fold lower levels in other tumors; 2, candidate was mutated in a tumor in which it was not deleted and was expressed at > 5 fold lower levels in other tumors. [2]Indicates genes within the deletion in addition to the presumptive target gene

Fig. 10

table S7. GBM *CAN*-genes*

Gene	Number of Mutations	Number of Amplifications	Number of Deletions	Passenger Probability Low
TP53	13	0	1	<0.001
CDKN2A	0	0	11	<0.001
PTEN	5	0	1	<0.001
EGFR	2	5	0	<0.001
IDH1	5	0	0	<0.001
CDK4	0	3	0	<0.001
GML	1	0	1	0.005
RB1	2	0	1	0.004
ENST00000355324	2	0	0	0.004
NF1	3	0	0	0.009
SKP2	2	0	0	0.009
COL3A1	3	0	0	0.009
ARNT2	2	0	0	0.009
KIAA1804	2	0	0	0.009
Q8NDH2_HUMAN	2	0	0	0.009
C6orf170	2	0	0	0.030
IMP4	2	0	0	0.030
IRX6	3	0	0	0.030
KIAA1441	2	0	0	0.030
LRP2	4	0	0	0.030
OR2L13	2	0	0	0.030
PIK3CA	2	0	0	0.030
PIK3R1	2	0	0	0.030
RBM27	2	0	0	0.030
SERPINA12	2	0	0	0.030
PKHD1	3	0	0	0.053
C21orf29	2	0	0	0.057
LMX1A	2	0	0	0.057
ZNF497	2	0	0	0.057
LRRC7	2	0	0	0.057
KIAA0133	2	0	0	0.087
MYO1B	2	0	0	0.087
TRPV5	2	0	0	0.087
DSG4	2	0	0	0.107
KIAA0774	2	0	0	0.107
NGEF	2	0	0	0.107
PHIP	2	0	0	0.108
ASTN	2	0	0	0.108
FRMPD4	2	0	0	0.108
SCN9A	2	0	0	0.108
GRM3	2	0	0	0.263

Fig. 10

CACNA1H	2	0	0	0.303

* *CAN*- genes were defined as those having at least two alterations in the Discovery Screen samples alterations per Mb sequence analyzed. Passenger probabilities were calculated as described in the Supporting Online Material.

Fig. 10

Passenger Probability Mid	Passenger Probability High
<0.001	<0.001
<0.001	<0.001
<0.001	<0.001
<0.001	<0.001
<0.001	<0.001
<0.001	<0.001
0.016	0.017
0.017	0.025
0.035	0.066
0.040	0.174
0.040	0.174
0.040	0.174
0.070	0.174
0.070	0.174
0.070	0.188
0.097	0.188
0.097	0.316
0.097	0.188
0.097	0.188
0.097	0.344
0.097	0.188
0.097	0.188
0.097	0.316
0.097	0.188
0.097	0.316
0.097	0.366
0.097	0.344
0.097	0.344
0.097	0.344
0.163	0.344
0.307	0.391
0.307	0.391
0.307	0.391
0.321	0.391
0.321	0.391
0.321	0.391
0.379	0.646
0.445	0.646
0.445	0.646
0.445	0.646
0.445	0.772

Fig. 10

0.445	0.772

(excluding Br27P) and at least ten
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Fig. 10

table S8. Candidate gene sets enriched for genetic alterations in GBMs

Gene Set	Pathway database	Set size	Number of mutations in set
ion transport	GO	555	55
negative regulation of cell-matrix adhesion	GO	6	5
calcium ion transport	GO	121	18
Cell adhesion_Cell-matrix interactions	GG	185	23
Cell adhesion_Integrin priming	GG	130	23
Cell adhesion_ECM remodeling	MA	70	13
Cytoskeleton remodeling_Cytoskeleton remodeling	MA	159	23
synaptic transmission	GO	239	22
positive regulation of epithelial cell proliferation	GO	33	7
Neurophysiological process_Transmission of nerve impulse	GG	262	26
Signal transduction_PTEN pathway	MA	56	25
Development_EGFR signaling via PIP3	MA	27	12
Translation _Non-genomic (rapid) action of Androgen Receptor	MA	70	15
Apoptosis and survival_DNA-damage-induced apoptosis	MA	18	15
Transcription_P53 signaling pathway	MA	48	18
negative regulation of neuroblast proliferation	GO	6	15
Cell adhesion_Chemokines and adhesion	MA	152	21
somatic stem cell division	GO	6	1
regulation of protein stability	GO	6	5
response to chemical stimulus	GO	20	16
Muscle contraction	GG	320	27
B cell lineage commitment	GO	6	13

Fig. 10

Cell adhesion_Attractive and repulsive receptors	GG	193	20
cell migration	GO	64	12
Transport_Sodium transport	GG	150	15
Cytoskeleton remodeling_FAK signaling	MA	66	14
Transport_Calcium transport	GG	182	19
response to retinoic acid	GO	7	15
G1/S transition of mitotic cell cycle	GO	55	7
Cell adhesion_Platelet-endothelium-leucocyte interactions	GG	184	20
Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling	MA	184	28
Development_Neurogenesis:Axonal guidance	GG	236	21
response to cytokine stimulus	GO	15	16
Proteolysis_ECM remodeling	GG	110	13
cell adhesion	GO	589	38
positive regulation of cell cycle	GO	8	12
Signal transduction_NOTCH signaling	GG	219	36
Cell adhesion_Integrin-mediated cell-matrix adhesion	GG	248	23
Reproduction_GnRH signaling pathway	GG	233	23
Development_PIP3 signaling in cardiac myocytes	MA	76	14
negative regulation of cell cycle	GO	139	30
Cell cycle_G0-G1	GG	95	18
Cardiac development_FGF_ErbB signaling	GG	143	16
response to drug	GO	162	24
negative regulation of apoptosis	GO	131	28
Cell cycle_G1-S	GG	217	26
potassium ion transport	GO	177	14
Inflammation_IL-2 signaling	GG	103	15
DNA damage_Brca1 as a transcription regulator	MA	30	16
response to X-ray	GO	20	16

Fig. 10

aging	GO	58	18
negative regulation of cell growth	GO	73	18
ER overload response	GO	10	12
Apoptosis and survival_p53-dependent apoptosis	MA	31	13
DNA damage_DNA-damage-induced responses	MA	10	13
response to organic substance	GO	59	6
wound healing	GO	45	20
Signal transduction_AKT signaling	MA	61	22
protein amino acid phosphorylation	GO	575	36
transmembrane receptor protein tyrosine kinase signaling pathway	GO	105	10
DNA damage_ATM/ATR regulation of G1/S checkpoint	MA	45	14
positive regulation of neuron apoptosis	GO	11	15
protein tetramerization	GO	11	14
Proliferation_Positive regulation cell proliferation	GG	235	18
Cell cycle_G1-S Interleukin regulation	GG	109	9
Cytoskeleton_Regulation of cytoskeleton rearrangement	GG	269	21
Development_Blood vessel morphogenesis	GG	356	25
cell proliferation	GO	357	36
cell-cell adhesion	GO	80	13
response to gamma radiation	GO	22	14
response to organic cyclic substance	GO	50	18
response to metal ion	GO	12	13
DNA damage_Checkpoint	GG	148	20
heart development	GO	151	19
Cardiac development_Wnt_beta-catenin, Notch, VEGF, IP3 and integrin signaling	GG	205	18
positive regulation of apoptosis	GO	99	20
response to inorganic substance	GO	13	13
Cell cycle_G1-S Growth factor regulation	GG	177	14

Fig. 10

Apoptosis and survival_Role of CDK5 in neuronal death and survival	MA	40	17
Proliferation_Negative regulation of cell proliferation	GG	198	25
proteolysis	GO	487	27
Development_Regulation of angiogenesis	GG	300	20
regulation of cell cycle	GO	127	20
nucleotide-excision repair	GO	28	14
central nervous system development	GO	131	26
Proteolysis_Putative SUMO-1 pathway	MA	28	13
Immune response _PIP3 signaling in B lymphocytes	MA	59	11
Development_Neurotrophin family signaling	MA	45	17
DNA damage_BER-NER repair	GG	97	18
Signal transduction_Androgen receptor signaling cross-talk	GG	99	9
response to organic nitrogen	GO	17	12
cell cycle checkpoint	GO	17	2

*The sets listed were genetically altered in at least 50% of the GBMs, contained >5 and <600 genes, and had a Q-value <0.20. See Sup

Fig. 10

Number of deletions in set	Number of amplifications in set	Number of altered samples	Statistical significance of altered genes in set
0	0	82%	<0.001
11	0	64%	<0.001
0	3	55%	<0.001
0	5	64%	<0.001
1	0	64%	<0.001
0	5	55%	<0.001
1	0	59%	<0.001
0	1	55%	<0.001
0	5	50%	<0.001
0	0	55%	<0.001
2	6	82%	0.001
1	5	59%	0.001
1	6	64%	0.001
1	0	55%	0.001
2	1	68%	0.001
1	0	55%	0.002
1	0	55%	0.002
11	0	50%	0.002
12	0	64%	0.002
1	0	59%	0.002
0	0	59%	0.002
1	0	50%	0.003

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Fig. 10

0	0	50%	0.004	
1	0	50%	0.004	
0	0	50%	0.005	
1	0	50%	0.005	
0	0	50%	0.005	
1	0	59%	0.005	
12	3	68%	0.006	
0	5	64%	0.006	
1	1	77%	0.006	
0	1	55%	0.006	
1	0	59%	0.009	
0	0	50%	0.009	
0	3	73%	0.013	
1	3	55%	0.013	
3	5	91%	0.013	
0	0	59%	0.014	
0	5	59%	0.015	
1	0	50%	0.018	
14	5	95%	0.019	
13	4	91%	0.028	
1	5	68%	0.032	
12	1	95%	0.033	
2	0	77%	0.034	
13	4	95%	0.035	
0	0	50%	0.037	
2	3	59%	0.043	
2	0	59%	0.045	
1	0	64%	0.045	

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Fig. 10

12	1	91%	0.045			
13	0	86%	0.046			
1	1	55%	0.046			
12	1	91%	0.046			
1	0	50%	0.046			
11	0	55%	0.048			
1	0	68%	0.049			
2	1	77%	0.051			
0	8	82%	0.051			
0	5	50%	0.051			
1	4	59%	0.051			
1	0	55%	0.051			
1	0	59%	0.052			
0	6	50%	0.052			
13	3	73%	0.053			
1	2	55%	0.054			
0	5	59%	0.056			
1	6	95%	0.062			
0	5	50%	0.068			
1	0	50%	0.073			
12	0	86%	0.073			
1	0	55%	0.076			
2	4	73%	0.077			
1	0	55%	0.083			
1	0	55%	0.084			
1	1	59%	0.091			
1	0	55%	0.095			
12	8	77%	0.101			

Fig. 10

1	0	68%	0.113	
3	2	77%	0.113	
0	1	68%	0.116	
0	0	59%	0.122	
2	4	73%	0.152	
1	0	55%	0.155	
2	0	77%	0.158	
1	1	59%	0.161	
1	0	50%	0.166	
1	0	68%	0.177	
1	0	68%	0.195	
0	6	50%	0.199	
12	0	86%	0.199	
12	0	55%	0.199	

oporting Online Material, Statistical Section, for details.

Fig. 10

table S9. GBM Overexpressed Genes*

	Normal Brain 1	Normal Brain 2	Br01X	Br02X	Br05X	Br07X	Br10PT	Br13X	Br14X	Br15X	Br16X	Br17X	Br18X	Br19X	Br20PT	Br23PT	Br25x	Br26X
Number of tags sequenced	5319813	5374760	3193979	7971688	4585886	4692453	2656151	6017541	2688581	6036214	4852790	6046592	7686292	7884769	2995314	3716505	6256355	9644975
Number of high quality sequence tags	3890781	3811603	2996803	3846546	1914626	1603509	2268438	5609235	2560845	5409160	3054466	4109053	3002707	1517919	2566499	3248601	5595470	3311260
Number of tags matching known transcripts	2539767	2539721	2210496	2626761	1253622	1124729	1127330	3445010	1330996	3880894	1951184	2896841	1816665	1032974	1779688	1987225	2410107	429345

Gene	Normal Brain 1	Normal Brain 2	Br01X	Br02X	Br05X	Br07X	Br10PT	Br13X	Br14X	Br15X	Br16X	Br17X	Br18X	Br19X	Br20PT	Br23PT	Br25x	Br26X	Overexpressed†
ANXA1	11	13	76	40	200	626	30	433	449	152	253	254	303	17	41	264	37	389	+
ANXA5	38	43	83	666	679	688	10	730	602	341	594	271	443	647	194	429	24	866	+
ASF1B	0	0	29	62	3	36	0	19	50	46	33	42	23	23	10	13	7	0	+
ASPM	2	0	36	62	98	189	26	53	46	68	40	133	67	138	60	18	87	7	+
ATAD2	10	9	219	187	276	229	35	96	240	467	296	426	220	365	96	215	153	203	+
ATAD5	0	0	12	7	5	7	7	2	3	8	0	10	0	5	30	9	0	2	+
AURKA	1	3	81	54	49	93	0	39	57	52	32	74	43	34	60	34	0	77	+
AURKB	0	0	81	16	10	6	0	6	30	46	19	49	28	6	22	16	9	2	+
BLM	0	0	2	16	22	7	0	8	22	5	4	17	0	3	9	2	0	12	+
BUB1	0	0	24	45	16	70	0	5	11	8	12	28	34	27	0	5	0	12	+
BUB1B	0	0	22	44	41	124	4	17	20	50	12	75	46	73	4	11	28	144	+
C13orf3	0	0	12	7	4	12	0	3	8	7	1	11	0	2	9	6	8	0	+
C14orf22	0	0	1	13	18	2	152	4	7	25	19	6	11	12	20	38	0	26	+
CASC5	0	0	54	68	333	203	0	55	122	178	97	263	129	112	100	54	10	47	+
CBX2	0	0	41	17	0	14	0	4	12	87	58	58	10	37	13	13	64	7	+
CCDC99	0	0	14	23	37	44	0	13	12	12	19	13	22	38	20	9	0	2	+
CCNB2	1	0	53	29	59	58	0	16	41	52	12	66	31	32	20	9	17	5	+
CDC14A	0	0	5	6	6	7	0	13	16	6	22	10	0	51	0	9	0	9	+
CDC2	2	3	306	270	335	525	18	67	262	465	184	297	140	145	31	65	117	42	+
CDC25A	0	1	29	39	61	57	3	6	23	78	28	67	2	103	0	43	22	16	+
CDC45L	0	0	66	25	33	28	0	13	48	31	23	66	47	18	0	5	0	84	+
CDCA8	1	1	13	15	9	27	0	17	14	15	7	8	6	16	2	10	10	0	+
CDK6	6	3	24	352	277	71	12	121	387	17	53	608	60	158	124	13	117	89	+
CDKN2C	6	12	10	353	350	268	0	80	125	144	152	133	99	253	124	47	49	189	+
CDKN3	2	2	46	49	58	72	0	64	29	56	14	103	30	15	9	28	0	12	+
CDT1	2	1	87	30	15	18	10	11	62	44	22	23	6	7	39	31	29	5	+
CENPA	0	0	65	58	30	67	0	20	34	42	22	71	23	24	19	34	0	12	+
CENPE	1	0	23	19	27	37	0	12	13	12	13	23	0	16	23	0	0	5	+
CENPF	0	0	57	83	41	42	4	28	69	89	50	101	46	64	71	48	5	130	+
CENPK	6	0	98	89	647	317	56	33	144	152	85	174	97	149	213	113	327	65	+
CEP55	0	0	67	38	40	96	12	38	45	87	9	44	43	25	6	30	27	0	+
CHEK1	2	1	33	45	39	101	9	10	36	11	20	41	1	47	9	18	43	7	+
CHRNA5	1	0	15	6	9	14	10	1	27	13	7	6	8	15	7	1	10	14	+
CHST9	0	0	3	0	0	0	6	38	32	2	10	4	0	15	8	8	0	5	+
CKAP2L	0	1	16	43	46	38	0	19	20	32	25	45	14	38	0	12	60	0	+
CKS1B	9	8	263	152	132	245	5	158	71	91	96	192	192	258	31	80	27	23	+
CNTLN	0	0	6	4	2	12	9	4	2	13	2	19	14	8	0	9	3	0	+
CRISPLD1	3	2	18	142	0	13	16	269	53	84	103	34	15	44	20	19	60	242	+
DEPDC1B	0	0	27	15	11	22	0	7	14	11	10	13	7	21	0	11	0	7	+
DLG7	0	0	45	38	34	65	0	11	14	40	13	41	6	11	0	0	25	0	+
DNAH11	0	0	3	22	18	4	0	8	8	9	5	11	8	3	15	0	0	2	+
DNAH9	0	0	28	5	7	4	0	6	5	19	12	7	10	1	0	33	12	7	+
DTL	2	0	43	34	34	32	12	21	34	61	26	59	22	61	31	30	0	30	+
E2F2	0	0	9	12	10	15	10	5	13	27	15	15	0	11	6	8	25	2	+

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E2F7	0	0	80	129	165	62	0	10	31	113	3	60	121	44	35	48	50	184	+
EPR1	1	1	118	124	30	131	5	42	86	69	14	76	48	26	39	45	70	84	+
ESCO2	0	0	12	14	16	26	11	3	11	15	0	22	12	15	0	5	7	5	+
ESPL1	0	0	28	20	27	29	0	21	23	41	25	49	9	22	0	9	30	0	+
EXO1	0	0	28	56	22	59	0	6	7	10	6	30	1	35	0	4	0	5	+
EZH2	7	11	357	418	589	172	35	147	456	690	476	888	297	375	55	374	172	54	+
FAM111B	0	0	3	17	34	36	1	19	55	33	16	36	9	31	7	32	0	0	+
FAM152A	3	4	28	47	76	122	10	67	46	53	49	62	53	90	28	24	0	5	+
FAM64A	0	0	41	105	227	92	0	46	240	168	159	458	51	96	61	163	0	37	+
FAM72B	6	5	83	88	152	146	0	39	53	98	91	142	94	159	38	102	0	19	+
FAM83D	1	1	55	6	22	50	1	20	35	35	22	33	12	44	0	3	0	0	+
FBXO5	3	3	37	72	119	128	0	26	49	254	56	93	142	288	23	68	0	35	+
FOXM1	2	2	108	98	78	36	73	90	135	114	76	159	70	21	121	181	147	70	+
GALR1	0	0	0	0	82	0	0	3	7	26	43	24	0	66	8	10	0	151	+
GEN1	0	0	4	10	6	12	17	10	22	12	9	11	16	6	7	6	6	2	+
GINS1	2	0	51	20	37	68	0	29	68	58	27	60	71	56	39	39	17	156	+
H3F3B	0	0	6	20	86	37	0	206	304	20	75	31	68	69	0	0	0	398	+
HBG1	0	0	198	119	92	172	0	346	372	525	100	26	9	90	0	0	0	172	+
HELLS	1	1	38	21	19	77	0	19	40	73	36	41	50	18	7	15	5	2	+
HIF1A	48	83	634	6439	11024	3963	106	1072	678	1252	3546	2460	2537	1237	531	1404	225	2294	+
HJURP	0	0	67	37	69	31	0	35	58	63	34	157	78	57	7	39	11	9	+
HMMR	0	0	95	6	38	23	0	34	29	97	38	104	24	29	48	27	0	0	+
HNF4G	0	0	5	32	0	11	0	19	6	0	1	10	0	8	0	9	44	16	+
HOXB3	2	6	188	377	38	175	0	66	92	0	6	120	159	27	187	1	1719	133	+
HOXB4	0	0	30	61	31	27	0	28	11	0	4	1	36	0	0	1	20	0	+
HOXB7	0	1	7	57	6	147	0	72	55	0	34	45	59	0	38	2	10	33	+
HOXD10	0	0	0	16	10	52	12	26	3	4	22	47	16	53	0	13	10	123	+
HOXD3	0	0	0	0	5	0	6	21	5	29	5	42	1	26	46	49	16	147	+
HOXD4	0	0	0	1	10	1	7	18	8	7	5	8	0	6	0	2	12	0	+
HOXD9	0	0	2	21	19	15	10	31	19	6	10	39	3	27	0	8	58	19	+
IGF2BP3	0	0	11	40	17	52	0	17	2	10	18	2	9	29	0	10	0	12	+
IGFBP2	19	39	1097	2401	290	142	9	1725	518	1179	145	1087	527	171	409	482	1153	26	+
IL1RAP	7	3	90	11	1027	437	37	224	202	115	123	396	287	156	242	33	14	533	+
IQGAP3	0	0	5	13	20	39	0	8	6	24	2	15	8	8	8	4	39	2	+
KIF14	0	0	13	25	21	51	0	11	10	34	9	33	5	45	25	14	10	14	+
KIF15	1	2	38	71	66	52	0	26	77	100	59	171	66	63	42	35	62	65	+
KIF20A	0	0	52	35	54	160	0	27	20	35	12	45	89	12	6	6	0	16	+
KIF23	0	1	35	41	49	124	0	30	31	30	19	51	15	41	0	12	0	72	+
KIF2C	0	1	25	34	38	28	0	10	24	36	13	21	27	15	3	10	0	14	+
KIF4A	2	2	86	145	160	251	0	91	158	128	101	215	157	119	43	159	30	30	+
KIFC1	0	1	25	25	22	48	0	10	34	62	10	71	16	13	45	36	31	0	+
KNTC1	0	0	5	6	7	5	0	6	5	18	6	33	14	50	0	8	0	7	+
LEPRE1	0	1	9	8	15	25	0	12	3	4	17	11	76	12	0	16	0	0	+
LHFPL3	12	3	0	131	281	122	321	17	319	236	1379	84	6	700	509	376	0	918	+
LMNB1	7	3	155	80	59	164	104	60	192	350	81	183	26	63	71	61	22	137	+
LOC100133109	1	0	3	9	10	4	0	53	190	10	16	16	8	12	0	0	47	12	+
LOC645688	0	0	4	24	72	55	0	176	223	16	26	28	46	62	0	0	24	184	+
LOC730087	0	0	6	1	13	1	12	4	5	4	14	9	0	2	26	2	7	5	+
MAD2L1	1	2	106	114	188	125	0	49	80	119	85	186	191	241	15	68	100	79	+
MELK	0	0	118	88	155	208	0	38	166	129	68	165	108	311	13	82	11	21	+
MEOX2	0	4	0	404	801	0	0	82	68	0	8	201	126	3	248	2	58	317	+
MEX3A	1	0	48	9	5	7	34	10	25	59	8	31	9	7	16	7	65	5	+
MKI67	1	0	69	60	51	70	0	21	51	75	24	62	13	18	9	24	27	2	+
MLF1IP	0	1	96	40	120	46	0	15	39	127	53	121	31	70	21	42	0	7	+

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MMP16	1	0	66	40	49	9	32	1	15	26	24	71	37	32	18	3	0	2	+					
MYBL2	0	0	57	20	10	17	0	13	74	35	11	19	4	15	0	14	0	2	+					
N4BP2_HUMAN	0	3	41	347	171	48	0	19	34	74	82	144	41	65	7	20	0	19	+					
NCAPG	0	1	27	26	34	27	5	7	32	31	11	41	12	17	37	10	6	77	+					
NCAPH	1	0	52	39	25	17	0	17	20	23	14	54	0	39	19	10	22	212	+					
NDC80	0	0	3	6	7	28	0	19	22	29	32	60	24	68	0	30	0	200	+					
NEK2	1	1	21	34	32	54	9	28	27	21	16	52	9	39	0	35	15	2	+					
NUF2	1	0	65	45	34	96	7	26	56	49	6	84	20	40	28	32	25	98	+					
NUSAP1	0	0	120	164	250	315	3	68	145	239	51	222	82	133	137	90	53	121	+					
ORC1L	0	1	61	61	84	84	0	21	47	50	31	46	108	90	0	76	29	42	+					
PBK	0	0	246	165	93	63	0	75	132	182	93	149	52	126	30	55	19	61	+					
PLOD2	2	1	124	489	124	1278	0	413	73	229	52	71	359	422	7	61	18	182	+					
POLQ	0	0	12	18	12	32	0	6	5	7	6	19	6	27	19	6	15	2	+					
PRKD1	2	2	4	19	57	35	28	21	18	31	33	32	10	24	0	29	1	12	+					
PTN	86	88	1107	2319	1027	558	81	2139	2147	2748	2824	1412	431	1924	516	1536	100	426	+					
PTPRZ1	58	139	1281	12076	18775	2474	742	3442	11129	2842	13668	5833	3492	16273	2415	3044	912	4067	+					
PTTG1	13	10	385	62	125	248	38	140	258	483	251	336	89	134	308	353	37	44	+					
Q59GN2_HUMAN	1	1	14	29	20	58	0	53	90	12	14	9	19	10	0	4	33	135	+					
RRM2	2	1	494	1154	790	953	0	229	328	659	191	667	284	583	89	233	131	242	+					
SAMD9	0	0	0	8	13	9	0	35	19	4	6	17	47	35	6	24	9	2	+					
SGOL1	0	1	22	29	16	13	5	5	17	18	7	42	9	19	2	16	63	2	+					
SHOX2	0	0	3	7	10	35	0	12	11	33	13	10	20	15	34	3	0	12	+					
SMC4	17	6	404	796	1242	3397	17	342	609	658	405	1056	817	445	176	367	1046	387	+					
SOX11	0	1	100	21	26	28	61	18	84	241	75	209	21	85	10	41	7	121	+					
STC1	1	2	69	41	2	34	0	25	4	96	44	48	112	15	7	27	65	0	+					
TACC3	1	2	64	124	79	229	0	23	27	82	15	109	61	54	12	86	4	35	+					
TBC1D8B	1	2	23	33	100	41	109	14	19	25	33	18	52	18	12	2	14	0	+					
tcag7.929	0	0	5	3	27	3	90	10	8	6	28	7	19	5	14	2	0	0	+					
TFPI	4	4	197	102	238	57	12	183	45	21	66	118	90	23	120	37	0	95	+					
TGIF1	2	0	24	16	23	15	61	54	44	18	50	89	10	64	106	51	53	28	+					
TMEM45A	4	8	0	248	2	667	13	94	52	343	139	46	987	449	277	134	11	678	+					
TMSL8	2	1	37	33	0	118	48	8	1	1	113	360	28	190	79	864	0	0	+					
TNC	3	9	9	110	61	368	12	148	104	100	200	214	398	155	15	61	24	12	+					
TNFAIP6	6	9	10	332	182	152	0	2126	140	51	544	181	569	1039	405	46	536	347	+					
TNFRSF19	2	12	51	163	969	267	0	70	125	69	319	640	326	58	176	43	29	135	+					
TOP2A	0	0	1650	1514	1792	2866	133	541	1746	2243	1546	3011	787	1919	1477	1273	907	894	+					
TPX2	2	1	131	69	25	108	4	53	137	81	51	97	35	22	61	62	47	5	+					
TROAP	0	0	97	50	2	15	5	21	58	55	67	68	54	25	43	44	96	2	+					
TSKU	1	2	17	41	2	54	20	62	16	12	14	22	4	25	14	14	32	9	+					
TYMS	12	11	448	228	457	832	13	130	232	251	147	483	77	291	87	91	108	282	+					
UBE2C	2	0	131	32	14	22	59	25	92	75	39	76	18	11	25	37	57	12	+					
VIM	457	1297	22980	21254	19283	25798	1231	15975	21114	12460	11290	20530	12515	4388	4184	14662	8599	18626	+					
WRN	1	1	62	29	49	11	4	12	8	21	25	33	29	59	40	28	0	5	+					
ZNF700	1	0	4	12	17	28	0	24	8	22	28	19	51	23	0	30	0	158	+					
ZNF93	0	0	4	15	14	9	3	6	17	10	10	8	8	11	4	9	0	0	+					

* Numbers indicated for each gene correspond to SAGE tags normalized per million tags. The total number of tags analyzed for each sample is indicated above each sample name.

† Genes were considered "overexpressed" if the tumor expression values were more than ten fold greater than the highest normal expression value for more than eight tumors.

‡ Genes are indicated as "extracellular" using annotation from Gene Ontology Cellular Component numbers related to the extracellular compartment, plasma membrane, and cell surface. This includes GO:0016324, GO:0016327, GO:0016328, GO:0019867, GO:0019897, GO:0019898, GO:0031012, GO:0031232, GO:0031233, GO:0031234, GO:0031362, GO:0044420, GO:0044421, GO:0044459, GO:0046658, and GO:0046196.

Fig. 10

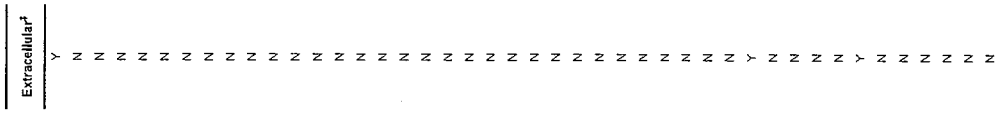
Extracellular
Y N N N N N N N N N N N N N N N N N N N N N N N N N N N N N Y N N N N Y N N N N N N

Fig. 10

Fig. 10

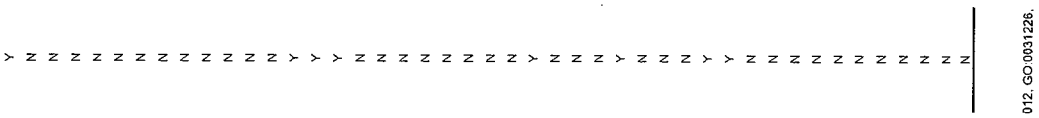

Fig. 10

table S10. GBM Overexpressed Extracellular Genes*

	Normal Brain 1	Normal Brain 2	Br01X	Br02X	Br05X	Br07X	Br10PT	Br13X	Br14X	Br15X	Br16X	Br17X	Br18X	Br19X	Br20PT	Br23PT	Br25x	Br26X		
Number of tags sequenced	5319813	5374760	3193979	7971688	4585886	4692453	2656151	6017541	2688681	6036214	4852790	6046592	7686292	7884769	2965314	3716505	6256355	9644975		
Number of high quality sequence	3890781	3811603	2996803	3846546	1914626	1603509	2268438	5609235	2560845	5409160	3054466	4109053	3002707	1517919	2566499	3248601	5595470	3311260		
Number of tags matching known	2539767	2539721	2210496	2626751	1253622	1124729	1127330	3445010	1330996	3880894	1951184	2896841	1816665	1032974	1779688	1997225	2410107	429345		
Gene	Normal Brain 1	Normal Brain 2	Br01X	Br02X	Br05X	Br07X	Br10PT	Br13X	Br14X	Br15X	Br16X	Br17X	Br18X	Br19X	Br20PT	Br23PT	Br25x	Br26X	Overexpressed†	Extracellular‡
ANXA1	11	13	76	40	200	626	30	433	449	152	253	254	303	17	41	264	37	389	+	Y
CHRNA5	1	0	15	6	9	14	10	1	27	13	7	6	8	15	7	1	10	14	+	Y
CRISPLD1	3	2	18	142	0	13	16	269	53	84	103	34	15	44	20	19	60	242	+	Y
GALR1	0	0	0	0	82	0	0	3	7	26	43	24	0	66	8	10	0	151	+	Y
HMMR	0	0	95	6	38	23	0	34	29	97	38	104	24	29	48	27	0	0	+	Y
IGFBP2	19	39	1097	2401	280	142	9	1725	518	1179	145	1087	527	171	409	482	1153	26	+	Y
IL1RAP	7	3	90	11	1027	437	37	224	202	115	123	396	287	156	242	33	14	533	+	Y
LEPRE1	0	1	9	8	15	25	0	12	3	4	17	11	76	12	0	16	0	0	+	Y
MMP16	1	0	66	40	49	9	32	1	15	26	24	71	37	32	18	3	0	2	+	Y
PRKD1	2	2	4	19	57	36	28	21	18	31	33	32	10	24	0	29	1	12	+	Y
PTN	86	86	1107	2319	1027	558	81	2139	2147	2748	2824	1412	431	1924	516	1536	100	426	+	Y
PTPRZ1	58	139	1281	12076	18775	2474	742	3442	11129	2842	13668	5833	3492	16273	2415	3044	912	4067	+	Y
STC1	1	2	69	41	2	34	0	25	4	96	44	48	112	15	7	27	65	0	+	Y
TFPI	4	4	197	102	238	57	12	183	45	21	66	118	90	23	120	37	0	95	+	Y
TNC	3	9	9	110	61	368	12	148	104	100	200	214	398	155	15	61	24	12	+	Y
TNFAIP6	5	9	10	332	162	152	0	2126	140	51	544	181	569	1039	405	46	536	347	+	Y

* Numbers indicated for each gene correspond to SAGE tags normalized per million tags. The total number of tags analyzed for each sample is indicated above each sample name.

† Genes were considered "overexpressed" if the tumor expression values were more than ten fold greater than the highest normal expression value for more than eight tumors.

‡ Genes are indicated as "extracellular" using annotation from Gene Ontology Cellular Component numbers related to the extracellular compartment, plasma membrane, and cell surface. This includes GO:0016324, GO:0016327, GO:0016328, GO:0019667, GO:0019897, GO:0019898, GO:0031012, GO:0031226, GO:0031232, GO:0031233, GO:0031234, GO:0031362, GO:0044420, GO:0044421, GO:0044459, GO:0046658, and GO:0048196.

Fig. 11

Summary of genetic and clinical characteristics of brain tumors analyzed

Tumor Classification	Tumors analyzed	Median age	Male (%)	Median survival (months)	Tumors with IDH1 mutations	Tumors with IDH2 mutations	Percent of tumors with IDH mutations	Median age of patients with IDH mutation	Median age of patients with wild type IDH	Percent of tumors with p53 mutations	Percent of tumors with 1p and 19q loss	Percent of tumors with PTEN mutations	Percent of tumors with EGFR amplification	Percent of tumors with CDK2NA/B loss
Diffuse astrocytoma	31	33	55%	132	25	1	84%	35	10	50%	NA	NA	0%	0%
Anaplastic astrocytoma	61	38	56%	42	41	2	70%	35	47	63%	11%	8%	2%	10%
Secondary GBM	13	33	70%	16	11	0	85%	32	62	60%	NA	NA	0%	22%
Primary Adult GBM	150	58.5	59%	12	7	NA	5%	32	59	24%	NA	25%	39%	44%
Primary Pediatric GBM	15	5	60%	8	0	NA	0%	ND	5	33%	NA	NA	NA	20%
Oligodendroglioma	51	37	63%	135	41	2	84%	37	19	16%	60%	0%	0%	3%
Anaplastic oligodendroglioma	36	45	64%	84	31	3	94%	45	32	10%	84%	0%	0%	14%
Oligoastrocytoma	3	38	67%	ND	3	NA	100%	38	ND	NA	NA	NA	0%	0%
Anaplastic Oligoastrocytoma	7	30	57%	ND	7	NA	100%	30	ND	NA	NA	NA	0%	0%
Pleomorphic xanthoastrocytoma	7	11	14%	44	1	NA	14%	20	11	NA	NA	NA	0%	NA
Pilocytic astrocytoma	21	5	48%	ND	0	NA	0%	NA	NA	NA	NA	NA	NA	NA
Subependymal giant cell astrocytoma	2	16	NA	ND	0	NA	0%	NA	NA	NA	NA	NA	NA	NA
Ependymoma	30	5.5	45%	ND	0	NA	0%	NA	NA	NA	NA	NA	NA	NA
Medulloblastoma	55	7	65%	27	0	NA	0%	NA	NA	NA	NA	NA	NA	NA

*Patient age refers to age at which the study sample was obtained. ^Secondary GBM designates a GBM which was resected > 1 year after a prior diagnosis of a lower grade glioma (WHO I-III). Abbreviations: WHO (World Health Organization), M (male), NA (not analyzed), ND (not determined due to limited sample size and data censoring status). Of the indicated tumors, six secondary and 50 primary GBMs used previously described in Parsons et al. (16). Copy number changes of EGFR and CDKN2A/B were determined by quantitative real time PCR (Q-PCR). For Q-PCR, copy number levels >3 or <0.3 were considered amplifications or losses, respectively.

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Fig. 12

Evaluation of the frequency of common genetic alterations in IDH1/2 mutated and wildtype gliomas.

Tumor type	IDH1/2 mutation status	Total number of patients	TP53 mutated (%)	PTEN mutated (%)	EGFR amplified (%)	CDKN2A/B deleted (%)	1p/19q LOH (%)
Oligodendroglioma	mut	43	5/24 (21%)	0/20 (0%)	0/43 (0%)	2/40 (5%)	18/23 (78%)
	wt	8	0/8 (0%)	0/4 (0%)	0/8 (0%)	0/8 (0%)	0/7 (0%)
	total	51	5/32 (16%)	0/24 (0%)	0/51 (0%)	2/48 (4%)	18/30 (60%)
Anaplastic oligodendroglioma	mut	34	3/30 (10%)	0/28 (0%)	0/33 (0%)	3/33 (9%)	27/30 (90%)
	wt	2	0/2 (0%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0/2 (0%)
	total	36	3/32 (10%)	0/30 (0%)	0/35 (0%)	5/35 (14%)	27/32 (84%)
Anaplastic astrocytoma	mut	43	24/29 (83%)	1/29 (3%)	0/40 (0%)	0/36 (0%)	0/15 (0%)
	wt	18	2/12 (17%)	2/7 (29%)	1/16 (6%)	5/16 (31%)	1/3 (33%)
	total	61	26/41 (63%)	3/36 (8%)	1/56 (2%)	5/52 (10%)	1/18 (6%)
Secondary GBM	mut	11	6/8 (75%)	nd	0/9 (0%)	1/7 (14%)	nd
	wt	2	0/2 (0%)	nd	0/2 (0%)	1/2 (50%)	nd
	total	13	6/10 (60%)	nd	0/11 (0%)	2/9 (22%)	nd
Primary GBM	mut	7	6/7 (86%)	0/7 (0%)	0/8 (0%)	0/8 (0%)	nd
	wt	143	30/140 (21%)	19/96 (20%)	28/102 (28%)	33/107 (31%)	nd
	total	150	36/147 (24%)	19/103 (19%)	28/102 (28%)	33/107 (31%)	nd

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/055803

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAISUKE KITA ET AL: "PIK3CA alterations in primary (de novo) and secondary glioblastomas" ACTA NEUROPATHOLOGICA, SPRINGER, BERLIN, DE, vol. 113, no. 3, 18 January 2007 (2007-01-18), pages 295-302, XP019491131 ISSN: 1432-0533 the whole document	58

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2009	15/02/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BALAKRISHNAN ASHA ET AL: "Novel somatic and germline mutations in cancer candidate genes in glioblastoma, melanoma, and pancreatic carcinoma" CANCER RESEARCH, vol. 67, no. 8, April 2007 (2007-04), pages 3545-3550, XP002555009 ISSN: 0008-5472 the whole document	1-97
X	TOBIAS SJ^BLOM ET AL: "The Consensus Coding Sequences of Human Breast and Colorectal Cancers" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, WASHINGTON, DC, vol. 314, 13 October 2006 (2006-10-13), pages 268-274, XP007901261 ISSN: 0036-8075 Supplementary table 4, line 257	26-45
X	US 2008/108061 A1 (INAZAWA JOHJI [JP] ET AL) 8 May 2008 (2008-05-08) the whole document	58
X,P	BLEEKER FONNET E ET AL: "IDH1 Mutations at Residue p.R132 (IDH1(R132)) Occur Frequently in High-Grade Gliomas But Not in Other Solid Tumors" HUMAN MUTATION, vol. 30, no. 1, January 2009 (2009-01), pages 7-11, XP002555010 ISSN: 1059-7794 the whole document	1-57
X,P	YAN HAI ET AL: "IDH1 and IDH2 Mutations in Gliomas" NEW ENGLAND JOURNAL OF MEDICINE, vol. 360, no. 8, February 2009 (2009-02), pages 765-773, XP002555011 ISSN: 0028-4793 the whole document	1-57
X,P	PARSONS D WILLIAMS ET AL: "An integrated genomic analysis of human glioblastoma Multiforme" SCIENCE (WASHINGTON D C), vol. 321, no. 5897, September 2008 (2008-09), pages 1807-1812, XP002555012 ISSN: 0036-8075 the whole document	1-47

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/055803

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	BALSS JOERG ET AL: "Analysis of the IDH1 codon 132 mutation in brain tumors" ACTA NEUROPATHOLOGICA, vol. 116, no. 6, December 2008 (2008-12), pages 597-602, XP002555013 ISSN: 0001-6322 the whole document	1-57
X	DATABASE UniProt [Online] 1 February 1996 (1996-02-01), "RecName: Full=Isocitrate dehydrogenase [NADP], mitochondrial; Short=IDH; EC=<A HREF="http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?[enzyme-ECNumber:1.1.1.42]+-e">1.1.1.42</A>; AltName: Full=Oxalosuccinate decarboxylase; AltName: Full=NADP(+)-specific ICDH; AltName: Full=IDP; AltName: Full=ICD-M;" XP002555014 retrieved from EBI accession no. UNIPROT:P48735 Database accession no. P48735 compound	26
X	DATABASE UniProt [Online] 10 May 2005 (2005-05-10), "SubName: Full=IDH1 protein; SubName: Full=Isocitrate dehydrogenase 1 (NADP+), soluble, isoform CRA_a; SubName: Full=Putative uncharacterized protein IDH1; Flags: Fragment;" XP002555015 retrieved from EBI accession no. UNIPROT:Q6FHQ6 Database accession no. Q6FHQ6 compound	26

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-57

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention: 1; Claims: 1-57

Methods of characterising glioblastoma by analysing codon 132 in IDH1 or codon 172 in IDH2. Antibodies to the mutated IDH1 or IDGH2, the respective mutant polypeptide and polynucleotide, methods of immunising with the mutant IDH1 or IDH2, method of screening using the mutant IDH1 or IDH2.

Invention: 2; Claims: 58-77, 88(partially)

A method of detecting or diagnosing or characterising glioblastoma multiforme by determining somatic mutations in TP53 (1st gene of Table S7 of Figue 10).

Inventions: 3-43; Claims: 58-77, 88(partially)

A method of detecting or diagnosing or characterising glioblastoma multiforme by determining somatic mutations in the respective genes of Table S7 of Figue 10).

Inventions: 44-148; Claims: 78-87(partially)

A method to detect or characterise or monitor GBM by determining the expression of at least 1 gene of Table S9, or S5. The number of inventions in this category could not be determined precisely since it is not clear how many genes Table S 5 encompasses.

Inventions: 149-150; Claims: 89-95(partially)

A method to detect, diagnose or monitor GBM by determining the expression of at least 1 gene of Table S6. It is not clear how many genes the Table S6 encompasses.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/055803

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008108061 A1	08-05-2008	NONE	