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(54) Title: SINGLE NUCLEOTIDE POLYMORPHISMS PREDICTING CARDIOVASCULAR DISEASE AND MEDICATION EFFICACY

(57) Abstract: The present invention relates to isolated polynucleotides encoding a cardiovascular associated (CA) gene polypeptide useful in methods to identify therapeutic agents and useful for preparation of a medicament to treat cardiovascular disease, the polynucleotide is selected from the group comprising:SEQ ID 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 with allelic variation as indicated in the sequences section contained in a functional surrounding like full length cDNA for CA gene polypeptide and with or without the CA gene promoter sequence.The invention also provides diagnostic methods and kits including antibodies determining whether a human subject is at risk for a cardiovascular disease. The invention provides further polymorphic sequences and other genes.

Single Nucleotide Polymorphisms predicting Cardiovascular Disease and Medication Efficacy

Technical Field

This invention relates to genetic polymorphisms useful for assessing cardiovascular risks in humans, including, but not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, myocardial infarction, and stroke. Specifically, the present invention identifies and describes gene variations which are individually present in humans with cardiovascular disease states, relative to humans with normal, or non-cardiovascular disease states, and/or in response to medications relevant to cardiovascular disease. Further, the present invention provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the efficacy of compounds in clinical trials. Still further, the present invention provides methods to use gene variations to predict personal medication schemes omitting adverse drug reactions. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions.

Background of the Invention

Cardiovascular disease is a major health risk throughout the industrialized world.

Cardiovascular diseases include but are not limited by the following disorders of the heart and the vascular system: congestive heart failure, myocardial infarction, atherosclerosis, ischemic diseases of the heart, coronary heart disease, all kinds of atrial and ventricular arrhythmias, hypertensive vascular diseases and peripheral vascular diseases.

Heart failure is defined as a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirement of the metabolizing tissue. It includes all forms of pumping failure such as high-output and low-output, acute and chronic, right-sided or left-sided, systolic or diastolic, independent of the underlying cause.

Myocardial infarction (MI) is generally caused by an abrupt decrease in coronary blood flow that follows a thrombotic occlusion of a coronary artery previously narrowed by arteriosclerosis. MI prophylaxis (primary and secondary prevention) is included as well as the acute treatment of MI and the prevention of complications.

Ischemic diseases are conditions in which the coronary flow is restricted resulting in an perfusion which is inadequate to meet the myocardial requirement for oxygen. This group of diseases include stable angina, unstable angina and asymptomatic ischemia.

Arrhythmias include all forms of atrial and ventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, atrio-ventricular reentrant tachycardia, preexitation syndrome, ventricular tachycardia, ventricular flutter, ventricular fibrillation) as well as bradycardic forms of arrhythmias.

Hypertensive vascular diseases include primary as well as all kinds of secondary arterial hypertension (renal, endocrine, neurogenic, others).

Peripheral vascular diseases are defined as vascular diseases in which arterial and/or venous flow is reduced resulting in an imbalance between blood supply and tissue oxygen demand. It includes chronic peripheral arterial occlusive disease (PAOD), acute arterial thrombosis and embolism, inflammatory vascular disorders, Raynaud's phenomenon and venous disorders.

Atherosclerosis, the most prevalent of vascular diseases, is the principal cause of heart attack, stroke, and gangrene of the extremities, and thereby the principal cause of death. Atherosclerosis is a complex disease involving many cell types and molecular factors (for a detailed review, see Ross, 1993, Nature 362: 801-809 and Lusis, A. J., Nature 407, 233-241 (2000)). The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions or plaques, preceded and accompanied by inflammation. The advanced lesions of atherosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult. For example, shear stresses are thought to be responsible for the frequent occurrence of atherosclerotic plaques in regions of the circulatory system where turbulent blood flow occurs, such as branch points and irregular structures.

The first observable event in the formation of an atherosclerotic plaque occurs when blood-borne monocytes adhere to the vascular endothelial layer and transmigrate through to the sub-endothelial space. Adjacent endothelial cells at the same time produce oxidized low density lipoprotein (LDL). These oxidized LDLs are then taken up in large amounts by the monocytes through scavenger receptors expressed on their surfaces. In contrast to the regulated pathway by which native LDL (nLDL) is taken up by nLDL specific receptors, the scavenger pathway of uptake is not regulated by the monocytes.

These lipid-filled monocytes are called foam cells, and are the major constituent of the fatty streak. Interactions between foam cells and the endothelial and SMCs which surround them lead to a state of chronic local inflammation which can eventually lead to smooth muscle cell proliferation and migration, and the formation of a fibrous plaque. Such plaques occlude the blood vessel concerned and thus restrict the flow of blood, resulting in ischemia.

Ischemia is a condition characterized by a lack of oxygen supply in tissues of organs due to inadequate perfusion. Such inadequate perfusion can have number of natural causes, including atherosclerotic or restenotic lesions, anemia, or stroke, to name a few. Many medical interventions, such as the interruption of the flow of blood during bypass surgery, for example, also lead to ischemia. In addition to sometimes being caused by diseased cardiovascular tissue, ischemia may sometimes affect cardiovascular tissue, such as in ischemic heart disease. Ischemia may occur in any organ, however, that is suffering a lack of oxygen supply.

The most common cause of ischemia in the heart is atherosclerotic disease of epicardial coronary arteries. By reducing the lumen of these vessels, atherosclerosis causes an absolute decrease in myocardial perfusion in the basal state or limits appropriate increases in perfusion when the demand for flow is augmented. Coronary blood flow can also be limited by arterial thrombi, spasm, and, rarely, coronary emboli, as well as by ostial narrowing due to luetic aortitis. Congenital abnormalities, such as anomalous origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults. Myocardial ischemia can also occur if myocardial oxygen demands are abnormally increased, as in severe ventricular hypertrophy due to hypertension or aortic stenosis. The latter can be present with angina that is indistinguishable from that caused by coronary atherosclerosis. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxy-hemoglobin, is a rare cause of myocardial ischemia. Not infrequently, two or more causes of ischemia will coexist, such as an increase in oxygen demand due to left ventricular hypertrophy and a reduction in oxygen supply secondary to coronary atherosclerosis.

The foregoing studies are aimed at defining the role of particular gene variations presumed to be involved in the misleading of normal cellular function leading to cardiovascular disease. However, such approaches cannot identify the full panoply of gene variations that are involved in the disease process.

At present, the only available treatments for cardiovascular disorders are pharmaceutical based medications that are not targeted to an individual's actual defect; examples include angiotensin converting enzyme (ACE) inhibitors and diuretics for hypertension, insulin supplementation for non-insulin dependent diabetes mellitus (NIDDM), cholesterol reduction strategies for dyslipidaemia, anticoagulants, β blockers for cardiovascular disorders and weight reduction strategies for obesity. If targeted treatment strategies were available it might be possible to predict the response to a particular regime of therapy and could markedly increase the effectiveness of such treatment. Although targeted therapy requires accurate diagnostic tests for disease susceptibility, once these tests are developed the opportunity to utilize targeted therapy will become widespread. Such diagnostic tests could initially serve to identify individuals at most risk of hypertension and could allow them to make changes in lifestyle or diet that would serve as preventative measures. The benefits associated by coupling the diagnostic tests with a system of targeted therapy could include the reduction in dosage of administered drugs and thus the amount of unpleasant side effects suffered by an individual. In more severe cases a diagnostic test may suggest that earlier surgical intervention would be useful in preventing a further deterioration in condition.

It is an object of the invention to provide genetic diagnosis of predisposition or susceptibility for cardiovascular diseases. Another related object is to provide treatment to reduce or prevent or delay the onset of disease in those predisposed or susceptible to this disease. A further object is to provide means for carrying out this diagnosis.

Accordingly, a first aspect of the invention provides a method of diagnosis of disease in an individual, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

In another aspect, the invention provides a method of identifying an individual

predisposed or susceptible to a disease, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

The invention is of advantage in that it enables diagnosis of a disease or of certain disease states via genetic analysis which can yield useable results before onset of disease symptoms, or before onset of severe symptoms. The invention is further of advantage in that it enables diagnosis of predisposition or susceptibility to a disease or of certain disease states via genetic analysis.

The invention may also be of use in confirming or corroborating the results of other diagnostic methods. The diagnosis of the invention may thus suitably be used either as an isolated technique or in combination with other methods and apparatus for diagnosis, in which latter case the invention provides a further test on which a diagnosis may be assessed.

The present invention stems from using allelic association as a method for genotyping individuals; allowing the investigation of the molecular genetic basis for cardiovascular diseases. In a specific embodiment the invention tests for the polymorphisms in the sequences of the listed genes in the Examples. The invention demonstrates a link between this polymorphisms and predispositions to cardiovascular diseases by showing that allele frequencies significantly differ when individuals with "bad" serum lipids are compared to individuals with "good" serum levels. The meaning of "good and bad" serum lipid levels is defined in Table 1.

Certain disease states would benefit, that is to say the suffering of the patient may be reduced or prevented or delayed, by administration of treatment or therapy in advance of disease appearance; this can be more reliably carried out if advance diagnosis of predisposition or susceptibility to disease can be diagnosed.

Detailed Description of the Invention

The present invention is based at least in part on the discovery that a specific allele of a polymorphic region of a so called "candidate gene" is associated with CVD.

"Candidate gene" as used herein includes genes that can be assigned to either normal cardiovascular function or to metabolic pathways that are related to onset and/or progression of cardiovascular diseases. As the development of cardiovascular diseases is not completely understood, the term "candidate gene" may also comprise genes with presently unknown function.

For the present invention the following candidate genes were analyzed:
-Genes found to be expressed in cardiac tissue (Hwang et al., Circulation 1997, 96:4146-4203).
-Genes from the following metabolic pathways and their regulatory elements:

Lipid metabolism

Numerous studies have shown a connection between serum lipid levels and cardiovascular diseases. Candidate genes falling into this group include but are not limited by genes of the cholesterol pathway, apolipoproteins and their modifiying factors.

Coagulation

Ischemic diseases of the heart and in particular myocardial infarction may be caused by a thrombotic occlusion. Genes falling into this group include all genes of the coagulation cascade and their regulatory elements.

Inflammation

Complications of atherosclerosis are the most common causes of death in Western societies. In broad outline atherosclerosis can be considered to be a form of chronic inflammation resulting from interaction modified lipoproteins, monocyte-derived

macrophages,T cells, and the normal cellular elements of the arterial wall. This inflammatory process can ultimately lead to the development of complex lesions, or plaques, that protrude into the arterial lumen. Finally plaque rupture and thrombosis result in the acute clinical complications of myocardial infarction and stroke (Glass et al., Cell 2001, 104:503-516).

It follows that all genes related to inflammatory processes, including but not limited by cytokines, cytokine receptors and cell adhesion molecules are candidate genes for CVD.

Glucose and energy metabolism

As glucose and energy metabolism is interdependent with the metabolism of lipids (see above) also the former pathways contain candidate genes. Energy metabolism in general also relates to obesity, which is an independent risk factor for CVD (Melanson et al., Cardiol Rev 2001 9:202-207). In addition high blood glucose levels are associated with many microvascular and macrovascular complications and may therefore affect an individuals disposition to CVD (Duckworth, Curr Atheroscler Rep 2001, 3:383-391).

Hypertension

As hypertension is an independent risk factor for CVD, also genes that are involved in the regulation of systolic and diastolic blood pressure affect an individuals risk for CVD (Safar, Curr Opin Cardiol 2000, 15:258-263). Interestingly hypertension and diabetes (see above) appear to be interdependent, since hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease. Conversely, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than are normotensive persons (Sowers et al., Hypertension 2001, 37:1053-1059).

Unclassified genes

As stated above, the mechanisms that lead to cardiovascular diseases are not completely elucidated. Hence also candidate genes were analysed, which could not be assigned to the above listed categories. The present invention is based at least in part on the discovery of polymorphisms, that lie in genomic regions of unknown physiological function.

Results

After conducting an association study, we surprisingly found polymorphic sites in a number of candidate genes which show a strong correlation between healthy and CVD prone individuals. "Healthy" as used herein refers to individuals that neither suffer from existing CVD, nor exihibit an increased risk for CVD through their serum lipid level profile. "CVD prone" as used herein refers to individuals with existing CVD and/or a serum lipid profile that confers a high risk to get CVD (see Table 1 for definitions of healthy and CVD prone serum lipid levels). Polymorphic sites in candidate genes that were found to be significantly associated with "healthy" or "CVD prone" phenotypes will be refered to as "CVD associated SNPs" (CA SNPs). The respective genomic loci that harbour CA SNPs will be refered to as "CVD associated genes" (CA genes), irrespective of the actual function of this gene locus.

In particular we surprisingly found CA SNPs in the following genes:

Apolipoprotein E

Chylomicron remnants and very low density lipoprotein (VLDL) remnants are rapidly removed from the circulation by receptor-mediated endocytosis in the liver. Apolipoprotein E, a main apoprotein of the chylomicron, binds to a specific receptor on liver cells and peripheral cells. ApoE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. The APOE gene is mapped to chromosome

19 in a cluster with APOC1 and APOC2. Defects in apolipoprotein E result in familial dysbetalipoproteinemia, or type III hyperlipoproteinemia (HLP III), in which increased plasma cholesterol and triglycerides are the consequence of impaired clearance of chylomicron and VLDL remnants.

Apolipoprotein e receptor 2 (low density lipoprotein receptor-related protein 8, LPR8)

This gene encodes an apolipoprotein E receptor, a member of the low density lipoprotein receptor (LDLR) family. Apolipoprotein E is a small lipophilic plasma protein and a component of lipoproteins such as chylomicron remnants, very low density lipoprotein (VLDL), and high density lipoprotein (HDL). The apolipoprotein E receptor is involved in cellular recognition and internalization of these lipoproteins. Alternative splicing generates three transcript variants for this gene; additional variants have been described, but their full length nature has not been determined.

Diazepam binding inhibitor, Endozepine

Diazepam binding inhibitor (acyl-CoA-binding protein); binds and induces medium-chain acyl-CoA ester synthesis

Nonmuscle type myosin heavy chain 9

Non-muscle myosin heavy chain 9; motor protein that provides force for muscle contraction, cytokinesis and phagocytosis; contains an ATPase head domain and a rod-like tail domain

Apolipoprotein A-I and C-III genomic locus

APOA1 promotes cholesterol efflux from tissues to the liver for excretion. Apolipoprotein A-I is the major protein component of high density lipoprotein (HDL) in the plasma. Synthesized in the liver and small intestine, it consists of two identical chains of 77 amino acids; an 18-amino acid signal peptide is removed co-translationally and a 6-amino acid propeptide is cleaved post-translationally. Variation in the latter step, in addition to modifications leading to so-called isoforms, is

responsible for some of the polymorphism observed. APOA1 is a cofactor for lecithin cholesterolacyltransferase (LCAT) which is responsible for the formation of most plasma cholesteryl esters. The APOA1, APOC3 and APOA4 genes are closely linked in both rat and human genomes. The A-I and A-IV genes are transcribed from the same strand, while the C-III gene is transcribed convergently in relation to A-I. Defects in the apolipoprotein A-1 gene are associated with HDL deficiency and Tangier disease.

Apolipoprotein C-III is a very low density lipoprotein (VLDL) protein. APOC3 inhibits lipoprotein lipase and hepatic lipase; it is thought to delay catabolism of triglyceride-rich particles. The APOA1, APOC3 and APOA4 genes are closely linked in both rat and human genomes. The A-I and A-IV genes are transcribed from the same strand, while the A-1 and C-III genes are convergently transcribed. An increase in apoC-III levels induces the development of hypertriglyceridemia.

Apolipoprotein B

Apolipoprotein B (ApoB) is the main apolipoprotein of chylomicrons and low density lipoproteins (LDL). The protein occurs in the plasma in 2 main isoforms, apoB-48 and apoB-100. The first is synthesized exclusively by the gut, the second by the liver. The intestinal (B-48) and hepatic (B-100) forms of apoB are coded by a single gene and by a single mRNA transcript larger than 16 kb. The 2 proteins share a common amino terminal sequence. In the ApoB-100 isoform the precursor has 4,563 amino acids, and the mature apoB-100 has 4,536 amino acid residues. Mature, circulating B-48 is homologous over its entire length (estimated to be between 2,130 and 2,144 amino acid residues) with the amino-terminal portion of B-100 and contains no sequence from the carboxyl end of B-100. From structural studies, it is thought that apoB-48 represents the amino-terminal 47% of apoB-100 and that the carboxyl terminus of apoB-48 is in the vicinity of residue 2151 of apoB-100. Apolipoprotein B-48 may be the product of an intestinal mRNA with an in-frame UAA stop codon resulting from a C-to-U change in the codon CAA encoding Gln(2153) in apoB-100 mRNA. Since only the sequence that codes B-100 is present

in genomic DNA, this presents the possibility of an organ-specific introduction of a stop codon to an mRNA and the change from CAA to UAA of codon 2153 of the message as a unique RNA editing process.

LIM domain kinase 1

There are approximately 40 known eukaryotic LIM proteins, so named for the LIM domains they contain. LIM domains are highly conserved cysteine-rich structures containing 2 zinc fingers. Although zinc fingers usually function by binding to DNA or RNA, the LIM motif probably mediates protein-protein interactions. LIM kinase-1 and LIM kinase-2 belong to a small subfamily with a unique combination of 2 N-terminal LIM motifs and a C-terminal protein kinase domain. LIMK1 is likely to be a component of an intracellular signaling pathway and may be involved in brain development. LIMK1 hemizygosity is implicated in the impaired visuospatial constructive cognition of Williams syndrome. Two splice variant have been identified.

Thermostable phenol sulfotransferase (STP2)

Sulfonation is an important pathway in the biotransformation of many drugs, xenobiotics, neurotransmitters, and steroid hormones. The phenol sulfotransferase STP2 maps to chromosome 16 (Dooley and Huang, 1996) and preferentially catalyzes the sulfonation of 'simple' planar phenols.

Low Density Lipoprotein Receptor

The low density lipoprotein receptor (LDLR) gene family consists of cell surface proteins involved in receptor-mediated endocytosis of specific ligands. Low density lipoprotein (LDL) is normally bound at the cell membrane and taken into the cell ending up in lysosomes where the protein is degraded and the cholesterol is made available for repression of microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. At the same time, a reciprocal stimulation of cholesterol ester synthesis takes place.

Mutations in the LDL receptor (LDLR) gene cause the autosomal dominant disorder, familial hypercholesterolemia.

ATP-binding cassette, sub-family B (MDR/TAP), member 1

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MDR/TAP subfamily. Members of the MDR/TAP subfamily are involved in multidrug resistance. The protein encoded by this gene is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. It is responsible for decreased drug accumulation in multidrug-resistant cells and often mediates the development of resistance to anticancer drugs. This protein also functions as a transporter in the blood-brain barrier.

Annexin VI (Calphobindin II)

Annexin VI belongs to a family of calcium-dependent membrane and phospholipid binding proteins. Although their functions are still not clearly defined, several members of the annexin family have been implicated in membrane-related events along exocytotic and endocytotic pathways. The annexin VI gene is approximately 60 kbp long and contains 26 exons. It encodes a protein of about 68 kDa that consists of eight 68-amino acid repeats separated by linking sequences of variable lengths. It is highly similar to human annexins I and II sequences, each of which contain four such repeats. Exon 21 of annexin VI is alternatively spliced, giving rise to two isoforms that differ by a 6-amino acid insertion at the start of the seventh repeat. Annexin VI has been implicated in mediating the endosome aggregation and vesicle fusion in secreting epithelia during exocytosis.

Protein C inhibitor (PCI-B)

Marlar and Griffin (J. Clin. Invest. 1980, 66: 1186-1189) identified in normal plasma a protein inhibitor of activated protein C. They showed, furthermore, that this inhibitor is deficient in combined factor V and VIII deficiency. Activated protein C is a potent anticoagulant.

Protein C inhibitor (plasminogen activator inhibitor III); may be a serine protease inhibitor; member of the serpin family of serine protease inhibitors.

NADH dehydrogenase 5

Subunit of NADH-ubiquinone oxidoreductase (complex I); transports electrons from NADH to ubiquinone.

Lysosomal alpha-glucosidase (acid maltase)

This gene encodes acid alpha-glucosidase, which is essential for the degradation of glycogen to glucose in lysosomes. Different forms of acid alpha-glucosidase are obtained by proteolytic processing. Defects in this gene are the cause of glycogen storage disease II, also known as Pompe's disease, which is an autosomal recessive disorder with a broad clinical spectrum.

In classic cases of Pompe disease, affected children are prostrate and markedly hypotonic with large hearts. The tongue may be enlarged. The liver is rarely enlarged (except as a result of heart failure), and hypoglycemia and acidosis do not occur as they do in type I glycogen storage disease. Death usually occurs in the first year of life in the classic form of the disorder and cardiac involvement is striking.

Interleukin 6

Interleukin 6 (interferon-beta 2); induces the maturation of B cells into immunoglobulin-secreting cells.

Fibrinogen gamma chain/fibrinogen alpha chain genes

The protein encoded by these genes is fibrinogen, a blood-borne glycoprotein comprised of three pairs of nonidentical polypeptide chains. Following vascular injury, fibrinogen is cleaved by thrombin to form fibrin which is the most abundant component of blood clots. In addition, various cleavage products of fibrinogen and fibrin regulate cell adhesion and spreading, display vasoconstrictor and chemotactic activities, and are mitogens for several cell types. Mutations in this gene lead to several disorders, including dysfibrinogenemia, hypofibrinogenemia and thrombophilia. Alternative splicing results in two isoforms, varying in the carboxy-terminus.

Paraoxonase 2 (PON2)

Paraoxonase/arylesterase 2; possibly functions in protecting low density lipoprotein against oxidative modification; member of a family that hydrolyzes toxic organophosphates.

Defensin, alpha 6

Defensins are a family of microbicidal and cytotoxic peptides thought to be involved in host defense. They are abundant in the granules of neutrophils and also found in the epithelia of mucosal surfaces such as those of the intestine, respiratory tract, urinary tract, and vagina. Members of the defensin family are highly similar in protein sequence and distinguished by a conserved cysteine motif. Several alpha defensin genes appear to be clustered on chromosome 8. The protein encoded by this gene, defensin, alpha 6, is highly expressed in the secretory granules of Paneth cells of the small intestine, and likely plays a role in host defense of human bowel.

Tetracycline transporter-like protein

Cardiac beta myosin heavy chain, myosin, heavy polypeptide 7

MYH7 encodes the cardiac muscle beta (or slow) isoform of myosin. Changes in the relative abundance of MYH7 and MYH6 (the alpha, or fast, isoform of cardiac

myosin heavy chain) correlate with the contractile velocity of cardiac muscle. Mutations in MYH7 are associated with familial hypertrophic cardiomyopathy.

Endothelial leukocyte adhesion molecule 1 (ELAM-1)

The endothelial leukocyte adhesion molecule-1 is expressed by cytokine-stimulated endothelial cells. It is thought to be responsible for the accumulation of blood leukocytes at sites of inflammation by mediating the adhesion of cells to the vascular lining. It exhibits structural features such as the presence of lectin- and EGF-like domains followed by short consensus repeat (SCR) domains that contain 6 conserved cysteine residues. These proteins are part of the selectin family of cell adhesion molecules. This gene is present in single copy in the human genome and contains 14 exons spanning about 13 kb of DNA. Adhesion molecules participate in the interaction between leukocytes and the endothelium and appear to be involved in the pathogenesis of atherosclerosis.

Lamin B2 (LAMB2)

Lamin B2 is a member of a family of structural nuclear envelope proteins.

Estrogen receptor 2 (ER beta)

Estrogen receptor beta 2 is a transcriptional activator involved in regulation of reproduction; exists in five isoforms.

Tissue plasminogen activator

This gene encodes tissue-type plasminogen activator, a secreted serine protease which converts the proenzyme plasminogen to plasmin, a fibrinolytic enzyme. Tissue-type plasminogen activator is synthesized as a single chain which is cleaved by plasmin to a two chain disulfide linked protein. This enzyme plays a role in cell migration and tissue remodeling. Increased enzymatic activity causes hyper-fibrinolysis, which manifests as excessive bleeding; decreased activity leads to hypofibrinolysis which can result in thrombosis or embolism. Alternative splicing of this gene produces three transcripts.

Laminin receptor 1

Laminins, a family of extracellular matrix glycoproteins, are the major non-collagenous constituent of basement membranes. They have been implicated in a wide variety of biological processes including cell adhesion, differentiation, migration, signaling, neurite outgrowth and metastasis. Many of the effects of laminin are mediated through interactions with cell surface receptors. These receptors include members of the integrin family, as well as non-integrin laminin-binding proteins. This gene encodes a high-affinity, non-integrin family, laminin receptor 1. This receptor has been variously called 67 kD laminin receptor, 37 kD laminin receptor precursor (37LRP) and p40 ribosome-associated protein. The amino acid sequence of laminin receptor 1 is highly conserved through evolution, suggesting a key biological function. It has been observed that the level of the laminin receptor transcript is higher in colon carcinoma tissue and lung cancer cell line than their normal counterparts. Also, there is a correlation between the upregulation of this polypeptide in cancer cells and their invasive and metastatic phenotype. Multiple copies of this gene exist, however, most of them are pseudogenes thought to have arisen from retropositional events.

Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)

The ITGB3 protein product is the integrin beta chain beta 3. Integrins are integral cell-surface proteins composed of an alpha chain and a beta chain. A given chain may combine with multiple partners resulting in different integrins. Integrin beta 3 is found along with the alpha IIb chain in platelets. Integrins are known to participate in cell adhesion as well as cell-surface mediated signalling.

Myeloid cell differentiation protein (MCL1)

Rinkenberger et al. (Genes Dev. 2000, 14: 23-27) disrupted the Mcl1 locus in murine ES cells to determine the developmental roles of this Bcl2 family member. Deletion of Mcl1 resulted in periimplantation embryonic lethality. Homozygous Mcl1-deficient embryos did not implant in utero, but could be recovered at E3.5 to E4.0.

Null blastocysts failed to hatch or attach in vitro, indicating a trophectoderm defect, although the inner cell mass could grow in culture. Of note, homozygous Mcl1-deficient blastocysts showed no evidence of increased apoptosis, but exhibited a delay in maturation beyond the precompaction stage. This model indicates that Mcl1 is essential for preimplantation development and implantation, and suggests that it has a function beyond regulating apoptosis.

Tumor necrosis factor type 1 receptor associated protein (TRAP1)

TRAP is a highly conserved member of a class of molecular chaperones with multiple functions. It is involved in the maturation of a subset of proteins involved in signal transduction.

Xanthine dehydrogenase/oxidase

Xanthine dehydrogenase belongs to the group of molybdenum-containing hydroxylases involved in the oxidative metabolism of purines. The enzyme is a homodimer. Xanthine dehydrogenase can be converted to xanthine oxidase by reversible sulfhydryl oxidation or by irreversible proteolytic modification. Defects in xanthine dehydrogenase cause xanthinuria, may contribute to adult respiratory stress syndrome, and may potentiate influenza infection through an oxygen metabolite-dependent mechanism.

Stromal cell-derived factor 1 (SDF 1)

Stromal cell-derived factor 1 is a lymphocyte chemoattractant that signals through the receptor CXCR4.

Diacylglycerol kinase delta

Diacylglycerol kinase delta phosphorylates the arachidonoyl type of diacylglycerol; contains a pleckstrin homology domain and an EPH domain.

Smooth muscle myosin heavy chain, MYH11

The protein encoded by this gene is a smooth muscle myosin belonging to the myosin heavy chain family. The gene product is a subunit of a hexameric protein that consists of 2 heavy chain subunits and 2 pairs of non-identical light chain subunits. It functions as a major contractile protein, converting chemical energy into mechanical energy through the hydrolysis of ATP. The gene encoding a human ortholog of rat NUDE1 is transcribed from the reverse strand of MYH11 gene, and its 3' end overlaps with that of the latter. The pericentric inversion of chromosome 16 [inv(16)(p13q22)] produces a chimeric transcript consisting of the first 165 residues from the N terminus of core-binding factor beta in a fusion with the C-terminal portion of the smooth muscle myosin heavy chain. This chromosomal rearrangement is associated with acute myeloid leukemia of the M4Eo subtype. Alternative splicing generates isoforms that are differentially expressed, with ratios changing during muscle cell maturation. Additional splice variants have been described but their full-length nature has not been determined.

Caveolin 1

The scaffolding protein encoded by this gene is the main component of the caveolae plasma membranes found in most cell types. The protein links integrin subunits to the tyrosine kinase FYN, an initiating step in coupling integrins to the Ras-ERK pathway and promoting cell cycle progression. The gene is a tumor suppressor gene candidate and a negative regulator of the Ras-p42/44 MAP kinase cascade. CAV1 and CAV2 are located next to each other on chromosome 7 and express colocalizing proteins that form a stable hetero-oligomeric complex. By using alternative initiation codons in the same reading frame, two isoforms (alpha and beta) are encoded by a single transcript from this gene.

AP-2 beta

Expression of AP-2 transcription factors has been detected previously in embryonic renal tissues. It was shown that AP-2beta -/- mice complete embryonic development and die at postnatal days 1 and 2 because of polycystic kidney disease. Analyses of

kidney development revealed that induction of epithelial conversion, mesenchyme condensation, and further glomerular and tubular differentiation occur normally in AP-2beta-deficient mice. At the end of embryonic development expression of bcl-X(L), bcl-w, and bcl-2 is down-regulated in parallel to massive apoptotic death of collecting duct and distal tubular epithelia. Addressing the molecular mechanism it was shown that transfection of AP-2 into cell lines in vitro strongly suppresses c-myc-induced apoptosis pointing to a function of AP-2 in programming cell survival during embryogenesis. The position of the human AP-2beta gene was identified at chromosome 6p12-p21.1, within a region that has been mapped for autosomal recessive polycystic kidney disease (ARPKD). Sequence analyses of ARPKD patients and linkage analyses using intragenic polymorphic markers indicate that the AP-2beta gene is located in close proximity to but distinct from the ARPKD gene (Moser et al., Genes Dev 1997, 11:1938-1948).

Transforming growth factor beta 2 (TGFB2)

Transforming growth factor-beta 2 (glioblastoma-derived T cell suppressor factor); suppresses IL2 - dependent growth of T cells and is a member of a family of cytokines that transmits signals through transmembrane serine/threonine kinases.

Tumor necrosis factor, alpha-induced protein 2 (TNFAIP2, B94)

Secreted by vascular endothelium, expression is induced by tumor necrosis factor alpha, interleukin-1 beta, and lipopolysaccharide.

Protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform

Magnesium- or manganese-dependent alpha protein phosphatase 1A; regulates cell stress responses.

ATPase, Ca++ transporting, plasma membrane 3 (PMCA3)

Osteonidogen (nidogen 2)

ATP-binding cassette, sub-family A (ABC1), member 1

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the ABC1 subfamily. Members of the ABC1 subfamily comprise the only major ABC subfamily found exclusively in multicellular eukaryotes. With cholesterol as its substrate, this protein functions as a cholesteral efflux pump in the cellular lipid removal pathway. Mutations in this gene have been associated with Tangier's disease and familial high-density lipoprotein deficiency.

Bromodomain-containing 3 (BRD3)

This gene was identified based on its homology to the gene encoding the RING3 protein, a serine/threonine kinase. The gene localizes to 9q34, a region which contains several major histocompatibility complex (MHC) genes. The function of the encoded protein is not known.

Peroxisome proliferator activated receptor-gamma (PPAR gamma)

Peroxisome proliferator activated receptor-gamma (PPAR gamma) regulates adipocyte and macrophage gene expression and differentiation.

Tumor necrosis factor beta (Lymphotoxin alpha, LTA)

Lymphotoxin alpha, a member of the tumor necrosis factor family, is a cytokine produced by lymphocytes. LTA is highly inducible, secreted, and exists as homo-trimeric molecule. LTA forms heterotrimers with lymphotoxin-beta which anchors lymphotoxin-alpha to the cell surface. LTA mediates a large variety of inflammatory, immunostimulatory, and antiviral responses. LTA is also involved in the formation of secondary lymphoid organs during development and plays a role in apoptosis.

DEK oncogene

Site-specific DNA binding protein; involved in transcriptional regulation and signal transduction.

S-adenosyl methionine transferase

S-adenosyl methionine transferase catalyzes the formation of S-adenosylmethionine from methionine and ATP. Both the beta and alpha isoforms may be encoded by one gene. Methionine adenosyltransferase deficiency is known to be caused by recessive as well as dominant mutations, the latter identified in autosomal dominant persistant hypermethioninemia.

Coagulation factor III (thromboplastin, tissue factor)

This gene encodes coagulation factor III which is a cell surface glycoprotein. This factor enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII. The resulting complex provides a catalytic event that is responsible for initiation of the coagulation protease cascades by specific limited proteolysis. Unlike the other cofactors of these protease cascades, which circulate as nonfunctional precursors, this factor is a potent initiator that is fully functional when expressed on cell surfaces. There are 3 distinct domains of this factor: extracellular, transmembrane, and cytoplasmic. This protein is the only one in the coagulation pathway for which a congenital deficiency has not been described.

Membrane protein palmitoylated 2 (MPP2)

Palmitoylated membrane protein 2 is a member of a family of membrane-associated proteins termed MAGUKs (membrane-associated guanylate kinase homologs). MAGUKs interact with the cytoskeleton and regulate cell proliferation, signaling pathways, and intracellular junctions. Palmitoylated membrane protein 2 contains a conserved sequence, called the SH3 (src homology 3) motif, found in several other proteins that associate with the cytoskeleton and are suspected to play important roles in signal transduction.

Granulocyte-macrophage colony stimulating factor 2 receptor, beta chain (CSF2RB)

CSF2RB is a common beta chain of the high affinity receptor for IL-3, IL-5 and CSF. Defective CSF2RB has been reported to be associated with protein alveolar proteinosis

Coagulation factor II (Prothrombin, F2)

Coagulation factor II is proteolytically cleaved to form thrombin in the first step of the coagulation cascade which ultimately results in the stemming of blood loss. F2 also plays a role in maintaining vascular integrity during development and postnatal life. Mutations in F2 leads to various forms of thrombosis and dysprothrombinemia.

Lipoprotein lipase (LPL)

LPL encodes lipoprotein lipase, which is expressed in heart, muscle, and adipose tissue. LPL functions as a homodimer, and has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated lipoprotein uptake. Severe mutations that cause LPL deficiency result in type I hyperlipoproteinemia, while less extreme mutations in LPL are linked to many disorders of lipoprotein metabolism.

activin beta-C chain (Inhibin beta C)

This gene encodes the beta C chain of inhibin, a member of the TGF-beta super-family. This subunit forms heterodimers with beta A and beta B subunits. Inhibins and activins, also members of the TGF-beta superfamily, are hormones with opposing actions and are involved in hypothalamic, pituitary, and gonadal hormone secretion, as well as growth and differentiation of various cell types.

Methylenetetrahydrofolate dehydrogenase, NADP+ dependent (MTHFD)

This gene encodes a protein that possesses three distinct enzymatic activities, 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methenyltetrahydrofolate cyclo-hydrolase and 10-formyltetrahydrofolate synthetase. Each of these activities catalyzes one of three sequential reactions in the interconversion of 1-carbon derivatives of

tetrahydrofolate, which are substrates for methionine, thymidylate, and de novo purine syntheses. The trifunctional enzymatic activities are conferred by two major domains, an aminoterminal portion containing the dehydrogenase and cyclohydrolase activities and a larger synthetase domain.

PACAP gene for pituitary adenylate cyclase activating polypeptide

This gene encodes adenylate cyclase activating polypeptide 1. Mediated by adenylate cyclase activating polypeptide 1 receptors, this polypeptide stimulates adenylate cyclase and subsequently increases the cAMP level in target cells. Adenylate cyclase activating polypeptide 1 is not only a hypophysiotropic hormone, but also functions as a neurotransmitter and neuromodulator. In addition, it plays a role in paracrine and autocrine regulation of certain types of cells. This gene is composed of five exons. Exons 1 and 2 encode the 5' UTR and signal peptide, respectively; exon 4 encodes an adenylate cyclase activating polypeptide 1-related peptide; and exon 5 encodes the mature peptide and 3' UTR. This gene encodes three different mature peptides, including two isotypes: a shorter form and a longer form.

Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 8

This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and its expression is induced by phenobarbital. The enzyme is known to metabolize many xenobiotics, including the anticonvulsive drug mephenytoin, benzo(a)pyrene, 7-ethyoxycoumarin, and the anti-cancer drug taxol. Two transcript variants for this gene have been described; it is thought that the longer form does not encode an active cytochrome P450 since its protein product lacks the heme binding site. This gene is located within a cluster of cytochrome P450 genes on chromosome 10q24.

Leucocyte adhesion receptor, L-selectin (SELL)

SELL is a cell surface component that is a member of a family of adhesion/homing receptors which play important roles in leukocyte-endothelial cell interactions. The molecule is composed of multiple domains: one homologous to lectins, one to epidermal growth factor, and two to the consensus repeat units found in C3/C4 binding proteins.

Mitochondrial ATP synthase c subunit (P1 form)

Isoform 1 (P1) of subunit c, H+-translocating subunit of F0 ATP synthase; catalyzes the synthesis of ATP during oxidative phosphorylation.

Calmodulin

Calmodulin binds Ca2+, regulates proteins and enzymes in a Ca2+-dependent manner

WNT1 inducible signaling pathway protein 1 (WISP1) gene

WISP1 is a member of the connective tissue growth factor family

Ribophorin I

Ribophorin I; subunit of oligosaccharyltransferase that binds ribosomes.

Nonsyndromic hearing impairment protein (DFNA5)

Hearing impairment is a heterogeneous condition with over 40 loci described. The protein encoded by this gene is expressed in fetal cochlea, however, its function is not known. Nonsyndromic hearing impairment is associated with a mutation in this gene.

Cytochrome P450 2E1 (CYP2E1)

This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids.

This protein localizes to the endoplasmic reticulum and is induced by ethanol, the diabetic state, and starvation. The enzyme metabolizes both endogenous substrates, such as ethanol, acetone, and acetal, as well as exogenous substrates including benzene, carbon tetrachloride, ethylene glycol, and nitrosamines which are premutagens found in cigarette smoke. Due to its many substrates, this enzyme may be involved in such varied processes as gluconeogenesis, hepatic cirrhosis, diabetes, and cancer.

Vacuolar H+ ATPase E subunit (ATP6E)

Subunit E of the vacuolar H+-ATPase proton pump; regulates ATP binding and hydrolysis by the A and B subunits

Retinoid X receptor, alpha

Retinoid X receptors (RXRs) and retinoic acid receptors (RARs), are nuclear receptors that mediate the biological effects of retinoids by their involvement in retinoic acid-mediated gene activation. These receptors exert their action by binding, as homodimers or heterodimers, to specific sequences in the promoters of target genes and regulating their transcription. The protein encoded by this gene is a member of the steroid and thyroid hormone receptor superfamily of transcriptional regulators.

Peroxisome proliferative activated receptor, delta (PPARD)

Peroxisome proliferator-activated receptor delta is a member of the steroid hormone receptor superfamily

Ataxin (SCA1)

The autosomal dominant cerebellar ataxias (ADCA) are a heterogeneous group of neurodegenerative disorders characterized by progressive degeneration of the cerebellum, brain stem and spinal cord. Clinically, ADCA has been divided into three groups: ADCA types I-III. ADCAI is genetically heterogeneous, with five genetic loci, designated spinocerebellar ataxia (SCA) 1, 2, 3, 4 and 6, being assigned

to five different chromosomes. ADCAII, which always presents with retinal degeneration (SCA7), and ADCAIII often referred to as the `pure' cerebellar syndrome (SCA5), are most likely homogeneous disorders. Several SCA genes have been cloned and shown to contain CAG repeats in their coding regions. ADCA is caused by the expansion of the CAG repeats, producing an elongated polyglutamine tract in the corresponding protein. The expanded repeats are variable in size and unstable, usually increasing in size when transmitted to successive generations. The function of the ataxins is not known. The SCA1 locus has been mapped to chromosome 6, and it has been determined that the diseased allele contains 41-81 CAG repeats, compared to 6-39 in the normal allele. Several transcript variants of SCA1 in the 5' UTR have been described; however, their full-length nature is not known.

Adducin 1 (alpha)

Adducins are a family of cytoskeleton proteins encoded by three genes (alpha, beta, gamma). Alpha- and gamma-adducins are ubiquitously expressed. In contrast, beta-adducin is expressed at high levels in brain and hematopoietic tissues. Adducin is a heterodimeric protein that consists of related subunits, alpha and beta, which are produced from distinct genes but share a similar structure. Alpha- and beta-adducin include a protease-resistant N-terminal region and a protease-sensitive, hydrophilic C-terminal region. Adducin binds with high affinity to Ca(2+)/calmodulin and is a substrate for protein kinases A and C.

Zinc finger protein 202 (ZNF202)

Zinc-finger protein 202; may repress genes involved in lipid metabolism; contains zinc fingers

Mevalonate pyrophosphate decarboxylase

The enzyme mevalonate pyrophosphate decarboxylase catalyzes the conversion of mevalonate pyrophosphate into isopentenyl pyrophosphate in one of the early steps in

cholesterol biosynthesis. It decarboxylates and dehydrates its substrate while hydrolyzing ATP.

Integrin, beta 2 (ITGB2, lymphocyte function-associated antigen 1, LFA1)

The ITGB2 protein product is the integrin beta chain beta 2. Integrins are integral cell-surface proteins composed of an alpha chain and a beta chain. A given chain may combine with multiple partners resulting in different integrins. For example, beta 2 combines with the alpha L chain to form the integrin LFA-1, and combines with the alpha M chain to form the integrin Mac-1. Integrins are known to participate in cell adhesion as well as cell-surface mediated signalling.

Adrenergic beta-3- receptor (ADRB3)

The ADRB3 gene product, beta-3-adrenergic receptor, is located mainly in adipose tissue and is involved in the regulation of lipolysis and thermogenesis. Beta adrenergic receptors are involved in the epenephrine and norepinephrine-induced activation of adenylate cyclase through the action of G proteins.

Cytochrome P450, subfamily IVF, polypeptide 8

This gene, CYP4F8, encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and functions as a 19-hydroxylase of prostaglandins in seminal vesicles. This gene is part of a cluster of cytochrome P450 genes on chromosome 19. Another member of this family, CYP4F3, is approximately 18 kb away.

Coagulation factor XIII, A subunit

This gene encodes the coagulation factor XIII A subunit. Coagulation factor XIII is the last zymogen to become activated in the blood coagulation cascade. Plasma factor XIII is a heterotetramer composed of 2 A subunits and 2 B subunits. The A subunits have catalytic function, and the B subunits do not have enzymatic activity and may

serve as a plasma carrier molecules. Platelet factor XIII is comprised only of 2 A subunits, which are identical to those of plasma origin. Upon activation by the cleavage of the activation peptide by thrombin and in the presence of calcium ion, the plasma factor XIII dissociates its B subunits and yields the same active enzyme, factor XIIIa, as platelet factor XIII. This enzyme acts as a transglutaminase to catalyze the formation of gamma-glutamyl-epsilon-lysine crosslinking between fibrin molecules, thus stabilizing the fibrin clot. It also crosslinks alpha-2-plasmin inhibitor, or fibronectin, to the alpha chains of fibrin. Factor XIII deficiency is classified into two categories: type I deficiency, characterized by the lack of both the A and B subunits; and type II deficiency, characterized by the lack of the A subunit alone. These defects can result in a lifelong bleeding tendency, defective wound healing, and habitual abortion.

Beta adaptin

The beta adaptin subunit is part of the clathrin coat assembly complex which links clathrin to receptors in coated pits and vesicles. These vesicles are involved in endocytosis and Golgi processing. The beta 1 subunit is one of the assembly proteins which binds to clathrin and initiates coat formation.

Transforming growth factor-beta 1 (TGFB1)

Transforming growth factor-beta 1; regulates cell proliferation, differentiation, and apoptosis

Transforming growth factor-beta 3 (TGFB3)

Transforming growth factor-beta 3; transmits signals through transmembrane serine/-threonine kinases, may be required for normal development of the lung and palate; member of family of cytokines, very strongly similar to murine Tgfb3.

Flavin containing monooxygenase 1 (FMO1)

Metabolic N-oxidation of the diet-derived amino-trimethylamine (TMA) is mediated by flavin-containing monooxygenase and is subject to an inherited FMO3 poly-

morphism in man resulting in a small subpopulation with reduced TMA N-oxidation capacity resulting in fish odor syndrome Trimethylaminuria. Three forms of the enzyme, FMO1 found in fetal liver, FMO2 found in adult liver, and FMO3 are encoded by genes clustered in the 1q23-q25 region. Flavin-containing monooxygenases are NADPH-dependent flavoenzymes that catalyzes the oxidation of soft nucleophilic heteroatom centers in drugs, pesticides, and xenobiotics.

Coagulation factor IX (F9)

This gene encodes vitamin K-dependent coagulation factor IX that circulates in the blood as an inactive zymogen. This factor is converted to an active form by factor XIa, which excises the activation peptide and thus generates a heavy chain and a light chain held together by one or more disulfide bonds. The role of this activated factor IX in the blood coagulation cascade is to activate factor X to its active form through interactions with Ca+2 ions, membrane phospholipids, and factor VIII. Alterations of this gene, including point mutations, insertions and deletions, cause factor IX deficiency, which is a recessive X-linked disorder, also called hemophilia B or Christmas disease.

Apical protein, Xenopus laevis-like (APXL)

May be an amiloride-sensitive sodium channel; similar to Xenopus laevis Apical Protein

As SNPs are linked to other SNPs in neighboring genes on a chromosome (Linkage Disequilibrium) those SNPs could also be used as marker SNPs. In a recent publication it was shown that SNPs are linked over 100 kb in some cases more than 150 kb (Reich D.E. et al. Nature 411, 199-204, 2001). Hence SNPs lying in regions neighbouring CA SNPs could be linked to the latter and by this being a CVD marker. These associations could be performed as described for the gene polymorphism in methods.

Definitions

For convenience, the meaning of certain terms and phrases employed in the specification, examples, and appended claims are provided below. Moreover, the definitions by itself are intended to explain a further background of the invention.

The term "allele", which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for the gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide, or several nucleotides, and can include substitutions, deletions, and insertions of nucleotides. An allele of a gene can also be a form of a gene containing a mutation.

The term "allelic variant of a polymorphic region of a gene" refers to a region of a gene having one of several nucleotide sequences found in that region of the gene in other individuals.

"Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40% identity, though preferably less than 25% identity, with one of the sequences of the present invention.

The term "a homologue of a nucleic acid" refers to a nucleic acid having a nucleotide sequence having a certain degree of homology with the nucleotide sequence of the

nucleic acid or complement thereof. A homologue of a double stranded nucleic acid having SEQ ID NO. X is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with SEQ ID NO. X or with the complement thereof. Preferred homologous of nucleic acids are capable of hybridizing to the nucleic acid or complement thereof.

The term "interact" as used herein is meant to include detectable interactions between molecules, such as can be detected using, for example, a hybridization assay.

The term interact is also meant to include "binding" interactions between molecules. Interactions may be, for example, protein-protein, protein-nucleic acid, protein-small molecule or small molecule-nucleic acid in nature.

The term "intronic sequence" or "intronic nucleotide sequence" refers to the nucleotide sequence of an intron or portion thereof.

The term "isolated" as used herein with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term isolated as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized.

Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides.

The term "lipid" shall refer to a fat or fat-like substance that is insoluble in polar solvents such as water. The term "lipid" is intended to include true fats (e.g. esters of

fatty acids and glycerol); lipids (phospholipids, cerebrosides, waxes); sterols (cholesterol, ergosterol) and lipoproteins (e.g. HDL, LDL and VLDL).

The term "locus" refers to a specific position in a chromosome. For example, a locus of a gene refers to the chromosomal position of the gene.

The term "modulation" as used herein refers to both up-regulation, (i.e., activation or stimulation), for example by agonizing, and down-regulation (i.e. inhibition or suppression), for example by antagonizing of a bioactivity (e.g. expression of a gene).

The term "molecular structure" of a gene or a portion thereof refers to the structure as defined by the nucleotide content (including deletions, substitutions, additions of one or more nucleotides), the nucleotide sequence, the state of methylation, and/or any other modification of the gene or portion thereof.

The term "mutated gene" refers to an allelic form of a gene, which is capable of altering the phenotype of a subject having the mutated gene relative to a subject which does not have the mutated gene. If a subject must be homozygous for this mutation to have an altered phenotype, the mutation is said to be recessive. If one copy of the mutated gene is sufficient to alter the genotype of the subject, the mutation is said to be dominant. If a subject has one copy of the mutated gene and has a phenotype that is intermediate between that of a homozygous and that of a heterozygous (for that gene) subject, the mutation is said to be co-dominant.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxy-ribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, including peptide nucleic acids (PNA), morpholino oligonucleotides (J. Summerton and D. Weller, Antisense and Nucleic Acid Drug Development 7:187 (1997)) and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded

polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine, and deoxythymidine. For purposes of clarity, when referring herein to a nucleotide of a nucleic acid, which can be DNA or an RNA, the term "adenosine", "cytidine", "guanosine", and "thymidine" are used. It is understood that if the nucleic acid is RNA, a nucleotide having a uracil base is uridine.

The term "nucleotide sequence complementary to the nucleotide sequence set forth in SEQ ID NO. x" refers to the nucleotide sequence of the complementary strand of a nucleic acid strand having SEQ ID NO. x. The term "complementary strand" is used herein interchangeably with the term "complement". The complement of a nucleic acid strand can be the complement of a coding strand or the complement of a non-coding strand. When referring to double stranded nucleic acids, the complement of a nucleic acid having SEQ ID NO. x refers to the complementary strand of the strand having SEQ ID NO. x or to any nucleic acid having the nucleotide sequence of the complementary strand of SEQ ID NO. x. When referring to a single stranded nucleic acid having the nucleotide sequence SEQ ID NO. x, the complement of this nucleic acid is a nucleic acid having a nucleotide sequence which is complementary to that of SEQ ID NO. x. The nucleotide sequences and complementary sequences thereof are always given in the 5' to 3' direction. The term "complement" and "reverse complement" are used interchangeably herein.

The term "operably linked" is intended to mean that the promoter is associated with the nucleic acid in such a manner as to facilitate transcription of the nucleic acid.

The term "polymorphism" refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a "polymorphic region of a gene". A polymorphic region can be a single nucleotide, the identity of which differs in different alleles. A polymorphic region can also be several nucleotides long.

A "polymorphic gene" refers to a gene having at least one polymorphic region.

To describe a "polymorphic site" in a nucleotide sequence often there is used an "ambiguity code" that stands for the possible variations of nucleotides in one site. The list of ambiguity codes is summarized in the following table:

Ambiguity Codes (IUPAC Nomenclature)	
B	c/g/t
D	a/g/t
H	a/c/t
K	g/t
M	a/c
N	a/c/g/t
R	a/g
S	c/g
V	a/c/g
W	a/t
Y	c/t

So, for example, a "R" in a nucleotide sequence means that either an "a" or a "g" could be at that position.

The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product.

A "regulatory element", also termed herein "regulatory sequence is intended to include elements which are capable of modulating transcription from a basic promoter and include elements such as enhancers and silencers. The term "enhancer", also referred to herein as "enhancer element", is intended to include regulatory elements capable of increasing, stimulating, or enhancing transcription from a basic

promoter. The term "silencer", also referred to herein as "silencer element" is intended to include regulatory elements capable of decreasing, inhibiting, or repressing transcription from a basic promoter. Regulatory elements are typically present in 5' flanking regions of genes. However, regulatory elements have also been shown to be present in other regions of a gene, in particular in introns. Thus, it is possible that genes have regulatory elements located in introns, exons, coding regions, and 3' flanking sequences. Such regulatory elements are also intended to be encompassed by the present invention and can be identified by any of the assays that can be used to identify regulatory elements in 5' flanking regions of genes.

The term "regulatory element" further encompasses "tissue specific" regulatory elements, i.e., regulatory elements which effect expression of the selected DNA sequence preferentially in specific cells (e.g., cells of a specific tissue). gene expression occurs preferentially in a specific cell if expression in this cell type is significantly higher than expression in other cell types. The term "regulatory element" also encompasses non-tissue specific regulatory elements, i.e., regulatory elements which are active in most cell types. Furthermore, a regulatory element can be a constitutive regulatory element, i.e., a regulatory element which constitutively regulates transcription, as opposed to a regulatory element which is inducible, i.e., a regulatory element which is active primarily in response to a stimulus. A stimulus can be, e.g., a molecule, such as a hormone, cytokine, heavy metal, phorbol ester, cyclic AMP (cAMP), or retinoic acid.

Regulatory elements are typically bound by proteins, e.g., transcription factors. The term "transcription factor" is intended to include proteins or modified forms thereof, which interact preferentially with specific nucleic acid sequences, i.e., regulatory elements, and which in appropriate conditions stimulate or repress transcription. Some transcription factors are active when they are in the form of a monomer. Alternatively, other transcription factors are active in the form of a dimer consisting of two identical proteins or different proteins (heterodimer). Modified forms of transcription factors are intended to refer to transcription factors having a post-

translational modification, such as the attachment of a phosphate group. The activity of a transcription factor is frequently modulated by a post-translational modification. For example, certain transcription factors are active only if they are phosphorylated on specific residues. Alternatively, transcription factors can be active in the absence of phosphorylated residues and become inactivated by phosphorylation. A list of known transcription factors and their DNA binding site can be found, e.g., in public databases, e.g., TFMATRIX Transcription Factor Binding Site Profile database.

As used herein, the term "specifically hybridizes" or "specifically detects" refers to the ability of a nucleic acid molecule of the invention to hybridize to at least approximately 6, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130 or 140 consecutive nucleotides of either strand of a gene.

The term "wild-type allele" refers to an allele of a gene which, when present in two copies in a subject results in a wild-type phenotype. There can be several different wild-type alleles of a specific gene, since certain nucleotide changes in a gene may not affect the phenotype of a subject having two copies of the gene with the nucleotide changes.

"Candidate gene" as used herein includes genes that can be assigned to either normal cardiovascular function or to metabolic pathways that are related to onset and/or progression of cardiovascular diseases. As the development of cardiovascular diseases is not completely understood, the term "candidate gene" may also comprise genes with presently unknown function.

"CA SNP" (cardiovascular disease associated SNP) refers to a polymorphic site which shows a significant association with the risk to develop cardiovascular diseases.

"CA gene" (cardiovascular disease associated gene) refers to a genomic locus harbouring a CA SNP, irrespective of the actual function of this gene locus.

CA gene polypeptide refers to a polypeptide encoded at least in part by a CA gene

Methods for Assessing Cardiovascular Status

The present invention provides diagnostic methods for assessing cardiovascular status in a human individual. Cardiovascular status as used herein refers to the physiological status of an individual's cardiovascular system as reflected in one or more markers or indicators. Status markers include without limitation clinical measurements such as, e.g., blood pressure, electrocardiographic profile, and differentiated blood flow analysis as well as measurements of LDL- and HDL-Cholesterol levels, other lipids and other well established clinical parameters that are standard in the art. Status markers according to the invention include diagnoses of one or more cardiovascular syndromes, such as, e.g., hypertension, acute myocardial infarction, silent myocardial infarction, stroke, and atherosclerosis. It will be understood that a diagnosis of a cardiovascular syndrome made by a medical practitioner encompasses clinical measurements and medical judgement. Status markers according to the invention are assessed using conventional methods well known in the art. Also included in the evaluation of cardiovascular status are quantitative or qualitative changes in status markers with time, such as would be used, e.g., in the determination of an individual's response to a particular therapeutic regimen.

The methods are carried out by the steps of:

(i) determining the sequence of one or more polymorphic positions within one, sseveral or all of the genes listed in Examples or other genes mentioned in this file in the individual to establish a polymorphic pattern for the individual; and

(ii) comparing the polymorphic pattern established in (i) with the polymorphic patterns of humans exhibiting different markers of cardiovascular status. The polymorphic pattern of the individual is, preferably, highly similar and, most preferably, identical to the polymorphic pattern of individuals who exhibit particular status markers, cardiovascular syndromes, and/or particular patterns of response to therapeutic interventions. Polymorphic patterns may also include polymorphic positions in other genes which are shown, in combination with one or more polymorphic positions in the genes listed in the Examples, to correlate with the presence of particular status markers. In one embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who have been shown to respond positively or negatively to a particular therapeutic regimen. Therapeutic regimen as used herein refers to treatments aimed at the elimination or amelioration of symptoms and events associated cardiovascular disease. Such treatments include without limitation one or more of alteration in diet, lifestyle, and exercise regimen; invasive and noninvasive surgical techniques such as atherectomy, angioplasty, and coronary bypass surgery; and pharmaceutical interventions, such as administration of ACE inhibitors, angiotensin II receptor antagonists, diuretics, alpha-adrenoreceptor antagonists, cardiac glycosides, phosphodiesterase inhibitors, beta-adrenoreceptor antagonists, calcium channel blockers, HMG-CoA reductase inhibitors, imidazoline receptor blockers, endothelin receptor blockers, organic nitrites, and modulators of protein function of genes listed in the Examples. Interventions with pharmaceutical agents not yet known whose activity correlates with particular polymorphic patterns associated with cardiovascular disease are also encompassed. It is contemplated, for example, that patients who are candidates for a particular therapeutic regimen will be screened for polymorphic patterns that correlate with responsivity to that particular regimen.

In a preferred embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more markers of cardiovascular disease, such as, e.g., elevated LDL-Cholesterol levels, high blood pressure, abnormal electrocardiographic profile, myocardial infarction, stroke, or atherosclerosis.

In practicing the methods of the invention, an individual's polymorphic pattern can be established by obtaining DNA from the individual and determining the sequence at predetermined polymorphic positions in the genes such as those described in this file.

The DNA may be obtained from any cell source. Non-limiting examples of cell sources available in clinical practice include blood cells, buccal cells, cervicovaginal cells, epithelial cells from urine, fetal cells, or any cells present in tissue obtained by biopsy. Cells may also be obtained from body fluids, including without limitation blood, saliva, sweat, urine, cerebrospinal fluid, feces, and tissue exudates at the site of infection or inflammation. DNA is extracted from the cell source or body fluid using any of the numerous methods that are standard in the art. It will be understood that the particular method used to extract DNA will depend on the nature of the source.

Diagnostic and Prognostic Assays

The present invention provides methods for determining the molecular structure of at least one polymorphic region of a gene, specific allelic variants of said polymorphic region being associated with cardiovascular disease. In one embodiment, determining the molecular structure of a polymorphic region of a gene comprises determining the identity of the allelic variant. A polymorphic region of a gene, of which specific alleles are associated with cardiovascular disease can be located in an exon, an intron, at an intron/exon border, or in the promoter of the gene.

The invention provides methods for determining whether a subject has, or is at risk, of developing a cardiovascular disease. Such disorders can be associated with an aberrant gene activity, e.g., abnormal binding to a form of a lipid, or an aberrant gene protein level. An aberrant gene protein level can result from an aberrant transcription or post-transcriptional regulation. Thus, allelic differences in specific regions of a gene can result in differences of gene protein due to differences in regulation of expression. In particular, some of the identified polymorphisms in the human gene may be associated with differences in the level of transcription, RNA maturation, splicing, or translation of the gene or transcription product.

In preferred embodiments, the methods of the invention can be characterized as comprising detecting, in a sample of cells from the subject, the presence or absence of a specific allelic variant of one or more polymorphic regions of a gene. The allelic differences can be: (i) a difference in the identity of at least one nucleotide or (ii) a difference in the number of nucleotides, which difference can be a single nucleotide or several nucleotides.

A preferred detection method is allele specific hybridization using probes over-lapping the polymorphic site and having about 5, 10, 20, 25, or 30 nucleotides around the polymorphic region. Examples of probes for detecting specific allelic variants of the polymorphic region located in intron X are probes comprising a nucleotide sequence set forth in any of SEQ ID NO. X. In a preferred embodiment of the invention, several probes capable of hybridizing specifically to allelic variants are attached to a solid phase support, e.g., a "chip". Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. For example a chip can hold up to 250,000 oligonucleotides (GeneChip, Affymetrix). Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (1996) Human Mutation 7:244 and in Kozal et al. (1996) Nature Medicine 2:753. In one embodiment, a chip comprises all the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is

detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment. For example, the identity of the allelic variant of the nucleotide polymorphism of nucleotide T or G at position 140 of Seq ID 1 (baySNP10948) and that of other possible polymorphic regions can be determined in a single hybridization experiment.

In other detection methods, it is necessary to first amplify at least a portion of a gene prior to identifying the allelic variant. Amplification can be performed, e.g., by PCR and/or LCR, according to methods known in the art. In one embodiment, genomic DNA of a cell is exposed to two PCR primers and amplification for a number of cycles sufficient to produce the required amount of amplified DNA. In preferred embodiments, the primers are located between 40 and 350 base pairs apart. Preferred primers for amplifying gene fragments of genes of this file are listed in Table 2 in the Examples.

Alternative amplification methods include: self sustained sequence replication (Guatelli, J. C. et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:1874-1878), transcriptional amplification system (Kwoh, D. Y. et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:1173-1177), Q-Beta Replicase (Lizardi, P. M. et al., 1988, Bio/Technology 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In one embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence at least a portion of a gene and detect allelic variants, e.g., mutations, by comparing the sequence of the sample sequence with the corresponding wild-type (control) sequence. Exemplary sequencing reactions include those based on techniques developed by Maxam and Gilbert (Proc. Natl Acad Sci USA (1977) 74:560) or Sanger (Sanger et al (1977) Proc. Nat. Acad. Sci 74:5463). It is also contemplated that any of a variety of automated sequencing procedures may

be utilized when performing the subject assays (Biotechniques (1995) 19:448), including sequencing by mass spectrometry (see, for example, U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/16101, entitled DNA Sequencing by Mass Spectrometry by H. Koster; U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/21822 entitled "DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation" by H. Koster), and U.S. Pat. No. 5,605,798 and International Patent Application No. PCT/US96/03651 entitled DNA Diagnostics Based on Mass Spectrometry by H. Koster; Cohen et al. (1996) Adv Chromatogr 36:127-162; and Griffin et al. (1993) Appl Biochem Biotechnol 38:147-159). It will be evident to one skilled in the art that, for certain embodiments, the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, e.g., where only one nucleotide is detected, can be carried out.

Yet other sequencing methods are disclosed, e.g., in U.S. Pat. No. 5,580,732 entitled "Method of DNA sequencing employing a mixed DNA-polymer chain probe" and U.S. Pat. No. 5,571,676 entitled "Method for mismatch-directed in vitro DNA sequencing".

In some cases, the presence of a specific allele of a gene in DNA from a subject can be shown by restriction enzyme analysis. For example, a specific nucleotide polymorphism can result in a nucleotide sequence comprising a restriction site which is absent from the nucleotide sequence of another allelic variant.

In other embodiments, alterations in electrophoretic mobility is used to identify the type of gene allelic variant. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) Proc Natl. Acad. Sci USA 86:2766, see also Cotton (1993) Mutat Res 285:125-144; and Hayashi (1992) Genet Anal Tech Appl 9:73-79). Single-stranded DNA fragments of sample and control nucleic acids are denatured and allowed to renature. The secondary structure of single-stranded

nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In another preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) Trends Genet 7:5).

In yet another embodiment, the identity of an allelic variant of a polymorphic region is obtained by analyzing the movement of a nucleic acid comprising the polymorphic region in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al (1985) Nature 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) Biophys Chem 265:1275).

Examples of techniques for detecting differences of at least one nucleotide between 2 nucleic acids include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes may be prepared in which the known polymorphic nucleotide is placed centrally (allele-specific probes) and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) Nature 324:163); Saiki et al (1989) Proc. Natl Acad. Sci USA 86:6230; and Wallace et al. (1979) Nucl. Acids Res. 6:3543). Such allele specific oligonucleotide hybridization techniques may be used for the simultaneous detection of several nucleotide changes in different polymorphic regions of gene. For example, oligonucleotides having nucleotide sequences of specific allelic variants are attached to a hybridizing

membrane and this membrane is then hybridized with labeled sample nucleic acid. Analysis of the hybridization signal will then reveal the identity of the nucleotides of the sample nucleic acid.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used. Oligonucleotides used as primers for specific amplification may carry the allelic variant of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al (1989) Nucleic Acids Res. 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) Tibtech 11:238; Newton et al. (1989) Nucl. Acids Res. 17:2503). This technique is also termed "PROBE" for Probe Oligo Base Extension. In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al (1992) Mol. Cell Probes 6:1).

In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, e.g., in U.S. Pat. No. 4,998,617 and in Landegren, U. et al., Science 241:1077-1080 (1988). The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. One of the oligonucleotides is linked to a separation marker, e.g,. biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be recovered using avidin, or another biotin ligand. Nickerson, D. A. et al. have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D. A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 87:8923-8927 (1990). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

Several techniques based on this OLA method have been developed and can be used to detect specific allelic variants of a polymorphic region of a gene. For example,

U.S. Pat. No. 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe et al. ((1996)Nucleic Acids Res 24: 3728), OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten, i.e. digoxigenin and fluorescein, each LA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

The invention further provides methods for detecting single nucleotide polymorphisms in a gene. Because single nucleotide polymorphisms constitute sites of variation flanked by regions of invariant sequence, their analysis requires no more than the determination of the identity of the single nucleotide present at the site of variation and it is unnecessary to determine a complete gene sequence for each patient. Several methods have been developed to facilitate the analysis of such single nucleotide polymorphisms.

In one embodiment, the single base polymorphism can be detected by using a specialized exonuclease-resistant nucleotide, as disclosed, e.g., in Mundy, C. R. (U.S. Pat. No. 4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was complementary to that of the nucleotide

derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

In another embodiment of the invention, a solution-based method is used for determining the identity of the nucleotide of a polymorphic site. Cohen, D. et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Pat. No. 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

An alternative method, known as Genetic Bit Analysis or GBA TM is described by Goelet, P. et al. (PCT Appln. No. 92/15712). The method of Goelet, P. et al. uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of the target molecule being evaluated. In contrast to the method of Cohen et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. et al. is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al., Nucl. Acids. Res. 17:7779-7784 (1989); Sokolov, B. P., Nucl. Acids Res. 18:3671 (1990); Syvanen, A. -C., et al., Genomics 8:684-692 (1990), Kuppuswamy, M. N. et al., Proc. Natl. Acad. Sci. (U.S.A.) 88:1143-1147 (1991); Prezant, T. R. et al., Hum. Mutat. 1:159-164 (1992); Ugozzoli, L. et al., GATA 9:107-112 (1992); Nyren, P. et al., Anal. Biochem. 208:171-175 (1993)). These methods differ from GBA TM in that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional

to the number of deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run (Syvanen, A.-C., et al., Amer. J. Hum. Genet. 52:46-59 (1993)).

For determining the identity of the allelic variant of a polymorphic region located in the coding region of a gene, yet other methods than those described above can be used. For example, identification of an allelic variant which encodes a mutated gene protein can be performed by using an antibody specifically recognizing the mutant protein in, e.g., immunohistochemistry or immunoprecipitation. Antibodies to wild-type gene protein are described, e.g., in Acton et al. (1999) Science 271:518 (anti-mouse gene antibody cross-reactive with human gene). Other antibodies to wild-type gene or mutated forms of gene proteins can be prepared according to methods known in the art. Alternatively, one can also measure an activity of an gene protein, such as binding to a lipid or lipoprotein. Binding assays are known in the art and involve, e.g., obtaining cells from a subject, and performing binding experiments with a labeled lipid, to determine whether binding to the mutated form of the receptor differs from binding to the wild-type of the receptor.

If a polymorphic region is located in an exon, either in a coding or non-coding region of the gene, the identity of the allelic variant can be determined by determining the molecular structure of the mRNA, pre-mRNA, or cDNA. The molecular structure can be determined using any of the above described methods for determining the molecular structure of the genomic DNA, e.g., sequencing and SSCP.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits, such as those described above, comprising at least one probe or primer nucleic acid described herein, which may be conveniently used, e.g., to determine whether a subject has or is at risk of developing a disease associated with a specific gene allelic variant.

Sample nucleic acid for using in the above-described diagnostic and prognostic methods can be obtained from any cell type or tissue of a subject. For example, a subject's bodily fluid (e.g. blood) can be obtained by known techniques (e.g. venipuncture) or from human tissues like heart (biopsies, transplanted organs). Alternatively, nucleic acid tests can be performed on dry samples (e.g. hair or skin). Fetal nucleic acid samples for prenatal diagnostics can be obtained from maternal blood as described in International Patent Application No.WO91/07660 to Bianchi. Alternatively, amniocytes or chorionic villi may be obtained for performing prenatal testing.

Diagnostic procedures may also be performed in situ directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents may be used as probes and/or primers for such in situ procedures (see, for example, Nuovo, G. J., 1992, PCR in situ hybridization: protocols and applications, Raven Press, New York).

In addition to methods which focus primarily on the detection of one nucleic acid sequence, profiles may also be assessed in such detection schemes. Fingerprint profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

In practicing the present invention, the distribution of polymorphic patterns in a large number of individuals exhibiting particular markers of cardiovascular status is determined by any of the methods described above, and compared with the distribution of polymorphic patterns in patients that have been matched for age, ethnic origin, and/or any other statistically or medically relevant parameters, who exhibit quantitatively or qualitatively different status markers. Correlations are achieved using any method known in the art, including nominal logistic regression, chi square tests or standard least squares regression analysis. In this manner, it is possible to establish statistically significant correlations between particular polymorphic patterns and particular cardiovascular statuses (given in p values). It is

further possible to establish statistically significant correlations between particular polymorphic patterns and changes in cardiovascular status such as, would result, e.g., from particular treatment regimens. In this manner, it is possible to correlate polymorphic patterns with responsivity to particular treatments.

Isolated Polymorphic Nucleic Acids, Probes, and Vectors

The present invention provides isolated nucleic acids comprising the polymorphic positions described herein for human genes; vectors comprising the nucleic acids; and transformed host cells comprising the vectors. The invention also provides probes which are useful for detecting these polymorphisms.

In practicing the present invention, many conventional techniques in molecular biology, microbiology, and recombinant DNA, are used. Such techniques are well known and are explained fully in, for example, Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; DNA Cloning: A Practical Approach, Volumes I and II, 1985 (D. N. Glover ed.); Oligonucleotide Synthesis, 1984, (M. L.Gait ed.); Nucleic Acid Hybridization, 1985, (Hames and Higgins); Ausubel et al., Current Protocols in Molecular Biology, 1997, (John Wiley and Sons); and Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively).

Insertion of nucleic acids (typically DNAs) comprising the sequences in a functional surrounding like full length cDNA of the present invention into a vector is easily accomplished when the termini of both the DNAs and the vector comprise compatible restriction sites. If this cannot be done, it may be necessary to modify the termini of the DNAs and/or vector by digesting back single-stranded DNA overhangs generated by restriction endonuclease cleavage to produce blunt ends, or to achieve the same result by filling in the single-stranded termini with an appropriate DNA polymerase.

Alternatively, any site desired may be produced, e.g., by ligating nucleotide sequences (linkers) onto the termini. Such linkers may comprise specific oligonucleotide sequences that define desired restriction sites. Restriction sites can also be generated by the use of the polymerase chain reaction (PCR). See, e.g., Saiki et al., 1988, Science 239:48. The cleaved vector and the DNA fragments may also be modified if required by homopolymeric tailing.

The nucleic acids may be isolated directly from cells or may be chemically synthesized using known methods. Alternatively, the polymerase chain reaction (PCR) method can be used to produce the nucleic acids of the invention, using either chemically synthesized strands or genomic material as templates. Primers used for PCR can be synthesized using the sequence information provided herein and can further be designed to introduce appropriate new restriction sites, if desirable, to facilitate incorporation into a given vector for recombinant expression.

The nucleic acids of the present invention may be flanked by native gene sequences, or may be associated with heterologous sequences, including promoters, enhancers, response elements, signal sequences, polyadenylation sequences, introns, 5'- and 3'-noncoding regions, and the like. The nucleic acids may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoroamidates, carbamates, morpholines etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.). Nucleic acids may contain one or more additional covalently linked moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (e.g., acridine, psoralen, etc.), chelators (e.g., metals, radioactive metals, iron, oxidative metals, etc.), and alkylators. PNAs are also included. The nucleic acid may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Further-

more, the nucleic acid sequences of the present invention may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

The invention also provides nucleic acid vectors comprising the gene sequences or derivatives or fragments thereof of genes described in the Examles. A large number of vectors, including plasmid and fungal vectors, have been described for replication and/or expression in a variety of eukaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple cloning or protein expression. Non-limiting examples of suitable vectors include without limitation pUC plasmids, pET plasmids (Novagen, Inc., Madison, Wis.), or pRSET or pREP (Invitrogen, San Diego, Calif.), and many appropriate host cells, using methods disclosed or cited herein or otherwise known to those skilled in the relevant art. The particular choice of vector/host is not critical to the practice of the invention.

Suitable host cells may be transformed/transfected/infected as appropriate by any suitable method including electroporation, $CaCl_2$ mediated DNA uptake, fungal or viral infection, microinjection, microprojectile, or other established methods. Appropriate host cells included bacteria, archebacteria, fungi, especially yeast, and plant and animal cells, especially mammalian cells. A large number of transcription initiation and termination regulatory regions have been isolated and shown to be effective in the transcription and translation of heterologous proteins in the various hosts. Examples of these regions, methods of isolation, manner of manipulation, etc. are known in the art. Under appropriate expression conditions, host cells can be used as a source of recombinantly produced peptides and polypeptides encoded by genes of the Examples. Nucleic acids encoding peptides or polypeptides from gene sequences of the Examples may also be introduced into cells by recombination events. For example, such a sequence can be introduced into a cell and thereby effect homologous recombination at the site of an endogenous gene or a sequence with substantial identity to the gene. Other recombination-based methods such as non-

homologous recombinations or deletion of endogenous genes by homologous recombination may also be used.

In case of proteins that form heterodimers or other multimers, both or all subunits have to be expressed in one system or cell.

The nucleic acids of the present invention find use as probes for the detection of genetic polymorphisms and as templates for the recombinant production of normal or variant peptides or polypeptides encoded by genes listed in the Examples.

Probes in accordance with the present invention comprise without limitation isolated nucleic acids of about 10-100 bp, preferably 15-75 bp and most preferably 17-25 bp in length, which hybridize at high stringency to one or more of the polymorphic sequences disclosed herein or to a sequence immediately adjacent to a polymorphic position. Furthermore, in some embodiments a full-length gene sequence may be used as a probe. In one series of embodiments, the probes span the polymorphic positions in genes disclosed herein. In another series of embodiments, the probes correspond to sequences immediately adjacent to the polymorphic positions.

Polymorphic Polypeptides and Polymorphism-Specific Antibodies

The present invention encompasses isolated peptides and polypeptides encoded by genes listed in the Examples comprising polymorphic positions disclosed herein. In one preferred embodiment, the peptides and polypeptides are useful screening targets to identify cardiovascular drugs. In another preferred embodiments, the peptides and polypeptides are capable of eliciting antibodies in a suitable host animal that react specifically with a polypeptide comprising the polymorphic position and distinguish it from other polypeptides having a different sequence at that position.

Polypeptides according to the invention are preferably at least five or more residues in length, preferably at least fifteen residues. Methods for obtaining these poly-

peptides are described below. Many conventional techniques in protein biochemistry and immunology are used. Such techniques are well known and are explained in Immunochemical Methods in Cell and Molecular Biology, 1987 (Mayer and Waler, eds; Academic Press, London); Scopes, 1987, Protein Purification: Principles and Practice, Second Edition (Springer-Verlag, N.Y.) and Handbook of Experimental Immunology, 1986, Volumes I-IV (Weir and Blackwell eds.).

Nucleic acids comprising protein-coding sequences can be used to direct the ITT recombinant expression of polypeptides encoded by genes disclosed herein in intact cells or in cell-free translation systems. The known genetic code, tailored if desired for more efficient expression in a given host organism, can be used to synthesize oligonucleotides encoding the desired amino acid sequences. The polypeptides may be isolated from human cells, or from heterologous organisms or cells (including, but not limited to, bacteria, fungi, insect, plant, and mammalian cells) into which an appropriate protein-coding sequence has been introduced and expressed. Furthermore, the polypeptides may be part of recombinant fusion proteins.

Peptides and polypeptides may be chemically synthesized by commercially available automated procedures, including, without limitation, exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. The polypeptides are preferably prepared by solid phase peptide synthesis as described by Merrifield, 1963, J. Am. Chem. Soc. 85:2149.

Methods for polypeptide purification are well-known in the art, including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and counter-current distribution. For some purposes, it is preferable to produce the polypeptide in a recombinant system in which the protein contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence. The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced

against peptides encoded by genes disclosed herein, can be used as purification reagents. Other purification methods are possible.

The present invention also encompasses derivatives and homologues of the polypeptides. For some purposes, nucleic acid sequences encoding the peptides may be altered by substitutions, additions, or deletions that provide for functionally equivalent molecules, i.e., function-conservative variants. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of similar properties, such as, for example, positively charged amino acids (arginine, lysine, and histidine); negatively charged amino acids (aspartate and glutamate); polar neutral amino acids; and non-polar amino acids.

The isolated polypeptides may be modified by, for example, phosphorylation, sulfation, acylation, or other protein modifications. They may also be modified with a label capable of providing a detectable signal, either directly or indirectly, including, but not limited to, radioisotopes and fluorescent compounds.

The present invention also encompasses antibodies that specifically recognize the polymorphic positions of the invention and distinguish a peptide or polypeptide containing a particular polymorphism from one that contains a different sequence at that position. Such polymorphic position-specific antibodies according to the present invention include polyclonal and monoclonal antibodies. The antibodies may be elicited in an animal host by immunization with peptides encoded by genes disclosed herein or may be formed by in vitro immunization of immune cells. The immunogenic components used to elicit the antibodies may be isolated from human cells or produced in recombinant systems. The antibodies may also be produced in recombinant systems programmed with appropriate antibody-encoding DNA. Alternatively, the antibodies may be constructed by biochemical reconstitution of purified heavy and light chains. The antibodies include hybrid antibodies (i.e., containing two sets of heavy chain/light chain combinations, each of which recognizes a different antigen), chimeric antibodies (i.e., in which either the heavy

chains, light chains, or both, are fusion proteins), and univalent antibodies (i.e., comprised of a heavy chain/light chain complex bound to the constant region of a second heavy chain). Also included are Fab fragments, including Fab' and F(ab).sub.2 fragments of antibodies. Methods for the production of all of the above types of antibodies and derivatives are well-known in the art and are discussed in more detail below. For example, techniques for producing and processing polyclonal antisera are disclosed in Mayer and Walker, 1987, Immunochemical Methods in Cell and Molecular Biology, (Academic Press, London). The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibody-producing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g., Schreier et al., 1980, Hybridoma Techniques; U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of monoclonal antibodies produced against peptides encoded by genes disclosed herein can be screened for various properties; i.e. for isotype, epitope affinity, etc.

The antibodies of this invention can be purified by standard methods, including but not limited to preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. Purification methods for antibodies are disclosed, e.g., in The Art of Antibody Purification, 1989, Amicon Division, W. R. Grace & Co. General protein purification methods are described in Protein Purification: Principles and Practice, R. K. Scopes, Ed., 1987, Springer-Verlag, New York, N.Y.

Methods for determining the immunogenic capability of the disclosed sequences and the characteristics of the resulting sequence-specific antibodies and immune cells are well-known in the art. For example, antibodies elicited in response to a peptide comprising a particular polymorphic sequence can be tested for their ability to specifically recognize that polymorphic sequence, i.e., to bind differentially to a peptide or polypeptide comprising the polymorphic sequence and thus distinguish it

from a similar peptide or polypeptide containing a different sequence at the same position.

Kits

As set forth herein, the invention provides diagnostic methods, e.g., for determining the identity of the allelic variants of polymorphic regions present in the gene loci of genes disclosed herein, wherein specific allelic variants of the polymorphic region are associated with cardiovascular diseases. In a preferred embodiment, the diagnostic kit can be used to determine whether a subject is at risk of developing a cardiovascular disease. This information could then be used, e.g., to optimize treatment of such individuals.

In preferred embodiments, the kit comprises a probe or primer which is capable of hybridizing to a gene and thereby identifying whether the gene contains an allelic variant of a polymorphic region which is associated with a risk for cardiovascular disease. The kit preferably further comprises instructions for use in diagnosing a subject as having, or having a predisposition, towards developing a cardiovascular disease. The probe or primers of the kit can be any of the probes or primers described in this file.

Preferred kits for amplifying a region of a gene comprising a polymorphic region of interest comprise one, two or more primers.

Antibody-based diagnostic methods and kits

The invention also provides antibody-based methods for detecting polymorphic patterns in a biological sample. The methods comprise the steps of: (i) contacting a sample with one or more antibody preparations, wherein each of the antibody preparations is specific for a particular polymorphic form of the proteins encoded by genes disclosed herein, under conditions in which a stable antigen-antibody complex

can form between the antibody and antigenic components in the sample; and (ii) detecting any antigen-antibody complex formed in step (i) using any suitable means known in the art, wherein the detection of a complex indicates the presence of the particular polymorphic form in the sample.

Typically, immunoassays use either a labelled antibody or a labelled antigenic component (e.g., that competes with the antigen in the sample for binding to the antibody). Suitable labels include without limitation enzyme-based, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays that amplify the signals from the probe are also known, such as, for example, those that utilize biotin and avidin, and enzyme-labelled immunoassays, such as ELISA assays.

The present invention also provides kits suitable for antibody-based diagnostic applications. Diagnostic kits typically include one or more of the following components:

(i) Polymorphism-specific antibodies. The antibodies may be pre-labelled; alternatively, the antibody may be unlabelled and the ingredients for labelling may be included in the kit in separate containers, or a secondary, labelled antibody is provided; and

(ii) Reaction components: The kit may also contain other suitably packaged reagents and materials needed for the particular immunoassay protocol, including solid-phase matrices, if applicable, and standards.

The kits referred to above may include instructions for conducting the test. Furthermore, in preferred embodiments, the diagnostic kits are adaptable to high-throughput and/or automated operation.

Drug Targets and Screening Methods

According to the present invention, nucleotide sequences derived from genes disclosed herein and peptide sequences encoded by genes disclosed herein, particularly those that contain one or more polymorphic sequences, comprise useful targets to identify cardiovascular drugs, i.e., compounds that are effective in treating one or more clinical symptoms of cardiovascular disease. Furthermore, especially when a protein is a multimeric protein that are build of two or more subunits, is a combination of different polymorphic subunits very useful.

Drug targets include without limitation (i) isolated nucleic acids derived from the genes disclosed herein, and (ii) isolated peptides and polypeptides encoded by genes disclosed herein, each of which comprises one or more polymorphic positions.

In vitro screening methods

In one series of embodiments, an isolated nucleic acid comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The methods comprise:

(i) providing a first nucleic acid containing a particular sequence at a polymorphic position and a second nucleic acid whose sequence is identical to that of the first nucleic acid except for a different sequence at the same polymorphic position;

(ii) contacting the nucleic acids with a multiplicity of test compounds under conditions appropriate for binding; and

(iii) identifying those compounds that bind selectively to either the first or second nucleic acid sequence.

Selective binding as used herein refers to any measurable difference in any parameter of binding, such as, e.g., binding affinity, binding capacity, etc.

In another series of embodiments, an isolated peptide or polypeptide comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The screening methods involve:

(i) providing a first peptide or polypeptide containing a particular sequence at a polymorphic position and a second peptide or polypeptide whose sequence is identical to the first peptide or polypeptide except for a different sequence at the same polymorphic position;

(ii) contacting the polypeptides with a multiplicity of test compounds under conditions appropriate for binding; and

(iii) identifying those compounds that bind selectively to one of the nucleic acid sequences.

In preferred embodiments, high-throughput screening protocols are used to survey a large number of test compounds for their ability to bind the genes or peptides disclosed above in a sequence-specific manner.

Test compounds are screened from large libraries of synthetic or natural compounds. Numerous means are currently used for random and directed synthesis of saccharide, peptide, and nucleic acid based compounds. Synthetic compound libraries are commercially available from Maybridge Chemical Co. (Trevillet, Cornwall, UK), Comgenex (Princeton, N.J.), Brandon Associates (Merrimack, N.H.), and Microsource (New Milford, Conn.). A rare chemical library is available from Aldrich (Milwaukee, Wis.). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available from e.g. Pan Laboratories (Bothell, Wash.) or MycoSearch (N.C.), or are readily producible. Additionally,

natural and synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means.

In vivo screening methods

Intact cells or whole animals expressing polymorphic variants of genes disclosed herein can be used in screening methods to identify candidate cardiovascular drugs.

In one series of embodiments, a permanent cell line is established from an individual exhibiting a particular polymorphic pattern. Alternatively, cells (including without limitation mammalian, insect, yeast, or bacterial cells) are programmed to express a gene comprising one or more polymorphic sequences by introduction of appropriate DNA. Identification of candidate compounds can be achieved using any suitable assay, including without limitation (i) assays that measure selective binding of test compounds to particular polymorphic variants of proteins encoded by genes disclosed herein; (ii) assays that measure the ability of a test compound to modify (i.e., inhibit or enhance) a measurable activity or function of proteins encoded by genes disclosed herein; and (iii) assays that measure the ability of a compound to modify (i.e., inhibit or enhance) the transcriptional activity of sequences derived from the promoter (i.e., regulatory) regions of genes disclosed herein.

In another series of embodiments, transgenic animals are created in which (i) one or more human genes disclosed herein, having different sequences at particular polymorphic positions are stably inserted into the genome of the transgenic animal; and/or (ii) the endogenous genes disclosed herein are inactivated and replaced with human genes disclosed herein, having different sequences at particular polymorphic positions. See, e.g., Coffman, Semin. Nephrol. 17:404, 1997; Esther et al., Lab. Invest. 74:953, 1996; Murakami et al., Blood Press. Suppl. 2:36, 1996. Such animals can be treated with candidate compounds and monitored for one or more clinical markers of cardiovascular status.

The following are intended as non-limiting examples of the invention.

Material and Methods

Genotyping of patient DNA with the Pyrosequencing™ Method as described in the patent application WO 9813523:

First a PCR is set up to amplify the flanking regions around a SNP. Therefor 2 ng of genomic DNA (patient sample) are mixed with a primerset (20 – 40 pmol) producing a 75 to 320 bp PCR fragment with 0,3 to 1 U Qiagens Hot Star Taq Polymerase™ in a total volume of 20 µL. One primer is biotinylated depending on the direction of the sequencing primer. To force the biotinylated primer to be incorporated it is used 0,8 fold.

For primer design, programms like Oligo 6™ (Molecular Biology Insights) or Primer Select™ (DNAStar) are used. PCR setup is performed by a BioRobot 3000 ™ from Qiagen. PCR takes place in T1 or Tgradient Thermocyclers ™ from Biometra.

The whole PCR reaction is transferred into a PSQ plate ™ (Pyrosequencing) and prepared using the Sample Prep Tool ™ and SNP Reagent Kit ™ from Pyrosequencing according to their instructions.

Preparation of template for Pyrosequencing™:

Sample preparation using PSQ 96 Sample Prep Tool

1. Mount the PSQ 96 Sample Prep Tool Cover onto the PSQ 96 Sample Prep Tool as follows: Place the cover on the desk, retract the 4 attachment rods by separating the handle from the magnetic rod holder, fit the magnetic rods into the holes of the cover plate, push the handle downward until a click is heard. The PSQ 96 Sample Prep Tool is now ready for use.

2. To transfer beads from one plate to another, place the covered tool into the PSQ 96 Plate containing the samples and lower the magnetic rods by separating the handle from the magnetic rod holder. Move the tool up and down a few times then wait for 30-60 seconds. Transfer the beads into a new PSQ 96 plate containing the solution of choice.

3. Release the beads by lifting the magnetic rod holder, bringing it together with the handle. Move the tool up and down a few times to make sure that the beads are released.

All steps are performed at room temperature unless otherwise stated.

Immobilization of PCR product:

Biotinylated PCR products are immobilized on streptavidin-coated Dynabeads™ M-280 Streptavidin. Parallel immobilization of several samples are performed in the PSQ 96 Plate.

1. Mix PCR product, 20 µl of a well optimized PCR, with 25 µl 2X BW-buffer II. Add 60-150 µg Dynabeads. It is also possible to add a mix of Dynabeads and 2X BW-buffer II to the PCR product yielding a final BW-buffer II concentration of approximately 1x.

2. Incubate at 65°C for 15 min agitation constantly to keep the beads dispersed. For optimal immobilization of fragments longer than 300 bp use 30 min incubation time.

Strand separation

4. For strand separation, use the PSQ 96 Sample Prep Tool to transfer the beads with the immobilized sample to a PSQ 96 Plate containing 50 µl 0.50 M NaOH per well. Release the beads.

5. After approximately 1 min, transfer the beads with the immobilized strand to a PSQ 96 Plate containing 99 µl 1x Annealing buffer per well and mix thoroughly.

6. Transfer the beads to a PSQ 96 Plate containing 45 µl of a mix of 1x Annealing buffer and 3-15 pmoles sequencing primer per well.

7. Heat at 80°C for 2 minutes in the PSQ 96 Sample Prep Thermoplate and move to room temperature.

8. After reaching room temperature, continue with the sequencing reaction.

Sequencing reaction

1. Choose the method to be used ("SNP Method") and enter relevant information in the PSQ 96 Instrument Control software.

2. Place the cartridge and PSQ 96 Plate in the PSQ 96 Instrument.

3. Start the run.

Genotyping with a service contractor

Qiagen Genomics, formerly Rapigene, is a service contractor for genotyping SNPs in patient samples. Their method is based on a primer extension method where two complementary primers are designed for each genotype that are labeled with different tags. Depending on the genotype only one primer will be elongated together with a certain tag. This tag can be detected with mass spectrometry and is a measure for the respective genotype. The method is described in the following patent: "Detection and

identification of nucleic acid molecules - using tags which may be detected by non-fluorescent spectrometry or potentiometry" (WO 9727325).

Examples

Table 1: Definition of "good" and "bad" serum lipid levels

	"Good"	"Bad"
LDL-Cholesterol [mg/dL]	125 -150	170 - 200
Cholesterol [mg/dL]	190 - 240	265 - 315
HDL-Cholesterol [mg/dL]	60 -105	30 - 55
Triglycerides [mg/dL]	45 - 115	170 – 450
Number of Patients	146	132

An informed consent was signed by the patients and control people. Blood was taken by a physician according to medical standard procedures.

Samples were collected anonymous and labeled with a patient number.

DNA was extracted using kits from Qiagen.

Table 2a: Oligonucleotide primers used for genotyping using mass spectrometry

The baySNP number refers to an internal numbering of the CA SNPs. Primer sequences are listed for preamplification of the genomic fragments (primers EF and ER) and for subsequent allele specific PCR of the SNP.

Primer Name	Primer Sequence	baySNP
11558_A251C_EF	AAAGAAAGTCAGGATAAAAA	11558
11558_A251C_ER	TTTGGTGAGAGTAAGGAG	
11558_A251C_AR	gggacggtcggtagatTTAGACAGGGGTCTTATT	
11558_A251C_CR	gctggctcggtcaagaTTAGACAGGGGTCTTATG	
1657_C236T_CF_	gggacggtcggtagatGCTCTGCTTCTTGGTGCC	1657
1657_C236T_EF_	CAGAAATACTCTGCTGTCTG	
1657_C236T_ER_U	GACGATGCCTTCAGCACAGTGAAAACCATCAAGG AA	
1657_C236T_TF_	gctggctcggtcaagaGCTCTGCTTCTTGGTGCT	
11652_C251T_EF	CACGAGGTCAGGAAGATG	11652
11652_C251T_ER	GACGGTGTCATAGGAAGAGA	
11652_C251T_CF	gggacggtcggtagatGAGATGAGGGCTCCTGGC	
11652_C251T_TF	gctggctcggtcaagaGAGATGAGGGCTCCTGGT	
6734_A251C_EF	AAGGAATGTTGTAGAGGGA	6734
6734_A251C_ER	AGAAAAAGAAAAGAAAAGGAG	
6734_A251C_AF	gggacggtcggtagatCTTCCCAGTAGTAAATAA	
6734_A251C_CF	gctggctcggtcaagaCTTCCCAGTAGTAAATAC	
1504_C180T_CF_	gggacggtcggtagatGTGACTTTTGGTTCCCAC	1504
1504_C180T_EF_	AACTCGGGGTCACTGGTCT	
1504_C180T_ER_U	GACGATGCCTTCAGCACACAGCGGGTATGGAGGA TG	
1504_C180T_TF_	gctggctcggtcaagaGTGACTTTTGGTTCCCAT	
11536_C50G_EF	GACCCACCTCCCCCTCCC	11536
11536_C50G_ER	TTGTTCAGACACTGAGAAGAGCTGTAT	
11536_C50G_CF	gggacggtcggtagatTGCCGCGTCCCTGCCCCC	

Primer Name	Primer Sequence	baySNP
11536_C50G_GF	gctggctcggtcaagaTGCCGCGTCCCTGCCCCG	
7363_A94G_EF	TGGTGTTAGGAGAAAAAGTAG	7363
7363_A94G_ER	AAGGGAAGAGGAGAGAAA	
7363_A94G_AF	gggacggtcggtagatAGGCTGGTTTCCCACACA	
7363_A94G_GF	gctggctcggtcaagaAGGCTGGTTTCCCACACG	
11001_C286T_EF	TTCCCAAAGACCCACA	11001
11001_C286T_ER	CCTCCACCGCTATCAC	
11001_C286T_CR	gggacggtcggtagatTGGCTGCAGGACGTCCAG	
11001_C286T_TR	gctggctcggtcaagaTGGCTGCAGGACGTCCAA	
10948_G140T_EF	AAGGACAGGGTCAGGAAAG	10948
10948_G140T_ER	CAGAGGGAGGAAGGAGGT	
10948_G140T_GF	gggacggtcggtagatATGGAGGAGGGTGTCTGG	
10948_G140T_TF	gctggctcggtcaagaATGGAGGAGGGTGTCTGT	
2353_A194G_AF_	gggacggtcggtagatATGAATCCTTTCCCTTTA	2353
2353_A194G_EF_	GAGCAAAGTCAGCCATCT	
2353_A194G_ER_U	GACGATGCCTTCAGCACACCCTCATTTATCCCTC AAC	
2353_A194G_GF_	gctggctcggtcaagaATGAATCCTTTCCCTTTG	
10785_C113T_EF	ATACTTCAACCGCATACACA	10785
10785_C113T_ER	GGAGGGGAAATCAGATAAA	
10785_C113T_CR	gggacggtcggtagatAATTGAACCTGTAAATCG	
10785_C113T_TR	gctggctcggtcaagaAATTGAACCTGTAAATCA	
4018_C251T_EF	CGAGTTAGAGCCAGTCAAG	4018
4018_C251T_ER	GGAGGGAAGAAATCAACA	
4018_C251T_CR	gggacggtcggtagatCATGGGGGCTCTGTGGCG	

Primer Name	Primer Sequence	baySNP
4018_C251T_TR	gctggctcggtcaagaCATGGGGGCTCTGTGGCA	
11654_A251G_EF	CGTATCTCTTGCCTTTCTT	11654
11654_A251G_ER	CTTCTCTTATGCCTTCCC	
11654_A251G_AF	gggacggtcggtagatTTACTTGAAAGGACACCA	
11654_A251G_GF	gctggctcggtcaagaTTACTTGAAAGGACACCG	
11655_A251C_EF	CGTATCTCTTGCCTTTCTT	11655
11655_A251C_ER	CTTCTCTTATGCCTTCCC	
11655_A251C_AF	gggacggtcggtagatTTCTGCACTAAAGCTGTA	
11655_A251C_CF	gctggctcggtcaagaTTCTGCACTAAAGCTGTC	
11637_A162C_EF	AAAGACCCTGAAAACACA	11637
11637_A162C_ER	AACTGACAAAGAACCATTTAC	
11637_A162C_AF	gggacggtcggtagatGTCCAAAAACTAAAAAGA	
11637_A162C_CF	gctggctcggtcaagaGTCCAAAAACTAAAAAGC	
11627_C251T_EF	TTTATCACTACACCCCCTACTC	11627
11627_C251T_ER	GACAGACCGACCAATCAC	
11627_C251T_CR	gggacggtcggtagatCCCTGGGAAGGTTGAGAG	
11627_C251T_TR	gctggctcggtcaagaCCCTGGGAAGGTTGAGAA	
2463_C479T_EF	GGCGATGGCCAAATAATAAA	2463
2463_C479T_ER	AACTCTCCCGCACAGTCG	
2463_C479T_CR	gggacggtcggtagatCTCATCCTTCGGATGCTG	
2463_C479T_TR	gctggctcggtcaagaCTCATCCTTCGGATGCTA	
11456_A251G_EF	GGTTTAGGGGTGGGGTAG	11456
11456_A251G_ER	CTGAGACTGTGGGTTCTGG	
11456_A251G_AR	gggacggtcggtagatCCATGCCCTTGTTACTAT	
11456_A251G_GR	gctggctcggtcaagaCCATGCCCTTGTTACTAC	

Primer Name	Primer Sequence	baySNP
4966_A251G_EF	CATTGCTCTTCCTCTCTGT	4966
4966_A251G_ER	GTGTCATCATTCCTTTCTTG	
4966_A251G_AR	gggacggtcggtagatTCAGAGACATGAGTCCAT	
4966_A251G_GR	gctggctcggtcaagaTCAGAGACATGAGTCCAC	
11531_A251G_EF	CTTTGACAGGTGGGGGTG	11531
11531_A251G_ER	TGCACTGAAATAATACTAGGCAGG	
11531_A251G_AR	gggacggtcggtagatGTGCACCGGGGCCAAGGT	
11531_A251G_GR	gctggctcggtcaagaGTGCACCGGGGCCAAGGC	
7075_C182G_EF	TGGCCAAATAATAAACTAACA	7075
7075_C182G_ER	CCATCCCCATAAACTCTC	
7075_C182G_CR	gggacggtcggtagatCTCAGTGCGCCTCGCTCG	
7075_C182G_GR	gctggctcggtcaagaCTCAGTGCGCCTCGCTCC	
6396_C199T_EF	CAGGGCAAAGGGAAGTAG	6396
6396_C199T_ER	GAAAGGTCAAGGCAGGAG	
6396_C199T_CR	gggacggtcggtagatCAAGGAGCAGAGCAAGGG	
6396_C199T_TR	gctggctcggtcaagaCAAGGAGCAGAGCAAGGA	
8480_C71G_EF	CCTAAAAGAGGGTGATAG	8480
8480_C71G_ER	GGAGAAAAGTCCATAAAG	
8480_C71G_CR	gggacggtcggtagatTTTTGAGAATAGTGTAAG	
8480_C71G_GR	gctggctcggtcaagaTTTTGAGAATAGTGTAAC	
4912_A74G_EF	CTTCACTGAGCGTCCGCAGAG	4912
4912_A74G_ER	CCGTCGGCCCGATTCA	
4912_A74G_AR	CAGGCGAGCCTCAGCCCT	
4912_A74G_GR	CAGGCGAGCCTCAGCCCC	

Primer Name	Primer Sequence	baySNP
6872_A254G_EF	CATCAAGGCAGACCAA	6872
6872_A254G_ER	GAAGGAGAGCAAAGGG	
6872_A254G_AF	gggacggtcggtagatAAGATACCTAAATAACAA	
6872_A254G_GF	gctggctcggtcaagaAAGATACCTAAATAACAG	
5704_C61T_EF	ACAGCCATAACAGGAGTG	5704
5704_C61T_ER	GGGTTACTCAACCTAAGAGA	
5704_C61T_CR	gggacggtcggtagatGTTCTCTTTGGGAAAACG	
5704_C61T_TR	gctggctcggtcaagaGTTCTCTTTGGGAAAACA	
8138_C251T_EF	TCCTGTTCCTGTCTCTCTCT	8138
8138_C251T_ER	CATCATCTCTGACTCCTGTG	
8138_C251T_CR	gggacggtcggtagatACTTAACTTTACAGGCGG	
8138_C251T_TR	gctggctcggtcaagaACTTAACTTTACAGGCGA	
10830_A194G_EF	AGAGTTGATAGTTCCGAGAGA	10830
10830_A194G_ER	CAGACATTTTGGTAGTGATTG	
10830_A194G_AR	gggacggtcggtagatAAAGTTAGTGAAAGAAGT	
10830_A194G_GR	gctggctcggtcaagaAAAGTTAGTGAAAGAAGC	
8168_A251C_EF	GAAGAGAAGCCAGGAATG	8168
8168_A251C_ER	CCTAGACCCATCCAGAAA	
8168_A251C_AF	gggacggtcggtagatTAATGGAGAGGGGGCCTA	
8168_A251C_CF	gctggctcggtcaagaTAATGGAGAGGGGGCCTC	
9883_A249G_EF	TCCACAACCTCAAAACCAC	9883
9883_A249G_ER	CACAGTCCTGCAAGCTCA	
9883_A249G_AR	gggacggtcggtagatCCGTGGCCGTGGCTCACT	
9883_A249G_GR	gctggctcggtcaagaCCGTGGCCGTGGCTCACC	
11462_G251T_EF	GAGAACAATAAAAGACCAAAAA	11462

Primer Name	Primer Sequence	baySNP
11462_G251T_ER	TAGCACAATCAACCCAGA	
11462_G251T_GF	gggacggtcggtagatCTGAAAGCTACTGGAAAG	
11462_G251T_TF	gctggctcggtcaagaCTGAAAGCTACTGGAAAT	
8241_A251G_EF	TTTTCTAACCCAGTCTTATTTT	8241
8241_A251G_ER	TGAAATCTGAAGTCTTACACC	
8241_A251G_AF	gggacggtcggtagatTTCTTCCACTTTTTCCAA	
8241_A251G_GF	gctggctcggtcaagaTTCTTCCACTTTTTCCAG	
11248_C225T_EF	TGAGTTGAACAGCACTTGG	11248
11248_C225T_ER	AGGGTAAGGGAGGGAAAA	
11248_C225T_CR	gggacggtcggtagatTGATTCTTTCGCTTGGCG	
11248_C225T_TR	gctggctcggtcaagaTGATTCTTTCGCTTGGCA	
11448_A251G_EF	ACAGAAGAACAACAACAAAAC	11448
11448_A251G_ER	TGCGTATGAGGTAAAGAGA	
11448_A251G_AF	gggacggtcggtagatGAAGCTGGGAGTGGTGAA	
11448_A251G_GF	gctggctcggtcaagaGAAGCTGGGAGTGGTGAG	
11449_C251G_EF	ACAGAAGAACAACAACAAAAC	11449
11449_C251G_ER	TGCGTATGAGGTAAAGAGA	
11449_C251G_CF	gggacggtcggtagatATGAGTGAAGCCTGTCTC	
11449_C251G_GF	gctggctcggtcaagaATGAGTGAAGCCTGTCTG	
11450_A251T_EF	ACAGAAGAACAACAACAAAAC	11450
11450_A251T_ER	TGCGTATGAGGTAAAGAGA	
11450_A251T_AR	gggacggtcggtagatGGACCATAATCTTGAAGT	
11450_A251T_TR	gctggctcggtcaagaGGACCATAATCTTGAAGA	
9940_C93T_EF	CATCTCCTGGAAGAACAA	9940

Primer Name	Primer Sequence	baySNP
9940_C93T_ER	CAAACATAAGTGCATGAAAG	
9940_C93T_CR	gggacggtcggtagatGTCAGGGCCCAATAGGTG	
9940_C93T_TR	gctggctcggtcaagaGTCAGGGCCCAATAGGTA	
11624_C251T_EF	TCGGGAGGTGTAAGTAAG	11624
11624_C251T_ER	CCACAGTCAGAAGAGACAA	
11624_C251T_CR	gggacggtcggtagatAGAGACCCTGGTCCCAAG	
11624_C251T_TR	gctggctcggtcaagaAGAGACCCTGGTCCCAAA	
10388_A251G_EF	CACCCCTATACACATATCC	10388
10388_A251G_ER	GTTTGGAATACATCATTGTC	
10388_A251G_AR	gggacggtcggtagatTATTTTTATTGGCTATAT	
10388_A251G_GR	gctggctcggtcaagaTATTTTTATTGGCTATAC	
10877_A251C_EF	CCTGTTTCTCAACCTTCTC	10877
10877_A251C_ER	ATGGTCTATGGAACCTAATCT	
10877_A251C_AF	gggacggtcggtagatGCACTGATTCTGCTTCCA	
10877_A251C_CF	gctggctcggtcaagaGCACTGATTCTGCTTCCC	
52_C397G_CR_	gggacggtcggtagatTATTTTATAATGCAAAAG	52
52_C397G_EF_U	GACGATGCCTTCAGCACAGTGAATTGCCAGATTA GTG	
52_C397G_ER_	TCTAAAGTGCTGGGATTG	
52_C397G_GR_	gctggctcggtcaagaTATTTTATAATGCAAAAC	
57_C290T_CR_	gggacggtcggtagatAGCAGCAGGTGGCAAGAG	57
57_C290T_EF_U	GACGATGCCTTCAGCACATAACATTAGGGCACAA CC	
57_C290T_ER_	CCCACAAGTAAGGACAGA	
57_C290T_TR_	gctggctcggtcaagaAGCAGCAGGTGGCAAGAA	

Primer Name	Primer Sequence	baySNP
118_C675T_CF_	gggacggtcggtagatGTGCTGCTATCTGCTTTC	118
118_C675T_EF_	TACCTGTTTCTCCCACAC	
118_C675T_ER_U	GACGATGCCTTCAGCACAAAAGACAGCCAAAAGA GA	
118_C675T_TF_	gctggctcggtcaagaGTGCTGCTATCTGCTTTT	
152_A587G_AF_	gggacggtcggtagatGGTGGGAGGTTCCAGCCA	152
152_A587G_EF_	GCAGGAAGAAAGCTAGAA	
152_A587G_ER_U	GACGATGCCTTCAGCACAAGGCAGGATAATGACA AC	
152_A587G_GF_	gctggctcggtcaagaGGTGGGAGGTTCCAGCCG	
288_C541G_CR_	gggacggtccgtagatGTGCCCTTCCTCCCGCCG	288
288_C541G_EF_U	GACGATGCCTTCAGCACATAGGTTTCTGTTCTAA CCTTG	
288_C541G_ER_	GGACTTTTCTCCTGACACT	
288_C541G_GR_	gctggctcggtcaagaGTGCCCTTCCTCCCGCCC	
307_C215T_CR_	gggacggtcggtagatGAGTGGGTGCTGTTCCCG	307
307_C215T_EF_U	GACGATGCCTTCAGCACAGTTACTGCCTCTCTGA CC	
307_C215T_ER_	AGTGTGACCTGCTCTCTT	
307_C215T_TR_	gctggctcggtcaagaGAGTGGGTGCTGTTCCCA	
384_C375G_CR_	gggacggtcggtagatCTCATGTTGCCACTCACG	384
384_C375G_EF_U	GACGATGCCTTCAGCACATCCGTTTCCAGGCCAT CT	
384_C375G_ER_	GTCCGTCTTATAGTGCAGGGTGT	
384_C375G_GR_	gctggctcggtcaagaCTCATGTTGCCACTCACC	

Primer Name	Primer Sequence	baySNP
533_A289G_AF_	gggacggtcggtagatCCTGGCCTGGACCCTACA	533
533_A289G_EF_	CTCCTGGAGACGCACGACTCT	
533_A289G_ER_U	GACGATGCCTTCAGCACAACAGCATCGGGAGGTACA	
533_A289G_GF_	gctggctcggtcaagaCCTGGCCTGGACCCTACG	
542_A402G_AR_	gggacggtcggtagatAGAAATTCCCTCCCAACT	542
542_A402G_EF_U	GACGATGCCTTCAGCACATGATTGAGCCAGTTGTTT	
542_A402G_ER_	GGGGTGTATTTTGAGAGTG	
542_A402G_GR_	gctggctcggtcaagaAGAAATTCCCTCCCAACC	
555_A202G_AF_	gggacggtcggtagatGTGAGAGGGGTTCCTGGA	555
555_A202G_EF_	GACTATGCGGAGAAGATG	
555_A202G_ER_U	GACGATGCCTTCAGCACACTTGGCTTGGAATAGAGA	
555_A202G_GF_	gctggctcggtcaagaGTGAGAGGGGTTCCTGGG	
576_C639T_CF_	gggacggtcggtagatCATCCCTTTTGCAGGAGC	576
576_C639T_EF_	ACCCTTAGAATGAAGTTGAGAG	
576_C639T_ER_U	GACGATGCCTTCAGCACAGCTTCGTAGACACGTTGAG	
576_C639T_TF_	gctggctcggtcaagaCATCCCTTTTGCAGGAGT	
608_A182G_AR_	gggacggtcggtagatCCTTGGCCTCTGTGAACT	608
608_A182G_EF_U	GACGATGCCTTCAGCACACTTATCCAGGGTGATGGT	
608_A182G_ER_	TGTCAGATCCCAGTTCAG	
608_A182G_GR_	gctggctcggtcaagaCCTTGGCCTCTGTGAACC	
614_A150G_AF_	gggacggtcggtagatTCGCAACATCCATGCCAA	614

Primer Name	Primer Sequence	baySNP
614_A150G_EF_	ACACACTTGTCCTTGTCTC	
614_A150G_ER_U	GACGATGCCTTCAGCACAGCTCATCGTTCCTACTAAA	
614_A150G_GF_	gctggctcggtcaagaTCGCAACATCCATGCCAG	
738_A120C_AR_	gggacggtcggtagatGAGGTGAAGAGGAATGTT	738
738_A120C_CR_	gctggctcggtcaagaGAGGTGAAGAGGAATGTG	
738_A120C_EF_U	GACGATGCCTTCAGCACACTCCTTCTCAACGCCACTTC	
738_A120C_ER_	CCTTCCCCCACCAACTCT	
777_C266T_CR_	gggacggtcggtagatTCCACAGGGCCTCTCCG	777
777_C266T_EF_U	GACGATGCCTTCAGCACAGGGGCAGGCCAGGAGGATGTA	
777_C266T_ER_	CCTGAGACGCGGACCGT	
777_C266T_TR_	gctggctcggtcaagaTCCACAGGGCCTCTCCA	
1056_A354G_AR_	gggacggtcggtagatGCGGCTGCCCCGTCCTGT	1056
1056_A354G_EF_U	GACGATGCCTTCAGCACAGTGTGTCTATGTGTCTGTGTG	
1056_A354G_ER_	CGGACTTCTCCTTCTTGT	
1056_A354G_GR_	gctggctcggtcaagaGCGGCTGCCCCGTCCTGC	
1275_C307G_CF_	gggacggtcggtagatCCTCCCGCCCTGGGAGAC	1275
1275_C307G_EF_	GAGAAAGAGAGAGAGAGAGAGAGAG	
1275_C307G_ER_U	GACGATGCCTTCAGCACAGTGGGTTTGGTTTTGGTT	
1275_C307G_GF_	gctggctcggtcaagaCCTCCCGCCCTGGGAGAG	
1524_A284C_AF_	gggacggtcggtagatCTCTCAAAGCCCACACAA	1524
1524_A284C_CF_	gctggctcggtcaagaCTCTCAAAGCCCACACAC	

Primer Name	Primer Sequence	baySNP
1524_A284C_EF_	AGAAAAAGAAAAGGAAAAAGA	
1524_A284C_ER_U	GACGATGCCTTCAGCACAGGAAAGTTACAAGGCTATGA	
1583_C491T_CR_	gggacggtcggtagatAGTTGATGGCAATGTATG	1583
1583_C491T_EF_U	GACGATGCCTTCAGCACAGGGATGAGAACAGAGAGAA	
1583_C491T_ER_	CCAGAAAAGCACAAACAC	
1583_C491T_TR_	gctggctcggtcaagaAGTTGATGGCAATGTATA	
1669_C317T_CR_	gggacggtcggtagatTGATAGGCGCTCAATAAG	1669
1669_C317T_EF_U	GACGATGCCTTCAGCACATCAGATAGCAGCAAGAGG	
1669_C317T_ER_	GTGCTTCATTTTCTTCACA	
1669_C317T_TR_	gctggctcggtcaagaTGATAGGCGCTCAATAAA	
1722_C89T_CF_	gggacggtcggtagatACCCCAGGATGCCCACAC	1722
1722_C89T_EF_	GTTTATCCTCCTCATGTCC	
1722_C89T_ER_U	GACGATGCCTTCAGCACAGTTACCTTTTCCACCTCTC	
1722_C89T_TF_	gctggctcggtcaagaACCCCAGGATGCCCACAT	
1757_A210G_AF_	gggacggtcggtagatGGAAACAAACCAAAATGA	1757
1757_A210G_EF_	CCAGCACCCAAAATAAGA	
1757_A210G_ER_U	GACGATGCCTTCAGCACAATAAGTTGAAGCCCTCCC	
1757_A210G_GF_	gctggctcggtcaagaGGAAACAAACCAAAATGG	
1765_A240G_AF_	gggacggtcggtagatGGCTTCACGGAGGAAGAA	1765
1765_A240G_EF_	TTAGGAGCTGTGAGGTATG	
1765_A240G_ER_U	GACGATGCCTTCAGCACATAAGATGGAGCAGGGT	

Primer Name	Primer Sequence	baySNP
	AG	
1765_A240G_GF_	gctggctcggtcaagaGGCTTCACGGAGGAAGAG	
1837_C413T_CF_	gggacggtcggtagatCTCAGCTTCATGCAGGGC	1837
1837_C413T_EF_	CCCACTCAGCCCTGCTCTT	
1837_C413T_ER_U	GACGATGCCTTCAGCACAGCATCCTTGGCGGTCTTG	
1837_C413T_TF_	gctggctcggtcaagaCTCAGCTTCATGCAGGGT	
1862_C109T_CF_	gggacggtcggtagatCTGGATGTGACGTCTAAC	1862
1862_C109T_EF_	TTGGGGGATGAAGAGGGA	
1862_C109T_ER_U	GACGATGCCTTCAGCACAAATGGTGGAATGGAAGACAGAAC	
1862_C109T_TF_	gctggctcggtcaagaCTGGATGTGACGTCTAAT	
2000_C349T_CR_	gggacggtcggtagatAGTATGGTAATTAGGAAG	2000
2000_C349T_EF_U	GACGATGCCTTCAGCACACTGACACTGAGCCACAAC	
2000_C349T_ER_	AACTGATGAGCAAGAAGGA	
2000_C349T_TR_	gctggctcggtcaagaAGTATGGTAATTAGGAAA	
2085_G415T_EF_	GCTTTTTCTTTTCATTACATC	2085
2085_G415T_ER_U	GACGATGCCTTCAGCACACCTCTTTTAGAATCAGAGACA	
2085_G415T_GF_	gggacggtcggtagatGGTAGTGTTACCAGAAAG	
2085_G415T_TF_	gctggctcggtcaagaGGTAGTGTTACCAGAAAT	
2093_C229T_CR_	gggacggtcggtagatGGCTCTCAGCAATCAAAG	2093
2093_C229T_EF_U	GACGATGCCTTCAGCACACTTTTGTGTTTGTGTGGG	
2093_C229T_ER_	CTGGTGTCAGGTGTAGTTATG	

Primer Name	Primer Sequence	baySNP
2093_C229T_TR_	gctggctcggtcaagaGGCTCTCAGCAATCAAAA	
2109_A543G_AR_	gggacggtcggtagatGCAATTCTGCAGTGACAT	2109
2109_A543G_EF_U	GACGATGCCTTCAGCACAGCATAAAACATACCTTGAGTG	
2109_A543G_ER_	CTTCCCTACATAATAACAACAGA	
2109_A543G_GR_	gctggctcggtcaagaGCAATTCTGCAGTGACAC	
2187_C99T_CR_	gggacggtcggtagatGAGTCCCTAAAGTTGGTG	2187
2187_C99T_EF_U	GACGATGCCTTCAGCACACGTAAGTGCCATGAAGAC	
2187_C99T_ER_	AGAAAAGCCAAAGAAAGTG	
2187_C99T_TR_	gctggctcggtcaagaGAGTCCCTAAAGTTGGTA	
2203_C745T_CF_	gggacggtcggtagatGAAGTAAATTATAGTGAC	2203
2203_C745T_EF_	GTGGGTTTTTGTTTTGTTT	
2203_C745T_ER_U	GACGATGCCTTCAGCACATTTTTGTTGATGGGTTTG	
2203_C745T_TF_	gctggctcggtcaagaGAAGTAAATTATAGTGAT	
2217_T281G_EF_U	GACGATGCCTTCAGCACATAACCTCACCAACCTCAA	2217
2217_T281G_ER_	TGTCACCAATTAACCAGAA	
2217_T281G_GR_	gctggctcggtcaagaAAAATGACAGCCATGGCC	
2217_T281G_TR_	gggacggtcggtagatAAAATGACAGCCATGGCA	
2284_A220G_AF_	gggacggtcggtagatGGAGGGCAGATCTAGGGA	2284
2284_A220G_EF_	TTGTAAAGGAAACCCTCCC	
2284_A220G_ER_U	GACGATGCCTTCAGCACATTTTCTCCTCCCCCTTCT	
2284_A220G_GF_	gctggctcggtcaagaGGAGGGCAGATCTAGGGG	

Primer Name	Primer Sequence	baySNP
2290_A404G_AR_	gggacggtcggtagatCACATCAGGAAAAACAGT	2290
2290_A404G_EF_U	GACGATGCCTTCAGCACACAGAAGTGACAAGGATGG	
2290_A404G_ER_	GGTGCTTTGAGTGATGTT	
2290_A404G_GR_	gctggctcggtcaagaCACATCAGGAAAAACAGC	
2297_C272T_CF_	gggacggtcggtagatAAGAAAAAGCCAATGCAC	2297
2297_C272T_EF_	TGCAGTAAGCTGAGATGG	
2297_C272T_ER_U	GACGATGCCTTCAGCACAGGAGGAGTAGGTTTTGTTTAG	
2297_C272T_TF_	gctggctcggtcaagaAAGAAAAAGCCAATGCAT	
2321_G516T_EF_U	GACGATGCCTTCAGCACAGGCTCGACGGGTAGGTAAC	2321
2321_G516T_ER_	GGGTCTTGGGTGAGGAACGAC	
2321_G516T_GR_	gggacggtcggtagatAGCCGCCGGTCCCTCTGC	
2321_G516T_TR_	gctggctcggtcaagaAGCCGCCGGTCCCTCTGA	
2354_C145T_CF_	gggacggtcggtagatAACTAGAGAGTACTTGGC	2354
2354_C145T_EF_	CAGAAGCACTAGGAAGACAA	
2354_C145T_ER_U	GACGATGCCTTCAGCACATCAAAGAAAACACAGCCA	
2354_C145T_TF_	gctggctcggtcaagaAACTAGAGAGTACTTGGT	
2371_A72C_AR_	gggacggtcggtagatCACCTTTGTTTAAAATCT	2371
2371_A72C_CR_	gctggctcggtcaagaCACCTTTGTTTAAAATCG	
2371_A72C_EF_U	GACGATGCCTTCAGCACACTGCGGTGTAACGGTGTC	
2371_A72C_ER_	CCCTCTCAAATTCCAGTGTTC	

Primer Name	Primer Sequence	baySNP
2376_C302T_CR_	gggacggtcggtagatCTGGTGGGACAGGATGTG	2376
2376_C302T_EF_U	GACGATGCCTTCAGCACAAGAGAAAAGGAAGAAA GAA	
2376_C302T_ER_	CAGGTAACAGGAATGTATG	
2376_C302T_TR_	gctggctcggtcaagaCTGGTGGGACAGGATGTA	
87148_A251C_EF	AAGGAATGTTGTAGAGGGA	6734
87148_A251C_ER	AGAAAAAGAAAAGAAAAGGAG	
87148_A251C_AF	gggacggtcggtagatCTTCCCAGTAGTAAATAA	
87148_A251C_CF	gctggctcggtcaagaCTTCCCAGTAGTAAATAC	

Table 2b: Oligonucleotide primers used for genotyping using Pyrosequencing

The baySNP number refers to an internal numbering of the CA SNPs. Primer sequences are listed for preamplification of the genomic fragments and for sequencing of the SNP using the pyrosequencing method.

Primer Name	Primer Sequence	baySNP
SP-1755FPy BIO	CCTCCATGTAGGTGCCACGG	1755
SP-1755 R Py	GGCCCTCCAGGATCTGC	
SP-1755 seq Py	GATGCTCACAGGGGAGAAGA	
SP-8816 F Py	AGGGAGCCCACGGTGATA	8816
SP-8816 R Py BIO	AGGGCACTCTGCTTGTTATTAGA	
SP-8816 seq Py F	GCCCCTCTGCTCCAAGCG	
SP-1653FPy: BIO	AAGTGAGGGATTTATTCATGAC	1653
SP-1653RPy:	TAAGATGCTAACTGTAGGGA	
SP-1653seqPy	GGAAGGCCAACTGAGGAG	
5564 FW	ACTCCCACAGGTTTAATTAGT	5564
5564 REbio	AGACAGTGCAGGTTATCTCA	
5564 SQ	ATCCTGGGAAAGGTACT	
5320 FW	TGCTAGGTGCTCGGGATA	5320
5320 REbio	GCACTGGCCAACTTAATCACT	
5320 SQ	GTAAGAGAGGTTAAGGAAAGC	
1062 FW	GAATGAGGTCCTGTGCGTTT	1062
1062 REbio	ACCACACTTCTCCTCGACCTG	
1062 SQ	CGTTTTGACACAGAAGAT	
SP10811Fint seq	TTCAGTTCCAGCTCTACCAT	10811

Primer Name	Primer Sequence	baySNP
SP10811F	AGATTTACTGAAGTGCGAGGTG	
SP10811RBio	GATCAGAGGCTCACAAAGGTT	
SP4383FPy	CCAGAACAAGAGTCCCTAAACCCAC	4383
SP4383RPy BIO	GGTTCAGGCACTTTTCGTTGAGTT	
SP4383seqPy	CTTACACAGAACGCTGCTGA	
SP-3843FPy	ATTGTTTGAGGCCAGGAGGTAGAAGT	3843
SP-3843RPy BIO	GGGGGAAATTTTGAATGTAGCA	
SP-3843seqPy	TTGCTGTTTTCTATTTTTGGTA	
SNP4527-FW	AAGCAGATAAAGCATATGATG	4527
SNP4527-REbio	GGGTTTCCACAAGCTGAC	
SNP4527-SQ	CAGAAGAAATAGATGCAAAGG	
SNP5019-FWbio	TCCTTGGGTCTCACCGTGTAT	5019
SNP5019-RE	AGCGCAGAAGGGTATAG	
SNP5019-SQrev	CAGTCCTGTGCTGGGGAGAAC	
SNP5093-FW	ATCTGGCATCTTGGCAAACCT	5093
SNP5093-REbio	CCCCACCTTCGTAACAGC	
SNP5093-SQ	CAGAGGCTGCCCTGAAGACAT	
SNP5717-FW	AATGGCAGAAATCCGGAGA	5717
SNP5717-REbio	CCGCAAAGAGCTTGACAATGT	
SNP5717-SQ	GGATATGATCTAAAAAGGGA	
SP5245Rint	CAAGATTGTAAAAGAATAGC	5245
SP5245FBio	TGGGGGCTGCTTAGATGCT	
SP5245R	GATGACGTTTCAATTTTAGGAG	

Primer Name	Primer Sequence	baySNP
SP1574F	CAATGCAGGCCAGGAAAACACT	1574
SP1574RBio	ACCCCCAAAAGACACCAAAAACA	
SP1574Fint	CCCTGGGCAATGAAAAAGT	
SP4838Rint	TGACTAAGAATGTAATGGGGAAGA	4838
SP4838FBio	CAAAGATGACCTTATGGCTCTGA	
SP4838R	GTCTCGGAACATGACCTTTAGT	
SP4856Fint	CTGCAGAAGCTGAGTTACC	4856
SP4856F	CGTGGTCCGGGCTCTTTTTGCT	
SP4856RBio	GGTGGGGGTCAGGCAGTGG	

Table 3: **CA SNPs and putative CA genes**

The baySNP number refers to an internal numbering of the CA SNPs. Listed are the different polymorphisms found in our association study. Also accession numbers and descriptions of those gene loci are given that are most homologous to the CA genes as listed in the sequences section (see below). Homologous genes and their accession numbers could be found by those skilled in the art in the Genbank database.

baySNP	GT 11	GT 12	GT 22	Accession	DESCRIPTION of putative CA genes
10948	GG	GT	TT	M10065	Apolipoprotein E
7363	AA	AG	GG	M15887	Endozepine (putative ligand of benzodiazepine receptor)
11377	CC	CT	TT	Z82215	DNA from clone RP1-68O2 on chromosome 22. MYH9 nonmuscle type myosin heavy chain 9
1837	CC	CT	TT	J00098	Apolipoprotein A-I and C-III genes
10830	AA	AG	GG	M14162	Apolipoprotein B-100
777	CC	CT	TT	U63721	elastin (ELN) gene, partial cds, and LIM-kinase (LIMK1) gene
555	AA	AG	GG	U34804	Thermostable phenol sulfotransferase (STP2),HAST
11652	CC	CT	TT	AH002776	LDL receptor
8138	CC	CT	TT	AC002457	BAC clone CTB-60P12 from 7q21, ABCB1 (MDR/TAP)
1765	AA	AG	GG	J05096	Na,K-ATPase subunit alpha 2 (ATP1A2) gene
5019	AA	AT	TT	D00510	mRNA for calphobindin II
2187	CC	CT	TT	U35464	Protein C inhibitor (PCI-B) mRNA

baySNP	GT 11	GT 12	GT 22	Accession	DESCRIPTION of putative CA genes
2000	CC	TT	-	P03915	NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 5 (EC 1.6.5.3).
11000	CC	CT	TT	Y00839	GAA mRNA for lysosomal alpha-glucosidase (acid maltase)
5564	GG	GT	TT	M14584	Interleukin 6 mRNA
2297	CC	CT	-	U36478	Fibrinogen gamma chain/fibrinogen alpha chain genes, intergenic region.
10388	AA	AG	GG	AC005021	BAC clone GS1-293C5 from 7q21-q22, PON2
1583	CC	CT	TT	U33317	Defensin 6 (HD-6) gene
11001	CC	CT	TT	Y00839	GAA mRNA for lysosomal alpha-glucosidase (acid maltase)
4856	AG	GG	-	L11669	Tetracycline transporter-like protein
1574	CC	CT	TT	X52889	Gene for cardiac beta myosin heavy chain
2354	CC	CT	TT	M24736	Endothelial leukocyte adhesion molecule 1 (ELAM-1)
608	AA	AG	GG	M94363	Lamin B2 (LAMB2) gene and ppv1 gene sequence.
11456	AA	AG	GG	AF051427	Estrogen receptor beta
6734	AA	AC	-	K03021	Tissue plasminogen activator (PLAT) gene, (elastin, LIM-kinase)
5320	AA	AG	GG	J03799	Colin carcinoma laminin-binding protein
152	AA	AG	GG	M32670	ITGB3 gene, intron 2, fragment C,Integrin beta 3 (GpIIIa)
1755	AA	AG	GG	U35464	Protein C inhibitor (PCI-B)
4838	AA	AG	GG	L08246	Myeloid cell differentiation protein (MCL1)
3843	AA	AT	TT	U12595	Tumor necrosis factor type 1 receptor associated protein (TRAP1)
10749	CC	CG	GG	U39487	Xanthine dehydrogenase/oxidase

baySNP	GT 11	GT 12	GT 22	Accession	DESCRIPTION of putative CA genes
2203	CC	CT	TT	U16752	Cytokine SDF-1-beta
1722	CC	CT	TT	D73409	mRNA for diacylglycerol kinase delta
576	CC	CT	-	D10667	mRNA for smooth muscle myosin heavy chain.
8168	AA	AC	CC	Z18951	mRNA for caveolin
2109	AA	AG	GG	Y09912	AP-2 beta gene (transcription factor)
11637	AA	AC	CC	M19154	transforming growth factor-beta-2
1862	CC	CT	TT	M92357	B94 protein mRNA
11073	CC	CG	GG	S87759	Protein phosphatase 2C alpha
1056	AA	AG	GG	Q16720	CALCIUM-TRANSPORTING ATPASE PLASMA MEMBRANE, (CALCIUM PUMP)
5245	AA	AG	GG	D86425	mRNA for osteonidogen
8241	AA	AG	GG	AF165281	ATP cassette binding transporter 1 (ABC1)
5093	AA	AG	GG	D26362	bromodomain-containing 3, BRD3
8480	CC	CG	GG	D83233	PPAR gamma2
1275	CC	CG	GG	M55913	Tumor necrosis factor-beta (TNFB) gene
118	CC	CT	TT	X64229	dek mRNA (oncogene)
738	AA	AC	CC	X68836	S-adenosylmethionine synthetase
8148	AA	AG	GG	U63721	Elastin (ELN) gene, partial cds, and LIM-kinase (LIMK1) gene
1657	CC	CT	TT	J02846	Tissue factor gene
533	AA	AG	GG	X82895	DLG2 (membrane protein palmitoylated 2, MPP2)

baySNP	GT 11	GT 12	GT 22	Accession	DESCRIPTION of putative CA genes
11462	GG	GT	TT	AF051427	Estrogen receptor beta mRNA
5717	AA	AG	GG	M59941	GM-CSF receptor beta chain mRNA
1669	CC	CT	TT	M17262	Prothrombin (F2) gene
2376	CC	CT	-	X54516	lipoprotein lipase
11558	AA	AC	CC	AC006312	chromosome 9, clone hRPK.401_G_18
10785	CC	CT	TT	D50678	Apolipoprotein E receptor 2
2085	GG	GT	TT	X82540	Activin beta-C chain
614	AA	AG	GG	J04031	Methylenetetrahydrofolate dehydrogenase- cyclohydrolase-formyltetrahydrofolate synthetas
11248	CC	CT	-	X60435	Gene PACAP for pituitary adenylate cyclase activating polypeptide
6396	CC	CT	TT	X54807	CYP2C8 gene for cytochrome P-450
9940	CC	CT	TT	X54807	CYP2C8 gene for cytochrome P-450
2353	AA	AG	GG	AJ246000	Leucocyte adhesion receptor, L-selectin
52	CC	CG	GG	X69907	Gene for mitochondrial ATP synthase c subunit (P1 form)
1757	AA	AG	GG	J04046	Calmodulin
1524	AA	AC	CC	AF223404	WNT1 inducible signaling pathway protein 1 (WISP1) gene
4912	AA	AG	GG	AF022375	Vascular endothelial growth factor
6957	CC	CT	TT	Y00281	Ribophorin I
8816	CC	CG	GG	U16752	Cytokine SDF-1-beta mRNA
1062	AA	AG	GG	AF073308	Nonsyndromic hearing impairment protein (DFNA5), ICERE-1

baySNP	GT 11	GT 12	GT 22	Accession	DESCRIPTION of putative CA genes
2463	CC	CT	TT	AF084225	Cytochrome P450 2E1 (CYP2E1) mRNA, partial cds.
4527	AA	AG	GG	X76228	Vacuolar H+ ATPase E subunit
11531	AA	AG	GG	X52773	Retinoic acid receptor-like protein
11536	CC	CG	GG	AL022721	DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the PPARD
10811	AA	AG	GG	D86425	Osteonidogen
288	CC	CG	GG	X79204	SCA1 mRNA for ataxin
2371	AA	AC	CC	Q92679	BETA-MYOSIN HEAVY CHAIN.
4383	AA	AG	GG	X58141	mRNA for erythrocyte adducin alpha subunit
11654	AA	AG	GG	AJ276180	ZNF202
11655	AA	AC	CC	AJ276180	ZNF202
11450	AA	AT	TT	AF050163	Lipoprotein lipase precursor, gene cds.
11448	AA	AG	GG	AF050163	Lipoprotein lipase precursor, gene
4018	CC	CT	TT	U49260	Mevalonate pyrophosphate decarboxylase (MPD)
2217	GG	GT	TT	M15395	Leukocyte adhesion protein (LFA-1/Mac-1/p150,95 family) beta subunit mRNA.
2321	GG	GT	TT	M29932	Beta-3-adrenergic receptor gene.
4966	AA	AG	GG	AF133298	Cytochrome P450 (CYP4F8) mRNA
2284	AA	AG	GG	AB021744	XIIIA gene for coagulation factor XIII A subunit, promoter sequence.
57	CC	CT	TT	M34175	Beta adaptin mRNA
11614	CC	CT	TT	AF107885	Chromosome 14q24.3 clone BAC270M14 (TGF-beta 3) gene

baySNP	GT 11	GT 12	GT 22	Accession	DESCRIPTION of putative CA genes
11645	AA	AG	GG	X05839	Transforming growth factor-beta precursor gene exon 1 and 5`flanking region (and joined CDS)
384	CC	CG	GG	U12595	Tumor necrosis factor type 1 receptor associated protein (TRAP1) mRNA, partial cds.
542	AA	AG	GG	M64082	Flavin-containing monooxygenase (FMO1) mRNA
2290	AA	AG	GG	M35672	Coagulation factor IX mRNA, partial cds.
2093	CC	CT	TT	X83543	APXL mRNA
11585	GG	GT	TT	AC073593	12 BAC RP11-13J12 (Roswell Park Cancer Institute BAC Library) complete sequence.

Table 4: **Cohorts**

Given are names (as used in table 5) and formations of the various cohorts that were used for genotyping

COHORT	Definition
HELD_ALL_GOOD/BAD	Healthy elderly individuals of both genders with good or bad serum lipid profiles (as defined in table 1)
HELD_FEM_GOOD/BAD	Healthy elderly individuals (female) with good or bad serum lipid profiles (as defined in table 1)
HELD_MAL_GOOD/BAD	Healthy elderly individuals (male) with good or bad serum lipid profiles (as defined in table 1)
CVD_ALL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (both genders)
CVD_FEM_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (female)
CVD_MAL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (male)

Table 5: **Cohort sizes and p-values of CA SNPs**

The baySNP number refers to an internal numbering of the CA SNPs. GTYPE P and A PVAL provide the p values obtained through chi square tests when comparing COHORTs A and B. For GTYPE P (p value of genotypes) the number of patients in cohort A carrying genotypes 11, 12 or 22 (FQ11 A, FQ 12 A, FQ 22 A) were compared with the respective patients in cohort B (FQ11 B, FQ 12 B, FQ 22 B) resulting in a chi square test with a 3×2 matrix. For A PVAL (p value of alleles) we compared the allele count of alleles 1 and 2 in cohorts A and B, respectively (chi square test with a 2×2 matrix). SIZE A and B: Number of patients in cohorts A and B, respectively. See table 4 for definition of COHORTs A and B.

BAYSNP	GTYPE P	A PVAL	COHORT A	SIZE A	FQ11 A	FQ12 A	FQ22 A	COHORT B	SIZE B	FQ11 B	FQ12 B	FQ22 B
10948	0,02	0,019	HELD_ALL_BAD	107	23	60	24	HELD_ALL_GOOD	125	48	56	21
7363	0,04	0,0149	HELD_ALL_BAD	107	8	44	55	HELD_ALL_GOOD	125	3	40	82
11377	0,0577	0,1103	HELD_ALL_BAD	107	12	62	33	HELD_ALL_GOOD	124	29	61	34
1837	0,0591	0,3602	HELD_ALL_BAD	106	60	33	13	HELD_ALL_GOOD	125	56	58	11
10830	0,0159	0,0036	HELD_ALL_BAD	105	22	47	36	HELD_ALL_GOOD	124	42	58	24
777	0,0631	0,0154	HELD_ALL_BAD	105	68	31	6	HELD_ALL_GOOD	124	96	26	2
555	0,0316	0,2062	HELD_ALL_BAD	103	48	40	15	HELD_ALL_GOOD	125	40	70	15
11652	0,0407	0,5098	HELD_ALL_BAD	104	24	59	21	HELD_ALL_GOOD	124	43	50	31
8138	0,0458	0,0782	HELD_ALL_BAD	100	21	39	40	HELD_ALL_GOOD	124	31	63	30
1765	0,093	0,5287	HELD_ALL_BAD	106	6	21	79	HELD_ALL_GOOD	118	3	37	78

BAYSNP	GTYPE P	A PVAL	COHORT A	SIZE A	FQ11 A	FQ12 A	FQ22 A	COHORT B	SIZE B	FQ11 B	FQ12 B	FQ22 B
5019	0,0205	0,0069	HELD_ALL_BAD	92	31	40	21	HELD_ALL_GOOD	109	27	37	45
2187	0,0113	0,8219	CVD_ALL_CASE	105	50	36	19	CVD_ALL_CTRL	74	29	40	5
2000	0,0425	0,0035	CVD_ALL_CASE	105	101	4	0	CVD_ALL_CTRL	74	65	9	0
11000	0,0041	1	CVD_ALL_CASE	104	3	38	63	CVD_ALL_CTRL	74	9	14	51
5564	0,0048	0,0519	CVD_ALL_CASE	104	14	76	14	CVD_ALL_CTRL	74	25	40	9
2297	0,0211	0,0222	CVD_ALL_CASE	104	103	1	0	CVD_ALL_CTRL	74	68	6	0
10388	0,0263	0,0398	CVD_ALL_CASE	104	11	61	32	CVD_ALL_CTRL	74	19	38	17
1583	0,0343	0,0398	CVD_ALL_CASE	104	3	20	81	CVD_ALL_CTRL	74	2	27	45
11001	0,0116	0,795	CVD_ALL_CASE	103	3	38	62	CVD_ALL_CTRL	74	9	16	49
4856	0,0118	0,0123	CVD_ALL_CASE	103	0	103	0	CVD_ALL_CTRL	74	5	69	0
1574	0,0193	0,224	CVD_ALL_CASE	103	3	20	80	CVD_ALL_CTRL	74	0	26	48
2354	0,0406	0,0436	CVD_ALL_CASE	103	74	28	1	CVD_ALL_CTRL	74	64	9	1
608	0,0094	0,0027	CVD_ALL_CASE	103	2	21	80	CVD_ALL_CTRL	73	9	18	46
11456	0,0016	0,0239	CVD_ALL_CASE	99	81	18	0	CVD_ALL_CTRL	74	71	2	1
6734	0,0404	0,0462	CVD_ALL_CASE	102	87	15	0	CVD_ALL_CTRL	71	68	3	0
5320	0,0405	0,0222	CVD_ALL_CASE	101	35	48	18	CVD_ALL_CTRL	72	19	28	25
152	0,0552	0,0373	CVD_ALL_CASE	101	59	37	5	CVD_ALL_CTRL	71	34	26	11
1755	0,0104	0,8179	CVD_ALL_CASE	100	48	33	19	CVD_ALL_CTRL	71	28	38	5
4838	0,0432	0,7409	CVD_ALL_CASE	102	19	58	25	CVD_ALL_CTRL	69	21	26	22

BAYSNP	GTYPE P	A PVAL	COHORT A	SIZE A	FQ11 A	FQ12 A	FQ22 A	COHORT B	SIZE B	FQ11 B	FQ12 B	FQ22 B
3843	0,0167	0,0355	CVD_ALL_CASE	99	44	34	21	CVD_ALL_CTRL	71	17	37	17
10749	0,0647	0,0249	HELD_FEM_BAD	86	48	33	5	HELD_FEM_GOOD	83	33	39	11
2203	0,0074	0,0097	HELD_FEM_BAD	85	6	45	34	HELD_FEM_GOOD	83	4	26	53
1722	0,0308	0,5747	CVD_ALL_CASE	95	22	29	44	CVD_ALL_CTRL	73	12	37	24
576	0,0574	0,0585	HELD_FEM_BAD	85	85	0	0	HELD_FEM_GOOD	83	79	4	0
8168	0,0201	0,1107	HELD_FEM_BAD	84	4	15	65	HELD_FEM_GOOD	83	2	30	51
2109	0,0498	0,0224	HELD_FEM_BAD	85	64	20	1	HELD_FEM_GOOD	82	48	31	3
11637	0,0098	0,0208	HELD_FEM_BAD	82	38	31	13	HELD_FEM_GOOD	83	47	34	2
1862	0,0553	0,0288	HELD_FEM_BAD	85	48	34	3	HELD_FEM_GOOD	80	32	40	8
11073	0,0644	0,0172	HELD_FEM_BAD	83	17	39	27	HELD_FEM_GOOD	82	9	33	40
1056	0,0472	0,0613	HELD_FEM_BAD	83	33	36	14	HELD_FEM_GOOD	81	39	38	4
5245	0,0698	0,0601	CVD_ALL_CASE	96	2	41	53	CVD_ALL_CTRL	68	6	33	29
8241	0,0113	0,0082	HELD_FEM_BAD	81	64	17	0	HELD_FEM_GOOD	81	51	26	4
5093	0,0357	0,0667	CVD_ALL_CASE	90	23	33	34	CVD_ALL_CTRL	72	7	34	31
8480	0,0014	0	CVD_ALL_CASE	86	71	10	5	CVD_ALL_CTRL	74	73	1	0
1275	0,0105	0,0004	CVD_ALL_CASE	81	27	23	31	CVD_ALL_CTRL	34	21	8	5
118	0,0462	0,0509	CVD_MAL_CASE	70	51	19	0	CVD_MAL_CTRL	34	19	13	2
738	0,0062	0,001	CVD_MAL_CASE	69	17	32	20	CVD_MAL_CTRL	34	17	15	2
8148	0,0126	0,182	CVD_MAL_CASE	69	17	42	10	CVD_MAL_CTRL	34	9	12	13

BAYSNP	GTYPEP	APVAL	COHORT A	SIZEA	FQ11A	FQ12A	FQ22A	COHORT B	SIZEB	FQ11B	FQ12B	FQ22B
1657	0,0382	0,8798	CVD_MAL_CASE	70	22	39	9	CVD_MAL_CTRL	33	14	10	9
533	0,0095	0,0038	CVD_MAL_CASE	68	3	27	38	CVD_MAL_CTRL	34	0	5	29
11462	0,0488	0,06	CVD_MAL_CASE	68	53	15	0	CVD_MAL_CTRL	34	32	2	0
5717	0,0245	0,0646	CVD_MAL_CASE	67	3	40	24	CVD_MAL_CTRL	33	7	18	8
1669	0,0068	0,236	CVD_MAL_CASE	64	4	11	49	CVD_MAL_CTRL	34	0	15	19
2376	0,0473	0,0511	CVD_MAL_CASE	69	66	3	0	CVD_MAL_CTRL	29	24	5	0
11558	0,0168	0,084	HELD_ALL_CASE	49	42	5	2	HELD_ALL_CTRL	43	28	14	1
10785	0,0344	0,0442	HELD_ALL_CASE	49	0	5	44	HELD_ALL_CTRL	43	0	12	31
2085	0,0518	0,0503	HELD_ALL_CASE	49	19	27	3	HELD_ALL_CTRL	43	11	22	10
614	0,0045	0,0083	HELD_ALL_CASE	48	9	17	22	HELD_ALL_CTRL	43	6	4	33
11248	0,0089	0,0351	HELD_ALL_CASE	48	30	18	0	HELD_ALL_CTRL	43	15	28	0
6396	0,0309	0,0387	HELD_ALL_CASE	49	1	5	43	HELD_ALL_CTRL	42	1	13	28
9940	0,0337	0,0419	HELD_ALL_CASE	48	42	5	1	HELD_ALL_CTRL	43	29	13	1
2353	0,0065	0,1234	HELD_ALL_CASE	49	43	3	3	HELD_ALL_CTRL	41	28	12	1
52	0,0207	0,0039	HELD_ALL_CASE	48	13	22	13	HELD_ALL_CTRL	42	23	14	5
1757	0,0223	0,5028	HELD_ALL_CASE	49	7	16	26	HELD_ALL_CTRL	40	0	20	20
1524	0,0509	0,0235	HELD_ALL_CASE	48	1	15	32	HELD_ALL_CTRL	41	6	15	20
4912	0,0153	0,0285	CVD_MAL_CASE	58	3	25	30	CVD_MAL_CTRL	30	8	10	12
6957	0,0613	0,0218	HELD_ALL_CASE	45	5	20	20	HELD_ALL_CTRL	43	11	22	10

BAYSNP	GTYPEP	APVAL	COHORT A	SIZEA	FQ11A	FQ12A	FQ22A	COHORT B	SIZEB	FQ11B	FQ12B	FQ22B
8816	0,0418	0,0055	CVD_MAL_CASE	60	9	16	35	CVD_MAL_CTRL	27	1	3	23
1062	0,0465	0,0345	CVD_MAL_CASE	56	0	10	46	CVD_MAL_CTRL	31	1	11	19
2463	0,0187	0,0217	HELD_ALL_CASE	49	0	8	41	HELD_ALL_CTRL	37	0	0	37
4527	0,001	0,4255	CVD_MAL_CASE	51	0	23	28	CVD_MAL_CTRL	25	5	5	15
11531	0,0345	0,0622	CVD_FEM_CASE	36	0	18	18	CVD_FEM_CTRL	39	0	10	29
11536	0,0455	0,0272	CVD_FEM_CASE	35	20	13	2	CVD_FEM_CTRL	40	32	8	0
10811	0,0515	0,0354	CVD_FEM_CASE	34	21	11	2	CVD_FEM_CTRL	40	34	5	1
288	0,04	0,0437	CVD_FEM_CASE	33	1	18	14	CVD_FEM_CTRL	39	0	12	27
2371	0,068	0,0432	CVD_FEM_CASE	33	11	19	3	CVD_FEM_CTRL	39	23	15	1
4383	0,0646	0,0594	CVD_FEM_CASE	34	0	9	25	CVD_FEM_CTRL	36	1	17	18
11654	0,009	0,0434	HELD_MAL_BAD	21	1	17	3	HELD_MAL_GOOD	42	2	18	22
11655	0,009	0,0434	HELD_MAL_BAD	21	3	17	1	HELD_MAL_GOOD	42	22	18	2
11450	0,03	0,0046	HELD_MAL_BAD	21	4	9	8	HELD_MAL_GOOD	42	2	10	30
11448	0,0176	0,0076	HELD_MAL_BAD	21	2	9	10	HELD_MAL_GOOD	41	2	5	34
4018	0,0245	0,0071	HELD_MAL_BAD	20	0	6	14	HELD_MAL_GOOD	42	6	21	15
2217	0,0124	0,0211	HELD_MAL_BAD	21	11	10	0	HELD_MAL_GOOD	40	34	6	0
2321	0,0278	0,0335	HELD_MAL_BAD	20	14	6	0	HELD_MAL_GOOD	41	38	3	0
4966	0,0158	0,0114	HELD_MAL_BAD	20	0	11	9	HELD_MAL_GOOD	40	9	24	7
2284	0,0416	0,0114	HELD_MAL_BAD	17	0	2	15	HELD_MAL_GOOD	41	3	16	22

BAYSNP	GTYPE P	A PVAL	COHORT A	SIZE A	FQ11 A	FQ12 A	FQ22 A	COHORT B	SIZE B	FQ11 B	FQ12 B	FQ22 B
57	0,0065	0,0063	HELD_FEM_CASE	33	16	16	1	HELD_FEM_CTRL	23	20	3	0
11614	0,0531	0,0634	HELD_FEM_CASE	33	0	10	23	HELD_FEM_CTRL	23	4	6	13
11645	0,0533	0,0623	HELD_FEM_CASE	33	0	2	31	HELD_FEM_CTRL	23	0	6	17
384	0,0618	0,0212	HELD_FEM_CASE	33	13	15	5	HELD_FEM_CTRL	23	3	12	8
542	0,0003	0,0001	HELD_MAL_CASE	16	2	8	6	HELD_MAL_CTRL	20	0	1	19
2290	0,0298	0,0007	HELD_MAL_CASE	16	10	0	6	HELD_MAL_CTRL	20	19	0	1
2093	0,0301	0,0043	HELD_MAL_CASE	16	9	1	6	HELD_MAL_CTRL	20	18	0	2
11585	0,0533	0,0508	HELD_MAL_CASE	16	8	8	0	HELD_MAL_CTRL	20	6	8	6

Table 6: **Correlation of genotypes of CA SNPs to relative risk**

For diagnostic conclusions to be drawn from genotyping a particular patient we calculated the relative risk RR1, RR2, RR3 for the three possible genotypes of each SNP. Given the genotype frequencies as

	gtype1	gtype2	gtype3
case	N11	N12	N13
control	N21	N22	N23

we calculate

$$RR1 = \frac{N11}{N21} \Big/ \frac{N12 + N13}{N22 + N23}$$

$$RR2 = \frac{N12}{N22} \Big/ \frac{N11 + N13}{N21 + N23}$$

$$RR3 = \frac{N13}{N23} \Big/ \frac{N11 + N12}{N21 + N22}$$

Here, the *case* and *control* populations represent any case-control-group pair, or bad(case)-good(control)-group pair, respectively. A value RR1>1, RR2>1, and RR3>1 indicates an increased risk for individuals carrying genotype 1, genotype 2, and genotype 3, respectively. For example, RR1=3 indicates a 3-fold risk of an individual carrying genotype 1 as compared to individuals carrying genotype 2 or 3 (a detailed description of relative risk calculation and statistics can be found in (Biostatistics, L. D. Fisher and G. van Belle, Wiley Interscience 1993)). The baySNP number refers to an internal numbering of the CA SNPs and can be found in the sequence listing.

BAYSNP	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3	FREQ1_A	FREQ2_A	FREQ3_A	FREQ1_B	FREQ2_B	FREQ3_B
52	CC	CG	GG	0,56	1,27	1,49	13	22	13	23	14	5
57	CC	CT	TT	0,52	1,83	1,72	16	16	1	20	3	0
118	CC	CT	TT	1,3	0,84	0	51	19	0	19	13	2
152	AA	AG	GG	1,19	1	0,51	59	37	5	34	26	11
288	CC	CG	GG	2,22	1,68	0,56	1	18	14	0	12	27
384	CC	CG	GG	1,63	0,9	0,59	13	15	5	3	12	8
533	AA	AG	GG	1,52	1,44	0,66	3	27	38	0	5	29
542	AA	AG	GG	2,43	3	0,26	2	8	6	0	1	19
555	AA	AG	GG	1,39	0,68	1,13	48	40	15	40	70	15
608	AA	AG	GG	0,3	0,9	1,38	2	21	80	9	18	46
614	AA	AG	GG	1,17	1,83	0,55	9	17	22	6	4	33
738	AA	AC	CC	0,66	1,03	1,5	17	32	20	17	15	2
777	CC	CT	TT	0,73	1,26	1,67	68	31	6	96	26	2
1056	AA	AG	GG	0,84	0,93	1,65	33	36	14	39	38	4
1062	AA	AG	GG	0	0,68	1,56	0	10	46	1	11	19
1275	CC	CG	GG	0,7	1,07	1,36	27	23	31	21	8	5
1524	AA	AC	CC	0,25	0,89	1,42	1	15	32	6	15	20
1574	CC	CT	TT	1,74	0,69	1,33	3	20	80	0	26	48
1583	CC	CT	TT	1,03	0,66	1,45	3	20	81	2	27	45
1657	CC	CT	TT	0,85	1,39	0,7	22	39	9	14	10	9
1669	CC	CT	TT	1,57	0,57	1,44	4	11	49	0	15	19
1722	CC	CT	TT	1,19	0,68	1,27	22	29	44	12	37	24
1755	AA	AG	GG	1,15	0,69	1,44	48	33	19	28	38	5
1757	AA	AG	GG	1,95	0,71	1,06	7	16	26	0	20	20
1765	AA	AG	GG	1,43	0,71	1,25	6	21	79	3	37	78

BAYSNP	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3	FREQ1 A	FREQ2 A	FREQ3 A	FREQ1 B	FREQ2 B	FREQ3 B
1837	CC	CT	TT	1,29	0,7	1,21	60	33	13	56	58	11
1862	CC	CT	TT	1,38	0,82	0,51	48	34	3	32	40	8
2000	CC	TT		1,98	0,51	0	101	4	0	65	9	0
2085	GG	GT	TT	1,31	1,08	0,4	19	27	3	11	22	10
2093	CC	CT	TT	0,43	2,33	2,1	9	1	6	18	0	2
2109	AA	AG	GG	1,5	0,7	0,49	64	20	1	48	31	3
2187	CC	CT	TT	1,15	0,71	1,43	50	36	19	29	40	5
2203	CC	CT	TT	1,2	1,54	0,62	6	45	34	4	26	53
2217	GG	GT	TT	0,39	2,56	0	11	10	0	34	6	0
2284	AA	AG	GG	0	0,3	4,26	0	2	15	3	16	22
2290	AA	AG	GG	0,4	0	2,49	10	0	6	19	0	1
2297	CC	CT		4,22	0,24	0	103	1	0	68	6	0
2321	GG	GT	TT	0,4	2,48	0	14	6	0	38	3	0
2353	AA	AG	GG	1,92	0,33	1,4	43	3	3	28	12	1
2354	CC	CT	TT	0,72	1,41	0,86	74	28	1	64	9	1
2371	AA	AC	CC	0,56	1,52	1,7	11	19	3	23	15	1
2376	CC	CT		1,96	0,51	0	66	3	0	24	5	0
2463	CC	CT	TT	0	1,9	0,53	0	8	41	0	0	37
3843	AA	AT	TT	1,43	0,73	0,94	44	34	21	17	37	17
4018	CC	CT	TT	0	0,56	2,66	0	6	14	6	21	15
4383	AA	AG	GG	0	0,61	1,74	0	9	25	1	17	18
4527	AA	AG	GG	0	1,41	0,93	0	23	28	5	5	15
4838	AA	AG	GG	0,75	1,37	0,86	19	58	25	21	26	22
4887	AA	AC	CC	0	0,36	3,1	0	3	13	1	11	8
4912	AA	AG	GG	0,38	1,15	1,17	3	25	30	8	10	12
4966	AA	AG	GG	0	0,87	2,25	0	11	9	9	24	7
5019	AA	AT	TT	1,25	1,24	0,6	31	40	21	27	37	45

BAYSNP_ID	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3	FREQ1_A	FREQ2_A	FREQ3_A	FREQ1_B	FREQ2_B	FREQ3_B
5093	AA	AG	GG	1,51	0,82	0,91	23	33	34	7	34	31
5245	AA	AG	GG	0,41	0,91	1,23	2	41	53	6	33	29
5320	AA	AG	GG	1,17	1,16	0,66	35	48	18	19	28	25
5564	GG	GT	TT	0,55	1,45	1,05	14	76	14	25	40	9
5717	AA	AG	GG	0,42	1,07	1,19	3	40	24	7	18	8
6396	CC	CT	TT	0,93	0,46	2,02	1	5	43	1	13	28
6734	AA	AC		0,67	1,48	0	87	15	0	68	3	0
6957	CC	CT	TT	0,56	0,88	1,55	5	20	20	11	22	10
7363	AA	AG	GG	1,62	1,23	0,73	8	44	55	3	40	82
8138	CC	CT	TT	0,88	0,76	1,47	21	39	40	31	63	30
8148	AA	AG	GG	0,97	1,41	0,59	17	42	10	9	12	13
8168	AA	AC	CC	1,34	0,59	1,5	4	15	65	2	30	51
8241	AA	AG	GG	1,54	0,74	0	64	17	0	51	26	4
8480	CC	CG	GG	0,53	1,78	1,91	71	10	5	73	1	0
8816	CC	CG	GG	1,36	1,3	0,7	9	16	35	1	3	23
9940	CC	CT	TT	1,97	0,47	0,95	42	5	1	29	13	1
10388	AA	AG	GG	0,58	1,13	1,17	11	61	32	19	38	17
10749	CC	CG	GG	1,37	0,84	0,59	48	33	5	33	39	11
10785	CC	CT	TT	0	0,5	1,99	0	5	44	0	12	31
10811	AA	AG	GG	0,56	1,73	1,48	21	11	2	34	5	1
10830	AA	AG	GG	0,68	0,96	1,47	22	47	36	42	58	24
10948	GG	GT	TT	0,62	1,28	1,2	23	60	24	48	56	21
11000	CC	CT	TT	0,41	1,4	0,86	3	38	63	9	14	51
11001	CC	CT	TT	0,41	1,33	0,9	3	38	62	9	16	49
11073	CC	CG	GG	1,38	1,14	0,71	17	39	27	9	33	40
11248	CC	CT		1,7	0,59	0	30	18	0	15	28	0
11377	CC	CT	TT	0,59	1,21	1,09	12	62	33	29	61	34

BAYSNP	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3	FREQ1 A	FREQ2 A	FREQ3 A	FREQ1 B	FREQ2 B	FREQ3 B
11448	AA	AG	GG	1,53	2,57	0,37	2	9	10	2	5	34
11450	AA	AT	TT	2,24	1,74	0,4	4	9	8	2	10	30
11456	AA	AG	GG	0,62	1,7	0	81	18	0	71	2	1
11462	GG	GT	TT	0,74	1,35	0	53	16	0	32	3	0
11531	AA	AG	GG	0	1,68	0,6	0	18	18	0	10	29
11536	CC	CG	GG	0,59	1,52	2,21	20	13	2	32	8	0
11558	AA	AC	CC	1,89	0,44	1,26	42	5	2	28	14	1
11585	GG	GT	TT	1,57	1,25	0	8	8	0	6	8	6
11614	CC	CT	TT	0	1,09	1,28	0	10	23	4	6	13
11637	AA	AC	CC	0,81	0,94	1,88	38	31	13	47	34	2
11645	AA	AG	GG	0	0,39	2,58	0	2	31	0	6	17
11652	CC	CT	TT	0,72	1,43	0,86	24	59	21	43	50	31
11654	AA	AG	GG	1	3,4	0,25	1	17	3	2	18	22
11655	AA	AC	CC	0,25	3,4	1	3	17	1	22	18	2

Claims

1. An isolated polynucleotide encoded by a cardiovascular associated (CA) gene; the polynucleotide is selected from the group comprising

SEQ ID 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 with allelic variation as indicated in the sequences section contained in a functional surrounding like full length cDNA for CA gene polypeptide and with or without the CA gene promoter sequence.

2. An expression vector containing one or more of the polynucleotides of claim 1.

3. A host cell containing the expression vector of claim 2.

4. A substantially purified CA gene polypeptide encoded by a polynucleotide of claim 1.

5. A method for producing a CA gene polypeptide, wherein the method comprises the following steps:

   a) culturing the host cell of claim 3 under conditions suitable for the expression of the CA gene polypeptide; and

   b) recovering the CA gene polypeptide from the host cell culture.

6. A method for the detection of a polynucleotide of claim 1 or a CA gene polypeptide of claim 4 comprising the steps of:

contacting a biological sample with a reagent which specifically interacts with the polynucleotide or the CA gene polypeptide.

7. A method of screening for agents which regulate the activity of a CA gene comprising the steps of:

contacting a test compound with a CA gene polypeptide encoded by any polynucleotide of claim 1; and detecting CA gene activity of the polypeptide, wherein a test compound which increases the CA gene polypeptide activity is identified as a potential therapeutic agent for increasing the activity of the CA gene polypeptide and wherein a test compound which decreases the CA activity of the polypeptide is identified as a potential therapeutic agent for decreasing the activity of the CA gene polypeptide.

8. A reagent that modulates the activity of a CA polypeptide or a polynucleotide wherein said reagent is identified by the method of the claim 7.

9. A pharmaceutical composition, comprising:
the expression vector of claim 2 or the reagent of claim 8 and a pharmaceutically acceptable carrier.

10. Use of the reagent according to claim 8 for the preparation of a medicament.

11. A method for determining whether a human subject has, or is at risk of developing a cardiovascular disease, comprising determining the identity of nucleotide variations as indicated in the sequences section of SEQ ID 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47,

48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 of the CA gene locus of the subject; whereas a "risk" genotype has a risk ratio of greater than 1 as can be seen from table 6.

12. A kit for assessing cardiovascular status, said kit comprising

a) sequence determination primers and

b) sequence determination reagents,

wherein said primers are selected from the group comprising primers that hybridize to polymorphic positions in human CA genes according to claim 1; and primers that hybridize immediately adjacent to polymorphic positions in human CA genes according to claim 1.

13. A kit as defined in claims 12 detecting a combination of two or more, up to all, polymorphic sites selected from the groups of sequences as defined in claim 1.

14. A kit for assessing cardiovascular status, said kit comprising one or more antibodies specific for a polymorphic position defined in claim 1 within the human CA gene polypeptides and combinations of any of the foregoing.

SEQUENCE LISTING

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<120> Single Nucleotide Polymorphisms predicting Cardiovascular Disease and Medication Efficacy

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<170> PatentIn version 3.1

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<223> BaySNP 5564, G1050T

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<222> (286)..(286)

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<211> 555

<212> DNA

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<222> (321)..(321)

<223> BaySNP 4856, A321G

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<223> BaySNP 1574, C412T

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<222> (194)..(194)

<223> BaySNP 2353, A194G

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<211> 652

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<213> Homo Sapiens

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<221> variation

<222> (182)..(182)

<223> BaySNP 608, A182G

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<211> 641

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (348)..(348)

<223> baySNP: 11456, A348G

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<211> 3350

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (274)..(274)

<223> BaySNP: 6734, A274C

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<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (152)..(152)

<223> BaySNP:152, A587G

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<211> 574

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (390)..(390)

<223> BaySNP:1755, A390G

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<210> 25

<211> 801

<212> DNA

<213> Homo Sapiens

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<222> (583)..(583)

<223> BaySNP:4838, A583G

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gagactgaag ctttcaaatg accctagttc caatatagac actttcttca gtttatcagt 720

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<222> (319)..(319)

<223> BaySNP3843. A319T

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tgccccactg cactccaacc tgggggacag agtgagaccc tgtctcaaaa attaaaatac 240

tacttaggct acattgtggg gggggtggta agtctatgga ttttgatttc ctttttgctg 300

ttttctattt ttggtaacwt gtttatgtaa cttcattttt taaaaaattg ctacattcaa 360

aatttccccc aaaaaagaaa cttcatatac aagttagttc atatacaagt tagaaaatga 420

aattttaaaa taccccataa gacacatcaa agaataattc tttaaaaatg gtaccagaac 480

cctacagaga atgtaaggta ccaaaggatg ttaaagacct aaatagatca cattcatggg 540

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accggggcca cagagaaacc cacacaagcc ccagacacgt ggacaagaat actcagagca 780

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<211> 615

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<222> (288)..(288)

<223> BaySNP10749, C288G

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aggttctgat tagggaaaga gaagctctct gaattgttga ctctctcttt ccataaatga 540

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<211> 1302

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (745)..(745)

<223> BaySNP 2203, C745T

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gggtccatgg gcagagccca agggaattcg gtgtgcacca gggttgaccc cagaggattg 180

ctgccccatc agtgctccct cacatgtcag taccttcaaa ctagggccaa gcccagcact 240

gcttgaggaa aacaagcatt cacaacttgt ttttggtttt taaaacccag tccacaaaat 300

aaccaatcct ggacatgaag attctttccc aattcacatc taacctcatc ttcttcacca 360

tttggcaatg ccatcatctc ctgccttcct cctgggccct ctctgctctg cgtgtcacct 420

gtgcttcggg cccttcccac aggacatttc tctaagagaa caatgtgcta tgtgaagagt 480

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atctgtaggg taattagtaa catgtgttaa gtattttcat aagtatttca aattggagct 840

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<210> 29

<211> 813

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (89)..(89)

<223> BaySNP 1722, C89T

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ggactgcggg acaggttccc atcatctcct gtgttagccc attccacctg ggaaaccaag 180

cgactgccgt ggctggctta tttctccctc tgccaacccc catctacaat gttctgggga 240

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aggcagctaa gtccaccaac agagcgtggg agagtctttc atccaaaaat cccaacacgt 360

cgcatgcagc gacaggaggc tgtgctgggg aaacccaagg cctggctcag cctccatact 420

ctaagggcct cgggccagaa cgaccacgag aggggagcac ccaaaggcac gcagaggggc 480

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cccgcaggtg cagcccagct tctgcacatc agatggagtg acgctgacta aaggacctgg 660

acagcgccgg cagatactcc caacactgtc cttctctttg ggagccaaag agaagccacg 720

cagatactcc caacactgtc ctttttttg ggagccaaaa gaaaaccccg gccaggcagc 780

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<211> 688

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (639)..(639)

<223> BaySNP:576, C639T

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tcaaataagt tcttagaacc acagagtcta gggccagggt cccaactcat aggtgacgga 240

gttcccttca agccacagat tctgtttttt ttgtgtgtgt gtgtgttttt ttttttttt 300

atcagagtcc catacctcac gggtattttc tcaatcagtg aacacctcaa gtactagccc 360

atgtgttttg agtaaaaagg gctcctttca acgaggatcc ccttctagag gctttgacta 420

accagtctct tggcaccctt agaatgaagt tgagagcgtc acagggatgc ttaacgaggc 480

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cacccaggtg agtgtcctgc cacatcatcc aggggacctg gggggtggcc ttcctcgggg 600

caggtccctg ggacctcttt gcatcccttt tgcaggagyt gcttcaagaa gaaacccggc 660

agaagctcaa cgtgtctacg aagctgcg 688

<210> 31

<211> 455

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (337)..(337)

<223> baySNP: 8168, A337C

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gaggtaggca tccgtggggg ggcgccggct cgggcgtgcg gggagtgtcc gcttctgcta 180

tctgcctctc caaatatccc gactgctgcc ctggccccag ccctctctcc acttcggagc 240

actcctctgg cgttggcacc gctgaggaat gggcctgggc ggggaggtga agagaagcca 300

ggaatgtttt atgttttcct aatggagagg gggcctmggg agcccctgag ctaggaggac 360

acggaaaagg ggattggggt cctgagattg ggtctgttgg gcccaggacg cgttttctgg 420

atgggtctag gatgctcccc tgtcgcggga ccccc 455

<210> 32

<211> 650

<212> DNA

<213> Homo Sapiens

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<223> n=Unsure

<220>

<221> variation

<222> (543)..(543)

<223> BaySNP:2109, A543G

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<221> misc_feature

<222> (22)..(22)

<223> n=Unsure

<220>

<221> misc_feature

<222> (97)..(97)

<223> n=Unsure

<400> 32

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ttaggggcct gtaaaaccta cataaagaaa atgggcttaa gcagtgaagt ccaagggaaa 180

atactgccag ggaactggga gatkgactgt tcctcattcc cagccttctg gttccactga 240

gcctagcctc tttctgacat gcagatgaca ctgaaacaca attaagcaga aatacaggct 300

ggagaggctg aatgcaccag ggtagcagtg gcaaccagct gtcaactctt attaacttct 360

gcataaaaca taccttgagt gcggtttgtt atcaattact tgccgaaaag aaacaactgg 420

ggcaaggcaa gaccgccgct catatgaatt agagtgattg gttgattgat cagggcacct 480

gttgtaaatc ataactgttc caaacaatca ctagccggtg ctttaatttg taaacaaaat 540

tcrtgtcact gcagaattgc tttcactgaa gatgagcatt tgggttcctt tctaaatgaa 600

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<210> 33

<211> 600

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (162)..(162)

<223> baySNP: 11637, A162C

<400> 33

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ctgcctaagg aagcttcttg taaggtccaa aaactaaaaa gmctgttaat aaaagaaact 180

ttcagtcaga ataagtctgt aagtttttt ttttcttttt aattgtaaat ggttctttgt 240

cagtttagta aaccagtgaa atgttgaaat gttttgacat gtactggtca aacttcagac 300

cttaaaatat tgctgtatag ctatgctata ggtttttcc tttgttttgg tatatgtaac 360

catacctata ttattaaaat agatggatat agaagccagc ataattgaaa acacatctgc 420

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<210> 34

<211> 518

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (109)..(109)

<223> BaySNP:1862, C109T

<400> 34

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cggccccacc cacgaggagg acagtcatga ggccgactgt ggaggggctc tggacagagg 360

tgtccgggga tccctgagcc tggctgcact ctccctcctg gttctttcct tgcgtgcaca 420

cgatcagcta tcgtttacaa agagtccttg gtgttgcctg gttggctgcc caggatggga 480

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<210> 35

<211> 1051

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (215)..(215)

<223> BaySNP:11073, C215G

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gcgcctcagc tgtctagagt ccccccaccc ccccctcccc aaccacccgt tccggagcaa 180

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aagatggtgt acacgcagcc ccgagcacag acccgaagct gtccaccctt cttgggcgcc 840

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gcaggtgcca cggccacaca cctcgcgacc caaagggcag agacacaagc acgctaccac 1020

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<211> 668

<212> DNA

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<222> (354)..(354)

<223> BaySNP:1056, A354G

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gtctatgtgt ctgtgtgtat gcacgtgcgt gatctgcccc ctgcagccaa acarcaggac 360

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aggaagaagg ccagcatgca caagaaggag aagtccgtgc tgcagggcaa gctcaccaag 480

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cacaggggga ccccaggcag agccctgccc catgctcggc ctcagttacc tcatctgcaa 600

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<211> 555

<212> DNA

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<222> (173)..(173)

<223> BaySNP:5245, A173G

<400> 37

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ggagatggag atcactgggg gctgcttaga tgctgcctac cacaggctac atrgctattc 180

ttttacaatc ttgattttta acttacagca acttgtactg gacagactgg aatagagaag 240

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acattggatt gcccaatggc ttaacctttg acccttctc taaactgctc tgctgggcag 360

atgcaggtaa tactactgat ggaatgcaaa tagataacct ctcatcacag tgaatgtgag 420

cactaacaga ttttactaca aaatgaaatc ccatcactta gatctccttt ctttggtctg 480

taaactttta agtactagta aatttaagta ctagtaaatg agtcttaaaa tgaactttct 540

ggggtttggg tggag 555

<210> 38

<211> 549

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (464)..(464)

<223> baySNP: 8241, A464G

<400> 38

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aacttgctga aaaacacaac ttgtgtttat ggcatttagt accttcaaat aattggcttt 180

gcagatattg gataccccat taaatctgac agtctcaaat ttttcatctc ttcaatcact 240

agtcaagaaa aatataaaaa caacaaatac ttccatatgg agcatttttc agagttttct 300

aacccagtct tatttttcta gtcagtaaac atttgtaaaa atactgtttc actaatactt 360

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agtgatcttt caatatcatt actaacttct tccacttttt ccaraatttg aatattaacg 480

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<212> DNA

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<222> (71)..(71)

<223> BaySNP:8480, C71G

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<212> DNA

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<222> (675)..(675)

<223> BaySNP:118 , C675T

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caataaataa tttatttagt taaaatatta aactaccttc aggctattta agatgaatat 360

gaaacatgaa tgaatttcat gtttagactg ggtcccatcc ccaagatatc tctctctctg 420

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tctcccacac acttaaatac tatgtacaac atattaatat atgctatatc tttaaagttg 600

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aagtacacat attgatgaga ttcaatgcta tcccatccca tccctctact tcccctatgc 840

cccttaataa tattagagaa aaccaatata tttggtatca gcaattaaaa attctttttg 900

agagatgact aatatacaac aattttatcc caacacaagt ctaagcatga caaatcacaa 960

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<210> 41

<211> 739

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<213> Homo Sapiens

<220>

<221> variation

<222> (120)..(120)

<223> BaySNP:738, A120C

<400> 41

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acattcctct tcacctcaga gttggtgggg gaaggcccac ccagataaga tctgtgacca 180

gatcagtgag gctgtccttg atgcccacct tcaacaaaat cctgatgcca aagtagcttg 240

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tgttgactaa cagaaaatgc ttcgtgaagc tattaaacac attggatatg atgattcttc 360

caaagggttt gactacaaga cttgtaatgt gctggtagcc ttggagcaac agtcaccaga 420

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tcttagcata caagcttaaa gccaaactgg cagaactacg ccataatggc actttgccct 600

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<211> 3350

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (3116)..(3116)

<223> BaySNP:8148, C3116T

<400> 42

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attaaggaat gttgtagagg gaacagataa tagtagtaca tgtatgtgat tcaggtgctt 240

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caaattcagt aaataaagct ttaagatagt aaaataagat tgcaaattct ttcagatcca 360

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<211> 479

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<213> Homo Sapiens

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<222> (263)..(263)

<223> BaySNP:1657, A263G

<400> 43

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aagatctcta ccaagcctcc tagaacattt caaaaaccaa aaacttgcca agaatatggt 180

gaaaaccatc aaggaagtca taacctttag attgaacatg ctgaattatc gcctcctggg 240

gacagctgcc agtcagagtt gargcaccaa gaagcagagc cacaccagac ccagagggtg 300

cagacagcag agtatttctg ctctgccagg ctcagtgagt cacgcatttg gcctcctcca 360

ctaagatcat gtattctacc agatttcgat tcatggagtc caaagatgaa tgaatcaaac 420

actgcttaag ggcaatgtat acattgggat tcctccccac ctcttcccta aggtgttag 479

<210> 44

<211> 637

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (289)..(289)

<223> BaySNP:533, A289G

<400> 44

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cattgtccct tctcttccca ccacccccca gtccctcctg gagacgcacg actctgtggc 240

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gcctgtacct cccgatgctg tgcgcatggt gggcatccgc aagacagccg gagaacatct 360

ggtgaggact gggcagggcc agaggtggtg ctggtgaggg tgggggatt gagaataacc 420

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agggaaggat tgatgcagca aagggtcggg ggaagaccca ggagaccata gacactgcac 540

acacacctgt gtccgcacct ctccagtctg cccacctctc ccctcattag tacctgctgt 600

aagtgaagaa tttaggcaga aggatggagg aggactt 637

<210> 45

<211> 626

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (452)..(452)

<223> baySNP: 11462, G452T

<400> 45
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ctgagctgca ggaggtgcgc tcgctttcct caacaggtgg cggcggggcg cgcgccggga 240

gacccccccc aatgcgggaa aagcacgtgt ccgcatttta gagaaggcaa ggccggtgtg 300

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gaaatcctgc ggtgagaaac cagtcgtgtt gagaacaata aaagaccaaa aaacgatcac 420

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<210> 46

<211> 2246

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (1960)..(1960)

<223> BaySNP:5717, A1960G

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aaggcatcaa ggttataagc attctctttt ttcttttggg tagactgaag ctcagagagg 180

ttgagtggct tacttaaagc tgcacagcta ttagtaggca gatcaagatt agagttcaga 240

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tctgccggcc aggtgggagg tgctgtctgc aaagggcttc cctttctctt tggccactat 360

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<211> 472

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (302)..(302)

<223> BaySNP:2376, C302T

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tgttttggac acataagtct ccttctccca gtcttacctc catccagttg ataaaccggg 300

cyacatcctg tcccaccagt ttggtgtagc ccgcggacac tgggtaatgc tcctgagccc 360

gtgacagcca gtccaccaca atgacattgg agtctggttc tctcttgtac agggcggcca 420

caagttttgg cacccaactc tcatacattc ctgttacctg aagatgatga ca 472

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<211> 590

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (377)..(377)

<223> baySNP: 11558, A377C

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cctgggcgac agagtgagac tctgtctcaa aaaaaaaaaa aattatgaaa aaagttatgg 240

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aagtggggcc ggaggctccg cccccatcat gtgcctgcca ccccttccca gtcatccctt 360

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<210> 49

<211> 603

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (113)..(113)

<223> baySNP: 10785, C113T

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gtaaaatcct tctagattta tctgatttcc cctccctaca gtctttttat tgctgatctt 240

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<211> 503

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (415)..(415)

<223> BaySNP:2085, G415T

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<211> 385

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (211)..(211)

<223> BaySNP:614, C211T

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<210> 52

<211> 455

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (199)..(199)

<223> baySNP: 6396, C199T

<400> 52
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agtgagttag agcattatca atgcaccagt aaaagatttt gtattagaat cccagttttc 420

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<210> 53

<211> 618

<212> DNA

<213> Homo Sapiens

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<222> (93)..(93)

<223> baySNP: 9940, C93T

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<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (194)..(194)

<223> BaySNP 2353, A194G

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<211> 606

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (175)..(175)

<223> BaySNP52, C175T

<400> 55

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tgagggatga ttgcaccact gcactccagc ctgggcaaca gagtgagacc ctgtytctaa 180

aaamaaaaaa aaattattaa aaaaaaaaaa gttttcttaa gagtccagac ttgtgaattg 240

ccagattagt gtaattttta aaatatgttt ctattataaa ttacccatac tcataaaaat 300

ataaatcaat ttattacacc ctctagaatt cactattaat tttcaacatt tttttcattc 360

tttttccatg catatttttt cacaattcta tgcatasttt tgcattataa aatatttctc 420

aatataaaat cttcttcaag gccaggcgca gtggctcatg cctgcaatcc cagcacttta 480

gaaggccaag gcgagcagat cacttgaggt cangaattca agaccagcct gaccaacatg 540

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<212> DNA

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<222> (210)..(210)

<223> BaySNP:1757, A210G

<400> 56

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cttgtccctc ccagcaggtc ccgggacagg gctggcagcc accccagcac ccaaaataag 180

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acgtggatgg aagaggcgag ggcaaaagga agagatgagg ggcatggaga gagactcagg 360

gaagaaggag aaagagcaat catgcagctt gggacaaatc ttttgttgct ttatcagatt 420

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<211> 663

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<213> Homo Sapiens

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<222> (284)..(284)

<223> BaySNP1524, A284C

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cgacagagcg agactctgtc tcaaaaaaaa aaaaaaaaaa aaaaaaaaaa agaaaagaaa 180

agaaaaagaa aaagaaaagg aaaaagaaaa ccagaagtag gagcagcctg aagaaatgac 240

agggagttga tttcccactg ggagccctct caaagcccac acamccgcct gcctggggta 300

acagtatctc ctcggacatc ctgcaccctc ccaygctccc ccctccctac agtagtgaaa 360

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ggaggtgggg acagagggaa gaaagaaaaa aaaaaaagag agagaggcag gaaaagtttt 540

ttcagaggaa aatgcagggt ttgtccttca ccctgacgtc agatcttgct ttataaaaac 600

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<211> 921

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (133)..(133)

<223> baySNP: 4912, C133G

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<211> 3051

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (368)..(368)

<223> BaySNP:6957
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gggacaagca gatccaggaa aacaaaaccg ggatatgaaa tcccagcccc ggggtctggc 240

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gagtgygtaa gtctaacaag gtgggcccas gctgacaggt tggacacaga gccagacttg 360

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<213> Homo Sapiens

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acatctaagg ttgggggagg tgcaaccttc tgctattcag cccctctgct ccaagcggaa 180

sctttttct caggaggtaa tctctaataa caagcagagt gccctctgga gcctcctcgc 240

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caatcccaac acacagccag tcaacgagcc tctggcccct tcctctgggt cctgatacag 360

agctggcagc gagggcctct gaagaggtta cagggagccc aagggagtgt caggtagagg 420

cagcaccagg tcccggaggg acagatgagg gatccctagt aaacagctcg tggacgcact 480

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<210> 61

<211> 833

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (166)..(166)

<223> BaySNP:1062, A166G

<400> 61

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ggagggaagg aatgaggtcc tgtgcgtttt gacacagaag atcacracga tgcagaagtg 180

tgtgatctct gagcacatgc aggtcgagga gaagtgtggt ggcatcgtgg gcatccagac 240

caagacggtg caggtgcgtg cagtcgggct gccatgcgtt catggctgag cagtcctgga 300

gaccttggtt gggggcctct ttgggtggtg tcttcattag tcaggactct ttctgtagca 360

agttaacaga aacccaactc acgttgtctt aaatgagcaa gagtgtattg gctcatgtag 420

ctgaaacact tggggaaact ggctccagtc actgctggat ccaggccttg aggatatagg 480

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tgaacacaca gcactgatca ggccaaatgc agaaaatccc tagagccttt caagctgggc 780

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<210> 62

<211> 593

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (479)..(479)

<223> baySNP: 2463, C479T

<400> 62

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cgggctggac aaagacagct tttccccacg tccctctggg ttctctagag caacagcaat 120

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actacaagga cgagttctcg ggcagaggcg acctccccgc gttccatgcg cacagggaca 360

ggggtgagtc cgcgtccctg gcacggagcg gggggtgcat aacacgcccc gggacagtta 420

cgggcgctag ccacgtcggc gatggccaaa taataaacta acagtaatat tatagtaaya 480

gcatccgaag gatgagatca ggattagggc gatggccccc gcgcgttgcc tgcggagcga 540

ggcgcactga gtcgcccagg aatccggcct ctcggcgact gtgcgggaga gtt 593

<210> 63

<211> 634

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (187)..(187)

<223> BaySNP4527, A187G

<400> 63
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aagcatatga tggctttcat tgaataagaa gccaatgaga aagcagaaga aatagatgca 180

aaggcaraag aagagttcaa catagagaaa ggtcagcttg tggaaaccca aagactaaag 240

attatggaat atcatgagaa gaaagagaaa cagattgagt agcagaagaa aattcagata 300

tccaatttga tgaatcaagc aaggctcaaa gtcctcagag cgagagatga ccttatcaca 360

gacctactaa atgaagcaaa acagagactc agcaaggtgg taaaagatac aaccaggtac 420

caagtgctgc tagatggact ggttctccag ggtttgtacc agttgctgga gcaccgaatg 480

attgttcgtt gcaggaaaca agaccttcct ctggtaaagg ctgcggtgca aaaggcaatc 540

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<211> 586

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (274)..(274)

<223> baySNP: 11531, A274G

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agtattattt cagtgcatga agggtgcaca catggaaaaa gagaaaagca tgaggaggag 360

gctcagagcc ctgtgccagc cctgcctctg gggcatctgt aaccacaggg agcacttggc 420

ctatctccct ccatctcttc ttttttcacg atcccatgta tttatccgtg ggaaggaaag 480

cttcgtttct ttttaaagtg attataccgt agatgcagtt ttgtaaaagt gtcaattcca 540

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<210> 65

<211> 721

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (50)..(50)

<223> baySNP: 11536, C50G

<400> 65

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tttgctagga gccccagctt cctgtgtttt taatataaat agtgtacaca gactgacgaa 180

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aaggaggctt tgggctccaa aaccctcccc tgcctccacc tcgctttgct caccgcttgt 360

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caaaggactt gtggtgccct ggcctcacct ggtggagcac ttggggtctg gggaagggga 480

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aagagatcac ggctttcctc tcctttgctg ccacccagct ctctcctgtc tttcctgagt 600

gccatctccc cagcggtcca gtcgagccca gcccccggca gccatgggtt ttgtttgcag 660

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<211> 899

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<213> Homo Sapiens

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<222> (173)..(173)

<223> BaySNP:10811, A173G

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ccttagtaac acttattctt tgtgtataat aacatggaca attgtagtgc cttctccctc 360

tcagcactgt ggctttgcat ccactcaggt ttttgggatt tccttacaca ttttttcata 420

taaactcagg aggttcccaa gggaacacac tccaagaatt agatgaaaaa aactgcagaa 480

aaatccacct cacatgaaaa tctctgtatt taatattttt aaaaaattac cactgtgttt 540

gttgcagctg tgacctctac aagttccaga gactactctc tgacttttgg tgcaatcaac 600

caaacatggt cctaccgcat ccaccagaac atcacttacc aggtgtgcag gcacgccccc 660

agacacccgt ccttccccac cacccagcag ctgaacgtgg accgggtctt tgccttgtat 720

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<210> 67

<211> 2956

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (541)..(541)

<223> BaySNP:288, C541G

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cagcaagccc gcggcaacga ggaagaggag gtggtcggcg ccagagagcc gcaaactgga 240

gaagtcagaa gacgaaccac ctttgactct tcctaagcct tctctaattc ctcaggaggt 300

taagatttgc attgaaggcc ggtctaatgt aggcaagtag aggcagcgtg ggggaaagga 360

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gaacggggct tcacagtgcc tgccttctct agcggcacag aagcagccgg gggcgctgac 660

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<211> 802

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<213> Homo Sapiens

<220>

<221> variation

<222> (72)..(72)

<223> BaySNP:2371, A72C

<400> 68

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<211> 801

<212> DNA

<213> Homo Sapiens

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<222> (343)..(343)

<223> BaySNP:4383, A343G

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cacaaaacct gggactgagg gcccgccgtc ttaatgtcct gtaaattctg gctctcgatt 720

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<211> 501

<212> DNA

<213> Homo Sapiens

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<222> (402)..(402)

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tcaggtgatg aaatctttca tctctttagt ttgtgtactt ttaaccaagg actgcgtatc 180

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<211> 501

<212> DNA

<213> Homo Sapiens

<220>

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<222> (331)..(331)

<223> baySNP: 11655, A331C

<400> 71

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tcaggtgatg aaatctttca tctctttagt ttgtgtactt ttaaccaagg actgcgtatc 180

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tttccatttc catccattta tcttttactt gaaaggacac cgtatttttc acctaatccc 420

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<210> 72

<211> 1004

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (489)..(489)

<223> baySNP: 11450, A489T

<400> 72

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ttgtccaggt gaaaaaattt ttaataaatg ttgtgaactt ctgataacaa tctctatttt 240

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acaacaacaa aaccccacag ctactaaaag atgaagagac attgaattga gaattaagca 360

aaacccttgc aggcagcagg acaggccaga gctgaagaag ctgggagtgg tgaggtgccc 420

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tgtctctgwc ttcaagatta tggtcccaca gtcctctctt tacctcatac gcattgcctg 540

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<210> 73

<211> 1004

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (414)..(414)

<223> baySNP: 11448, A414G

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ttgtccaggt gaaaaaattt ttaataaatg ttgtgaactt ctgataacaa tctctatttt 240

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<210> 74

<211> 1516

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (1137)..(1137)

<223> baySNP: 4018, C1137T

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<211> 662

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (281)..(281)

<223> BaySNP:2217, G281T

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<211> 1025

<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (807)..(807)

<223> baySNP: 4966, A807G

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<210> 77

<211> 1281

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (220)..(220)

<223> BaySNP:2284, A220G

<400> 77

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<212> DNA

<213> Homo Sapiens

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<222> (290)..(290)

<223> BaySNP57, C290T

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<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (1049)..(1049)

<223> BaySNP:11614, C1049T

<400> 79

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agcagcttta ctggctgaac agcagctcgg gttagcccat ccccgtggcc aggtcatttg 900

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ctctctccca ggccttaact ggcctaaata aagtgggtgg cagctgcctt ccagacagat 1140

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<220>

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<222> (89)..(89)

<223> BaySNP:11645, A89G

<400> 80

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atgggggagg atggcacagt ggtcaagagc acagactcta gagactgtca gagctgaccc 180

cagctaaggc atggcaccgc ttctgtcctt tctaggacct cggggtccct ctgggcccag 240

tttccctatc tgtaaattgg ggacagtaaa tgtatggggt cgcagggtgt tgagtgacag 300

gaggctgctt agccacatgg gaggtgctca gtaaaggaga gcaattctta caggtgtctg 360

cctcctgacc cttccatcct tcaggtgtcc tgttgccccc tcctcccact gacaccctcc 420

ggaggccccc atgttgacag accctcttct cctaccttgt ttcccagcct gactctcctt 480

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<211> 846

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (375)..(375)

<223> BaySNP:384, C375G

<400> 81

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tcttctacgt gcccgacatg gtgaggcact gtggcagtcc cacggccctc agggtgactc 540

tgttgtcccc tgtggcatca gctctgcaga tgtcacatga ttaacatggc agtgtgaggg 600

catgaaaaac ataggtagtg ctgggtgtgg tggctcacgc ctgttatccc agcactttgg 660

gaggctgaga ggtggatcac ctgagcccag gagttgcaga ccaggctggc cacatagtga 720

gaccccatct ctgaaaaaaa aaaaaaaaaa catatgcctt tgggtgggga accccagagg 780

ttccttttc tcaggggtca cacatggcga ggaaggattt gatgggatct cattgcagct 840

ggggtg 846

<210> 82

<211> 832

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (402)..(402)

<223> BaySNP:542, A402G

<400> 82

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aaagtgttgc tgacaaggtg aaatacataa tttcactttc tgagtactta agaacagtta 180

gctgttatta tcaagcaaat ttgtatcaag tgttcccaca cattcagcca tgttgctgtg 240

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cagttgttta tctttcgctc catcaaccaa gtcacaattg grgttgggag ggaatttctc 420

aacatgttct gaaagcgtgt catgaacacc atgtcccatg ggtagcccga gtcaaagatt 480

cggctgatca cccatccccc tccggtggtg ctgaggaaca cctggaagca atcaaagaca 540

tcccttcatt tgacactgtg aacacggctg gctggttctg ccagagattc aagaagtgtc 600

atgaatggaa aggcactgaa aagtctgcac tctcaaaata caccccctgac aagatagtct 660

tggttcttct aacttctatt ttaaagttaa tccttttgag attaggattc agagcatcta 720

gagtattaaa atgccttaag acatattatt gatacttatt atctgccagc ctttagtaaa 780

ccatagggac cttaagtcta cgtaagaaac aatgaacagt gattgctact tg 832

<210> 83

<211> 582

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (404)..(404)

<223> BaySNP2290, A404G

<400> 83
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tcggagccaa atgttctttt catgaaggat ttgaaaactg tccatgaaaa taacgcaatc 180

aacctttttag cttgagactc tattcactga ttagattttt ttaaatactg atgggcctgc 240

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caatgagaaa tatcaggtta ctaatttttc ttctattttt ctagtgccat ttccatgtgg 360

aagagtttct gtttcacaaa cttctaagct cacccgtgct gagrctgttt ttcctgatgt 420

ggactatgta aattctactg aagctgaaac cattttggat aacatcactc aaagcaccca 480

atcatttaat gacttcactc gggttgttgg tggagaagat gccaaaccag gtcaattccc 540

ttggcaggta ctttatactg atggtgtgtc aaaactggag ct 582

<210> 84

<211> 549

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (229)..(229)

<223> BaySNP:2093, C229T

<400> 84
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tctgtgttca tggcctggaa agagacttct cccatagcaa agaggctgtt ataaaagcaa 180

taacttttgt gtttgtgtgg gatgatttat ttaatttttt agtttcccyt ttgattgctg 240

agagccattt tcctttacac ataactacac ctgacaccag gctctgctgg atgtgagttt 300

ccactgcatg ggctgtgggc tgggcctgtg gtgcctgccg agtggtcact gtcagtggga 360

aacccgttgt tcctcccgtc ttcagatgct gagccaactg cttggacagc agccagcgcg 420

tcatgacgtg catgagaggg ggaccctggt gctcatcttc tcttgtcatt catccaggca 480

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atgatgttc 549

<210> 85

<211> 590

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (467)..(467)

<223> BaySNP:11585, G467T

<400> 85
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gtgatttgtt atgcagcatt attttgtcaa tagataactg atacaaactc atataaaagg 180

ccccatctgt ttactcgcat attcaggtgt tccaacacaa ccttgtgaaa cacccactct 240

gtaaccaggg atagagcttc agcaaagcct tcgtgaagcc cacagctcag aagagagaga 300

aagattaaga cccaagtgct cactacacgt gattaagtga agagcccagg catagcctat 360

ggcaagagca cacagccaag gcttgagaga tcaaggaagt cttcccggag gaggagtgat 420

caaaatagag gcccgaagaa gaaggggggag aagacagatt gggggtkgca tccaggcagg 480

aacagaagaa gttccgggtg gaaaaaacaa ggataaatgc cgtggctggg tggcggggag 540

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<211> 481

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (266)..(266)

<223> baySNP:777, C266T

<400> 86
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ctgcgaggcc cagctgtctc ggagggccgc tagctctgct ggggcaggcc aggaggatgt 180

aggagcctag agaaggggcc tccgcttccc tgcgcgaggc ccccacagac ccaaaccagc 240

tgcagccggg aactcggatc agagcyggag aggccctgtg gacccccagg acactggtgg 300

tcgccttggg gaggggaggg aggcgggccg ggttttgtcc ctctctctga ggcctgcatt 360

gaggccaggc tgggcccggg gaaggtgacg gtccgcgtct caggcctcgc gaatgagcag 420

caccagagaa aggagcgagc ccctgccagg cggtgacagg tgtactcttc tcagtgccga 480

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<210> 87

<211> 1161

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (349)..(349)

<223> baySNP: 2000, C349T

<400> 87
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tctcttcccc acaacaatat tcatgtgcct agaccaagaa gttattatct cgaactgaca 180

ctgagccaca acccaaacaa cccagctctc cctaagcttc aaactagact acttctccat 240

aatattcatc cctgtagcat tgttcgttac atggtccatc atagaattct cactgtgata 300

tataaactca gacccaaaca ttaatcagtt cttcaaatat ctactcatyt tcctaattac 360

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aggaattata tccttcttgc tcatcagttg atgatacgcc cgagcagatg ccaacacagc 480

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atgatttatc ctacactcca actcatgaga cccacaacaa atagcccttc taaacgctaa 600

tccaagcctc accccactac taggcctcct cctagcagca gcaggcaaat cagcccaatt 660

aggtctccac ccctgactcc cctcagccat agaaggcccc accccagtct cagccctact 720

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aagtcaacta ggactcataa tagttacaat cggcatcaac caaccacacc tagcattcct 960

gcacatctgt acccacgcct tcttcaaagc catactattt atgtgctccg ggtccatcat 1020

ccacaacctt aacaatgaac aagatattcg aaaaatagga ggactactca aaaccatacc 1080

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<210> 88

<211> 598

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (272)..(272)

<223> baySNP: 2297, C272T

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gggcacctgt aatcccagct actcaggagg ctgaggcagg aaaatcgctt gaacccggga 180

ggcagaggtt gcagtaagct gagatggcgc tgttgcactc cagcctgggt ggcagagtga 240

gactccatct caaaaagaaa aagccaatgc ayggcagatt ataatttaag caactgaaaa 300

tttcttccat ctttttcca gttttgcaca tttaaagata cccttattgt cacatgcttt 360

ttaaaaaatg atactcgtat catgcctatt aatttgcatg gttttccagc taaacaaaac 420

ctactcctcc aaagcttaca atacagcctg ttcatggggc agagagccca gcctagtgag 480

cagcctgcag tgtggggcca aacagtgagc tacagaagtg cctcattagg gactcctggt 540

actacagtca aaacaaggga acattttatc atggagcatt gggatattct aggaacaa 598

<210> 89

<211> 640

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (491)..(491)

<223> baySNP:1583, C491T

<400> 89
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ctctgtcccc aggctcaaca agggctttca cttgccattg cagaaggtcc tgttattcaa 360

cagaatattc ctatgggacc tgcactgtca tgggtattaa ccacagattc tgctgcctct 420

gagggatgag aacagagaga aatatattca taatttactt tatgacctag aaggaaactg 480

tcgtgtgtcc yatacattgc catcaacttt gtttcctcat ctcaaataaa gtcctttcag 540

caagttcttt tgtgtttgtg cttttctggt gtttgataat tcaggattct tcagatgcaa 600

aaacaaaaac ccaagtcgta tctcagaaca ctagctcttc 640

<210> 90

<211> 1020

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (773)..(773)

<223> BaySNP 5093, A773G

<400> 90

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gactggggct gggcagctgc acggcagggc cctcaggacc ctggagcctg caccccaccc 180

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<210> 91

<211> 723

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (307)..(307)

<223> baySNP: 1275, C307G

<400> 91

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gggagasagc acccccgac ccccgagaga gagatcgaca gagaagggga caagatgcag 360

tcagagaaac cccaaggtga gcagagggag acagagagag acaggaaggg aacagagagg 420

aatcatggca gaaacagaga atgtgtgaca gagacaatga gactgacaga tggagagtca 480

gagacagaga aggaaaccaa aaccaaaccc accaaggccc aggcccaggc aggccgggga 540

tccaggcagc aggtgcagga gggaccgagg cccaggcaga gggcaggaca ctgctgggcg 600

gtagtccaaa gcacgaagca cgggcagccc aaggagatgg ggcaggagaa cctcacctgc 660

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tgc 723

<210> 92

<211> 903

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (317)..(317)

<223> baySNP:1669, C317T

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<222> (561)..(567)

<223> n: Unsure

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<223> n: Unsure

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<222> (572)..(574)

<223> n: Unsure

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<223> n: Unsure

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<222> (712)..(712)

<223> n: Unsure

<400> 92

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cagtcaccag tgagctcaga tagcagcaag aggctgcggg tagggaaatg ccattcattc 300

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cagcagggac ccagacggac aatgtctgtg ccctcagaga gcttccttcc taggagggca 420

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agggagagag aacggctgat gaagtgggct tctaaatagg gtggccagac caggctgggt 540

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ccttcctaaa aaaccaaaat taactgggcc tggggaccca tgccttgtgt tgcactttct 660

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<212> DNA

<213> Homo Sapiens

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<221> variation

<222> (225)..(225)

<223> baySNP: 11248, C225T

<400> 93

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cttcttgctt gctatagtta gaaaaaaata tatatatatg catctacccg gcgcccaata 180

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cccgctgcca ggagagctgc caggtaggac ggcgggcaaa gcgcttcttc aagttcctgc 360

gctggagtca ccacccgaga ggcatcgccg tctggcgttg gtgtctgagc agaagccgca 420

ggaaccagcg ggagcagcag gaggagctgc gggactcgtt tgccgaggct cgtgttctgc 480

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<210> 94

<211> 851

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (516)..(516)

<223> BaySNP 2321, G516T

<400> 94

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