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(54) **BIOMARKERS FOR ASSESSING PERIPHERAL NEUROPATHY RESPONSE TO CANCER TREATMENT**

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None  
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides methods for identifying patients at increased risk of developing an adverse neurological event in response to a cancer treatment. Methods also include modifying the treatment regimen of said patent dependent on the presence or absence of biomarkers in the patient.

**7 Claims, No Drawings**

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## BIOMARKERS FOR ASSESSING PERIPHERAL NEUROPATHY RESPONSE TO CANCER TREATMENT

### CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to provisional application Ser. No. 61/162,848, filed Mar. 24, 2009.

### FIELD OF THE INVENTION

The present invention relates generally to the field of pharmacogenomics, and more specifically to the pharmacogenomic analysis of peripheral neuropathy candidate genes.

### BACKGROUND OF THE INVENTION

Treatment with cancer drugs such as bortezomib has been associated with adverse events (AE) such as peripheral neuropathy (PN). Bortezomib-induced peripheral neuropathy typically occurs within the first courses of treatment with bortezomib and generally reaches a plateau at cycle 5 (Windebank & Grisold (2008) *J. Peripher. Nerv. Syst.* 13:27-46). Primarily, a small fiber and painful, axonal, sensory distal neuropathy is produced. The associated pain has a mean rating of 7.8 (on scale of 0 for no pain and 10 for worst imaginable pain) (Cata et al. (2007) *J. Pain* 8:296-306).

Bortezomib-induced pain is associated with three major fiber types (A $\beta$ , A $\delta$  and C caliber primary afferent fibers) in sensory nerves. An electrophysiologic nerve conduction study shows low amplitude of sensory action potential (distal, sensory, axonal neuropathy) (Richardson et al. (2006) *J. Clin. Oncol* 24:3113-3120). Conduction studies are consistent with primary or secondary demyelination process due to primary myelin-Schwann cell damage or degeneration of fast-conducting fibers (demyelination neuropathy noted in ulnar nerves) (Badros et al. (2007) *Cancer* 110:1042-1049).

Mitochondrial and endoplasmic reticulum damage in addition to other factors may play a key role in bortezomib-induced peripheral neuropathy development in humans. Bortezomib activates the mitochondrial-based apoptotic pathway (Pei et al. (2004) *Clin. Cancer Res.* 10:3839-3852). Bortezomib may also play a role in dysregulation of neurotrophins as evidenced by inhibition of NF- $\kappa$ B activation which has been shown to block transcription of nerve growth factor (NGF) mediated neuron survival (NGF induces differentiation and survival of sensory nerve cells) (Ladowski et al. (2005) *Cancer Res.* 65:3828-3836).

It has been observed that bortezomib-induced peripheral neuropathy is predominately sensory. Patients with pre-existing signs of peripheral neuropathy may experience worsening peripheral neuropathy during treatment. Dose reduction resulted in improvement or resolution of peripheral neuropathy in 51% of patients with >Grade 2 PN in a phase 2 multiple myeloma study. Dose discontinuation resulted in improvement or resolution of peripheral neuropathy in 73% of patients discontinuing due to Grade 2 peripheral neuropathy or who had >Grade 3 peripheral neuropathy in a phase 2 multiple myeloma study.

Adverse responses to drugs constitute a major medical problem. To the extent that some of these adverse events are due to genetically encoded biochemical diversity among patients in pathways that effect drug action, the identification of variances that are predictive of such effects will allow for

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more effective and safer drug use. Thus, there is a need for biomarkers useful for identifying patients most at risk for bortezomib-induced neuropathy.

### SUMMARY OF THE INVENTION

The invention provides a method for identifying whether a patient is at increased risk for developing an adverse neurological event in response to a cancer treatment, comprising: determining whether or not said patient possesses one or more biomarkers for said increased risk, wherein the presence of said biomarker indicates an increased risk for said adverse neurological event. The presence of biomarkers may be determined by obtaining a biological sample from said patient, and performing genotyping analysis on the sample. In certain embodiments, the adverse neurological event is peripheral neuropathy, peripheral sensory neuropathy or neuralgia. The cancer treatment may comprise administration of a proteasome inhibitor, such as bortezomib. The biomarkers may be one or more of rs4553808; rs1474642; rs12568757; rs11974610; or rs1261134.

Also provided are diagnostic kits for identifying patients likely to develop an adverse neurologic event in response to treatment for cancer and methods for treating cancer or individualizing a cancer treatment regimen.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention describes the identification of peripheral neuropathy candidate genes that serve as useful molecular tools for predicting an adverse response to cancer drugs. Specifically, the present invention is directed to methods of identifying whether or not a patient is at increased risk of suffering an adverse neurologic event in response to treatment with proteasome inhibitors such as bortezomib.

The present invention involves the identification of genetic variances also referred to herein as "variants", "markers" and/or "biomarkers", that correlate with an increased risk of adverse neurological response to a cancer treatment. The association of patient response to drug treatment with these markers can open up new opportunities for drug development or distinguish a drug's indication among other treatment choices because of higher confidence in the safety and/or efficacy.

The cancer treatment may include administration of a single drug or treatment, or administration of more than one drug or treatment. In certain embodiments, the cancer treatment comprises administering a proteasome inhibitor to a patient. Proteasome inhibitors include bortezomib, and/or compounds having structure similar to that of bortezomib. Proteasome inhibitors having structure similar to bortezomib include those compounds disclosed in U.S. Pat. Nos. 7,119,080; 6,747,150; 6,617,317; 6,548,668; 6,465,433; 6,297,217; 6,083,903; 5,780,454; 7,422,830; 7,109,323; 6,958,319; 6,713,446; and 6,699,835.

The adverse neurological event may be peripheral sensory neuropathy, neuralgia, peripheral neuropathy (NEC). The methods of the invention may identify increased risk of only one neurological event, or increased risk of more than one neurological event.

The increased risk may be any increase over the average risk, including increased risk of developing adverse neurological event in response to any level of treatment, increased risk of developing an adverse neurological event earlier in treatment, or increased risk of developing an adverse event

in response to higher treatment doses. The increased risk may be dose-dependent or dose-independent.

The presence or absence of a biomarker may be assessed by obtaining a biological sample from a patient and determining whether said biological sample contains the biomarker. A “biological sample” as used herein refers to a sample containing or consisting of cells or tissue matter, such as cells or biological fluids isolated from a subject. Examples of biological samples include, for example, sputum, blood, blood cells (e.g., white blood cells), amniotic fluid, plasma, serum, semen, saliva, bone marrow, tissue or fine-needle biopsy samples, urine, peritoneal fluid, pleural fluid, and cell cultures. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes. A test biological sample is the biological sample that has been the object of analysis, monitoring, or observation. A control biological sample can be either a positive or a negative control for the test biological sample. Often, the control biological sample contains the same type of tissues, cells and/or biological fluids of interest as that of the test biological sample. In particular embodiments, the biological sample is a “clinical sample,” which is a sample derived from a human patient.

As used herein, the terms “comprising”, “containing”, “having” and “including” are used in their open, non-limiting sense.

“Genotyping” refers to the process of determining the genotype of an individual by the use of biological assays. Current methods of doing this include PCR, DNA sequencing, antisense oligonucleotide probes, and hybridization to DNA microarrays or beads. The technology is employed in clinical research for the investigation of disease-associated and response-associated genes. Due to current technological limitations, almost all genotyping is partial. That is, only a small fraction of an individual’s genotype is determined.

A “single nucleotide polymorphism” (SNP, pronounced snip) is a DNA sequence variation occurring when a single nucleotide—A, T, C, or G—in the genome (or other shared sequence) differs between members of a species (or between paired chromosomes in an individual). For example, two sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTA, contain a difference in a single nucleotide. In this case it is said that there are two alleles: C and T. Almost all common SNPs have only two alleles.

Within a population, SNPs can be assigned a minor allele frequency—the lowest allele frequency at a locus that is observed in a particular population. This is simply the lesser of the two allele frequencies for single nucleotide polymorphisms. There are variations between human populations, so a SNP allele that is common in one geographical or ethnic group may be much rarer in another.

Biomarkers according to this invention which correlate with increased risk of adverse neurological events include rs4553808; rs1474642; rs12568757; rs11974610; and rs1261134.

This application concerns the field of mammalian therapeutics and the selection of therapeutic regimens utilizing host genetic information, including gene sequence variances within the human genome in human populations. The application further concerns methods for identification of DNA sequence variations likely to affect treatment response.

The present invention is concerned generally with the field of identifying an appropriate treatment regimen for a disease based upon genotype in mammals, particularly in humans. It is further concerned with the genetic basis of inter-patient variation in response to therapy, including drug therapy. Specifically, this invention describes the identifica-

tion of gene sequence variances useful in the field of therapeutics for optimizing efficacy and safety of drug therapy. These variances may be useful in guiding the optimal use of already approved compounds such as bortezomib. DNA sequence variances in candidate genes (i.e., genes that may plausibly affect the action of a drug) are tested in clinical trials, leading to the establishment of diagnostic tests useful for improving the development of new pharmaceutical products and/or the more effective use of existing pharmaceutical products. The identification of genetic variances and the determination of their utility in the selection of optimal therapy for specific patients are also described. In general, the invention relates to the identification of patient population subsets that respond to drug therapy with either therapeutic benefit or side effects (i.e., symptomatology prompting concern about safety or other unwanted signs or symptoms) such as peripheral neuropathy.

The identification of gene sequence variances in genes that may be involved in drug action are useful for determining whether genetic variances account for variable drug efficacy and safety and for determining whether a given drug or other therapy may be safe and effective in an individual patient. Provided in this invention are identifications of genes and sequence variances which can be useful in connection with predicting differences in response to treatment. A target gene and variances are useful, for example, in pharmacogenetic association studies and diagnostic tests to improve the use of certain drugs or other therapies.

In embodiments of this invention, the variance or variant form or forms of a gene is/are associated with a specific response to a drug. The frequency of a specific variance or variant form of the gene may correspond to the frequency of an efficacious response to administration of a drug. Alternatively, the frequency of a specific variance or variant form of the gene may correspond to the frequency of an adverse event resulting from administration of a drug. Alternatively the frequency of a specific variance or variant form of a gene may not correspond closely with the frequency of a beneficial or adverse response, yet the variance may still be useful for identifying a patient subset with high response or toxicity incidence because the variance may account for only a fraction of the patients with high response or toxicity. In such a case the preferred course of action is identification of a second or third or additional variances that permit identification of the patient groups not usefully identified by the first variance.

Also in other embodiments, the method of selecting a treatment includes excluding or eliminating a treatment, where the presence or absence of the at least one variance is indicative that the treatment will be ineffective or contraindicated. In other preferred embodiments, in cases in which undesirable side-effects may occur or are expected to occur from a particular therapeutic treatment, the selection of a method of treatment can include identifying both a first and second treatment, where the first treatment is effective to treat the disease or condition, and the second treatment reduces a deleterious effect of the first treatment.

The phrase “eliminating a treatment” or “excluding a treatment” refers to removing a possible treatment from consideration, e.g., for use with a particular patient based on the presence or absence of a particular variance(s) in one or more genes in cells of that patient, or to stopping the administration of a treatment.

Usually, the treatment will involve the administration of a compound preferentially active or safe in patients with a form or forms of a gene, where the gene is one identified

herein. The administration may involve a combination of compounds. Thus, in preferred embodiments, the method involves identifying such an active compound or combination of compounds, where the compound or combination is less active or is less safe or both when administered to a patient having a different form of the gene.

Also in preferred embodiments, the method of selecting a treatment involves selecting a method of administration of a compound, combination of compounds, or pharmaceutical composition, for example, selecting a suitable dosage level and/or frequency of administration, and/or mode of administration. The method of administration can be selected to provide better, preferably maximum therapeutic benefit. In this context, "maximum" refers to an approximate local maximum based on the parameters being considered, not an absolute maximum.

Also in this context, a "suitable dosage level" refers to a dosage level that provides a therapeutically reasonable balance between pharmacological effectiveness and deleterious effects. Often this dosage level is related to the peak or average serum levels resulting from administration of a drug at the particular dosage level.

Similarly, a "frequency of administration" refers to how often in a specified time period a treatment is administered, e.g., once, twice, or three times per day, every other day, once per week, etc. For a drug or drugs, the frequency of administration is generally selected to achieve a pharmacologically effective average or peak serum level without excessive deleterious effects (and preferably while still being able to have reasonable patient compliance for self-administered drugs). Thus, it is desirable to maintain the serum level of the drug within a therapeutic window of concentrations for the greatest percentage of time possible without such deleterious effects as would cause a prudent physician to reduce the frequency of administration for a particular dosage level.

The term "genotype" refers to the alleles present in DNA from a subject or patient, where an allele can be defined by the particular nucleotide(s) present in a nucleic acid sequence at a particular site(s). Often a genotype is the nucleotide(s) present at a single polymorphic site known to vary in the human population.

The detection of the presence or absence of at least one variance involves contacting a nucleic acid sequence corresponding to one of the genes identified herein or a product of such a gene with a probe. The probe is able to distinguish a particular form of the gene or gene product or the presence or a particular variance or variances, e.g., by differential binding or hybridization.

The terms "variant form of a gene", "form of a gene", or "allele" refer to one specific form of a gene in a population, the specific form differing from other forms of the same gene in the sequence of at least one, and frequently more than one, variant sites within the sequence of the gene. The sequences at these variant sites that differ between different alleles of the gene are termed "gene sequence variances" or "variances" or "variants". The term "alternative form" refers to an allele that can be distinguished from other alleles by having distinct variances at least one, and frequently more than one, variant sites within the gene sequence.

Variances occur in the human genome at approximately one in every 500-1,000 bases within the human genome when two alleles are compared. When multiple alleles from unrelated individuals are compared the density of variant sites increases as different individuals, when compared to a reference sequence, will often have sequence variances at different sites. At most variant sites there are only two

alternative nucleotides involving the substitution of one base for another or the insertion/deletion of one or more nucleotides. Within a gene there may be several variant sites. Variant forms of the gene or alternative alleles can be distinguished by the presence of alternative variances at a single variant site, or a combination of several different variances at different sites (haplotypes).

The "identification" of genetic variances or variant forms of a gene involves the discovery of variances that are present in a population. The identification of variances is required for development of a diagnostic test to determine whether a patient has a variant form of a gene that is known to be associated with a disease, condition, or predisposition or with the efficacy or safety of the drug. Identification of previously undiscovered genetic variances is distinct from the process of "determining" the status of known variances by a diagnostic test (often referred to as genotyping). The present invention provides exemplary variances in genes listed in the gene tables included and described herein.

In the context of this invention, the term "haplotype" refers to a cis arrangement of two or more polymorphic nucleotides, i.e., variances, on a particular chromosome, e.g., in a particular gene. The haplotype preserves information about the phase of the polymorphic nucleotides—that is, which set of variances were inherited from one parent, and which from the other. A genotyping test does not provide information about phase. For example, an individual heterozygous at nucleotide 25 of a gene (both A and C are present) and also at nucleotide 100 (both G and T are present) could have haplotypes 25A-100G and 25C-100T, or alternatively 25A-100T and 25C-100G. Only a haplotyping test can discriminate these two cases definitively.

The terms "variances", "variants" and "polymorphisms", as used herein, may also refer to a set of variances, haplotypes or a mixture of the two, unless otherwise indicated. Further, the term variance, variant or polymorphism (singular), as used herein, also encompasses a haplotype unless otherwise indicated. This usage is intended to minimize the need for cumbersome phrases such as: ". . . measure correlation between drug response and a variance, variances, haplotype, haplotypes or a combination of variances and haplotypes . . .", throughout the application. Similarly, the term "genotype", as used herein, means a procedure for determining the status of one or more variances in a gene, including a set of variances comprising a haplotype. Thus phrases such as ". . . genotype a patient . . ." refer to determining the status of one or more variances, including a set of variances for which phase is known (i.e. a haplotype).

In preferred embodiments of this invention, the frequency of the variance or variant form of the gene in a population is known. Measures of frequency known in the art include "allele frequency", namely the fraction of genes in a population that have one specific variance or set of variances. The allele frequencies for any gene should sum to 1. Another measure of frequency known in the art is the "heterozygote frequency" namely, the fraction of individuals in a population who carry two alleles, or two forms of a particular variance or variant form of a gene, one inherited from each parent. Alternatively, the number of individuals who are homozygous for a particular form of a gene may be a useful measure. The relationship between allele frequency, heterozygote frequency, and homozygote frequency is described for many genes by the Hardy-Weinberg equation, which provides the relationship between allele frequency, heterozygote frequency and homozygote frequency in a freely breeding population at equilibrium. Most human variances are substantially in Hardy-Weinberg equilibrium.

“Population” refers to a defined group of individuals or a group of individuals with a particular disease or condition or individuals that may be treated with a specific drug identified by, but not limited to geographic, ethnic, race, gender, and/or cultural indices. In most cases a population will preferably encompass at least ten thousand, one hundred thousand, one million, ten million, or more individuals, with the larger numbers being more preferable. In embodiments of this invention, the allele frequency, heterozygote frequency, or homozygote frequency of a specific variance or variant form of a gene is known. In preferred embodiments of this invention, the frequency of one or more variances that may predict response to a treatment is determined in one or more populations using a diagnostic test.

It should be emphasized that it is currently not generally practical to study an entire population to establish the association between a specific disease or condition or response to a treatment and a specific variance or variant form of a gene. Such studies are preferably performed in controlled clinical trials using a limited number of patients that are considered to be representative of the population with the disease. Since drug development programs are generally targeted at the largest possible population, the study population will generally consist of men and women, as well as members of various racial and ethnic groups, depending on where the clinical trial is being performed. This is important to establish the efficacy of the treatment in all segments of the population.

As used herein, the terms “effective” and “effectiveness” includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the treatment to result in a desired biological effect in the patient. Physiological safety refers to the level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (often referred to as side-effects) resulting from administration of the treatment. On the other hand, the term “ineffective” indicates that a treatment does not provide sufficient pharmacological effect to be therapeutically useful, even in the absence of deleterious effects, at least in the unstratified population. (Such a treatment may be ineffective in a subgroup that can be identified by the presence of one or more sequence variances or alleles.) “Less effective” means that the treatment results in a therapeutically significant lower level of pharmacological effectiveness and/or a therapeutically greater level of adverse physiological effects, e.g., greater liver toxicity.

Thus, in connection with the administration of a drug, a drug which is “effective against” a disease or condition indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, reduction in tumor mass or cell numbers, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of disease or condition.

Effectiveness is measured in a particular population. In conventional drug development the population is generally every subject who meets the enrollment criteria (i.e. has the particular form of the disease or condition being treated). It is an aspect of the present invention that segmentation of a study population by genetic criteria can provide the basis for identifying a subpopulation in which administration of a drug such as VELCADE™ may likely induce peripheral neuropathy.

The term “deleterious effects” refers to physical effects in a patient caused by administration of a treatment which are

regarded as medically undesirable. Thus, for example, deleterious effects can include a wide spectrum of toxic effects injurious to health such as death of normally functioning cells when only death of diseased cells is desired, nausea, fever, inability to retain food, dehydration, damage to critical organs such as arrhythmias, renal tubular necrosis, fatty liver, or pulmonary fibrosis leading to coronary, renal, hepatic, or pulmonary insufficiency among many others. In this regard, the term “contra-indicated” means that a treatment results in deleterious effects such that a prudent medical doctor treating such a patient would regard the treatment as unsuitable for administration. Major factors in such a determination can include, for example, availability and relative advantages of alternative treatments, consequences of non-treatment, and permanency of deleterious effects of the treatment.

It is recognized that many treatment methods, e.g., administration of certain compounds or combinations of compounds, may produce side-effects or other deleterious effects in patients. Such effects can limit or even preclude use of the treatment method in particular patients, or may even result in irreversible injury, dysfunction, or death of the patient. Thus, in certain embodiments, the variance information is used to select both a first method of treatment and a second method of treatment. Usually the first treatment is a primary treatment that provides a physiological effect directed against the disease or condition or its symptoms. The second method is directed to reducing or eliminating one or more deleterious effects of the first treatment, e.g., to reduce a general toxicity or to reduce a side effect of the primary treatment. Thus, for example, the second method can be used to allow use of a greater dose or duration of the first treatment, or to allow use of the first treatment in patients for whom the first treatment would not be tolerated or would be contra-indicated in the absence of a second method to reduce deleterious effects or to potentiate the effectiveness of the first treatment.

Similar to the above aspect, in an embodiment at least one method of treatment involves the administration of a compound effective in at least some patients with a disease or condition; the presence or absence of the at least one variance is indicative that the treatment will be effective in the patient; and/or the presence or absence of the at least one variance is indicative that the treatment will be ineffective or contra-indicated in the patient; and/or the treatment is a first treatment and the presence or absence of the at least one variance is indicative that a second treatment will be beneficial to reduce a deleterious effect of or potentiate the effectiveness of the first treatment; and/or the at least one treatment is a plurality of methods of treatment. For a plurality of treatments, preferably the selecting involves determining whether any of the methods of treatment will be more effective than at least one other of the plurality of methods of treatment.

In another aspect, the invention provides a method for selecting a patient for administration of a method of treatment for a disease or condition, or of selecting a patient for a method of administration of a treatment, by comparing the presence or absence of at least one variance in a gene as identified above in cells of a patient, with a list of variances in the gene, where the presence or absence of the at least one variance is indicative that the treatment or method of administration will be effective in the patient. If the at least one variance is present in the patient’s cells, then the patient is selected for consideration of alternative treatment.

In another aspect, the invention provides a method for identifying a subset of patients with enhanced or diminished

response or tolerance to a treatment method where the treatment is for a disease or condition in the patient. The method involves correlating one or more variances in one or more genes as identified in aspects above in a plurality of patients with response to a treatment method. The correlation may be performed by determining one or more variances in one or more genes in the plurality of patients and correlating the presence or absence of each of the variances (alone or in various combinations) with the patient's response to treatment and in particular to the development of peripheral neuropathy. The response should be statistically significant. A positive correlation between the presence of one or more variances and a response to treatment as demonstrated by evidence of peripheral neuropathy is indicative that the treatment is particularly ineffective in the group of patients having those variances. Such information is useful, for example, for selecting or de-selecting patients for a particular treatment or method of administration of a treatment, or for demonstrating that a group of patients exists for which the treatment or method of treatment would be particularly beneficial or contra-indicated.

In preferred embodiments, the correlation of patient responses to therapy according to patient genotype is carried out employing clinical trial data, e.g., as described herein according to any of the variations described.

A major goal of research is to identify markers that accurately predict a given patient's response to drugs in the clinic; such individualized assessment may greatly facilitate personalized treatment. An approach of this nature is particularly needed in cancer treatment and therapy, where commonly used drugs are ineffective in many patients, and side effects are frequent. The ability to predict drug sensitivity in patients is particularly challenging because drug responses reflect both the properties intrinsic to the target cells and also a host's metabolic properties.

All publications cited herein are hereby incorporated by reference. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains.

#### Example 1

A randomized, open-label, multicenter study was conducted, consisting of 3 Phases: a Pre-randomization (Screening) Phase, an Open-label Treatment Phase, and a Post-treatment Phase. Approximately 680 subjects with previously untreated multiple myeloma were randomly assigned to one of two treatment groups and were stratified according to baseline  $\beta$ 2-microglobulin, baseline albumin levels and region (North America, Europe, other). Subjects received either VELCADE™/Melphalan/Prednisone (VMP) (Treatment Group A) or Melphalan/Prednisone (MP) (Treatment Group B). Subjects in Treatment Group A received VELCADE™ 1.3 mg/m<sup>2</sup> (twice weekly [Weeks 1, 2, 4, and 5] for four 6-week cycles [8 doses per cycle] followed by once weekly [Weeks 1, 2, 4, and 5] for five 6-week cycles [4 doses per cycle]) in combination with melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> (once daily on Days 1 to 4 of each 6-week cycle). Subjects in Treatment Group B received 9 cycles of melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> once daily on Days 1 to 4 of each 6-week cycle. For both groups, treatment continued for a maximum of 9 cycles (54 weeks) and subjects were discontinued if disease progression or an unacceptable treatment-related toxicity occurred, or if a subject withdrew consent.

DNA samples from study subjects were plated and normalized to a concentration of  $\geq 50$  ng/ul using a liquid handling robot. The DNA plates were then transferred to Illumina for genotyping analysis using the GoldenGate platform, which relies on primer extension. One blinded control was included on each plate. The controls consisted of duplicated samples and Coriell DNA (Coriell Institute for Medical Research, 408 Haddon Avenue, Camden, N.J.) samples that were used to generate HapMap data (to verify genotyping accuracy through comparisons with publicly available genotype data for these samples).

The candidate genes included with examples have previous associations linked to hereditary neuropathy, peripheral neuropathy, energy production and fast axonal transport, nociception and pain transmission, neurogenesis and neuroprotection. The candidates that were genotyped in the examples include: ACCN2, ACE, ACTB, ACTG1, ACTR1A, ACTR1B, ADORA2A, ADRA2B, AGT, AGTR1, AKR1B1, AKT1, AKT2, APC, ARP11, AXIN1, BMF, CACNA1A, CACNA1B, CAPZA1, CAPZA2, CAPZA3, CAPZB, CD86, COMT, CTLA4, CTNNA1, CTNNA2, CYP3A4, CYP3A5, DCTN1, DCTN2, DCTN3, DCTN4, DCTN6, DNCL1, DNCL2A, DNM2, DVL1, DVL2, DVL3, DYNC1H1, DYNC1I1, DYNC1I2, DYNC1L1, DYNC1L2, DYNC2H1, DYNC2L1, DYNLL2, DYNLRB2, ECGF1, EGR2, FGD4, FIG4, GARS, GCH1, GDAP1, GJB1, GJB2, GJB3, GJE1, GLRA3, GLS2, GLUL, GSK3A, GSK3B, HAP1, HSN2, HSPB1, HSPB8, HTR1B, IKBKAP, IL6, KIF1A, KIF1B, KIF3A, KIF3B, KIF5A, KIF5B, KIF5C, LITAF, LMNA, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK3, MAPK4, MAPK6, MAPK7, MAPK8, MAPK9, MC1R, MFN2, Mitochondrial genome, MPZ, MTMR2, NDRG1, NEFL, NFE2L2, NGFB, NPY, NR1H2, NTRK1, OPRD1, OPRK1, OPRL1, OPRM1, PLP1, PMP22, PNOC, POLG, POLG2, PON1, PRPS1, PRX, PSMB1, PSMB10, PSMB2, PSMB3, PSMB4, PSMB5, PSMB6, PSMB7, PSMB8, PSMB9, PTGER1, PTGER2, PTGER3, PTGER4, PTGS1, PTGS2, SBF2, SCN3A, SCN9A, SH3TC2, SLC12A6, SPTBN1, SPTBN2, SPTBN4, SPTBN5, SPTLC1, SURF1, TCF1, TCF4, TH, TNF, TRAK2, TRPV1, TRPV4, TTR, VIP, WNT1, WNT10A, WNT10B, WNT11, WNT16, WNT2, WNT2B, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT8A, WNT8B, WNT9A, WNT9B and YARS.

Included in the analysis are the 368 subjects who met all of the following criteria: consented to DNA analysis; had usable genotype data for SNPs listed in Appendix 1; had Adverse Event related clinical data before treatment and after at least one cycle of VELCADE™ treatment (including those having neurological events and those completing treatment with no neurological event). These 368 subjects included: Treatment Group A (154 Caucasian, 2 black, 10 Asian); Treatment Group B (168 Caucasian, 4 black, 12 Asian), and 18 were not treated.

The primary adverse event endpoints are the treatment-emergent peripheral neuropathies caused by VELCADE™, including peripheral neuropathy NEC, peripheral sensory neuropathy, and neuralgia. For each specific peripheral neuropathy endpoint, the null hypothesis was that none of the successfully genotyped SNPs is associated with this specific treatment-emergent peripheral neuropathy. Each successfully genotyped SNP is tested to see whether there is a difference in the distribution of the genotypes of this SNP between patients with and without this specific VELCADE™ treatment-emergent peripheral neuropathy. The

test result is subsequently adjusted by total number of successfully genotyped SNPs to correct multiplicity.

The secondary adverse event endpoints are the time to the first onset of treatment-emergent peripheral neuropathy caused by VELCADE™, including time to onset of any peripheral neuropathy, time to onset of grade $\geq$ 2 peripheral neuropathy, and time to onset of grade $\geq$ 3 peripheral neuropathy. For each specific time to onset endpoint, the null hypothesis is that none of the successfully genotyped SNPs is associated with the time to onset of this specific treatment-emergent peripheral neuropathy. For each successfully genotyped SNP, the patients are stratified according to the genotype of this SNP and tested to see whether there is a difference in the probability of onset of treatment-emergent peripheral neuropathy at any time point between patients of different genotypes. The test result is subsequently adjusted by total number of successfully genotyped SNPs to correct multiplicity. Some subjects have multiple incidences of peripheral neuropathy: i.e., a resolved AE followed by one or more re-occurred events. In the case of multiple events in the same patient, the time to first neuropathy for the analysis of 'neuropathy of any grade' and the time to neuropathy of a particular grade was considered the first day this particular grade is reported.

A series of quality control (QC) steps were conducted to assure the genotype data quality used in the analysis. The genotype data quality was assessed using internal control (duplicated) samples. Seven subjects from this study were genotyped twice. The concordance rate between duplicate samples was 100%. The duplicated sample data from this study were handled in the following way. Data was merged together by the following rules: 1) consistent genotype calls were kept. 2) If one sample had a genotype call while the other sample had a missing value (NA), the merged data was assigned the called genotype. 3) If both samples had a missing value, the merged data had a missing value. 4) If both samples had genotype calls and they are inconsistent with each other, the merged data were assigned missing values.

Genotype data of a Coriell DNA sample that was used to generate HapMap data, was compared against publicly available genotype data to verify genotyping accuracy. The Hapmap CEU subject NA12043 was genotyped as the quality control (ID: GS0034314-DNAH11\_J369, CEPH1346-11). Of the 1927 non-mtSNPs successfully genotyped, 1921 of them were also genotyped in the Hapmap project. The concordance rate between these samples was 98.23%.

Samples with genotype call rates less than 0.9, i.e. more than 10% missing genotype data, were excluded from subsequent analysis. All genotyped samples had a call rate greater than 95%. Therefore, no samples were excluded due to more than 10% missing data. Three subject samples were not successfully genotyped after multiple attempts.

Sixty-four tagging SNPs of the human mitochondrial genome were also included in this analysis. The 64 tagging SNPs were selected based on the alignment of 928 publicly available European mitochondrial genome sequences to capture 144 common mitochondrial SNPs (mtSNPs) with MAF greater than 1% and 9 haplogroups (Saxena, R., etc. (2006) "Comprehensive association testing of common mitochondrial DNA variation in metabolic disease", *American Journal of Human Genetics* 79: 54-61).

Pair-wise correlation between genotypes of samples were calculated to identify questionable samples. If two subjects had identical genotype yet inconsistent phenotype data, both subjects were excluded from subsequent analysis. Heterozy-

gosity of X-chromosome SNPs were calculated to identify gender discrepancies with the demographic data. Three subjects had discrepancies under gender control loci analysis and were excluded from the analysis. One additional subject was identified by PLINK to have heterozygous haploid genotypes on an X chromosome SNP (rs12116382), indicating a potential gender error. This subject was excluded from subsequent analysis.

After the quality control measures and filtering by race, one hundred thirty nine VELCADE™ treated samples were included in the analysis.

#### Example 2

A randomized, open-label, multicenter study was conducted that compared vincristine/adriamycin/dexamethasone (VAD) and VELCADE™/Dexamethasone as induction treatment prior to autologous hematopoietic stem cell transplantation (AH SCT) in patients up to (and including) the age of 65 with newly diagnosed multiple myeloma. Approximately 480 patients were included in this study. Subjects were randomized at diagnosis into one of 4 induction treatment arms:

A1 VAD (4 cycles)

A2 VAD (4 cycles) followed by Dexamethasone/cyclophosphamide/etoposide/cis-Platinum (DCEP) (2 cycles)

B1 VELCADE+dexamethasone (4 cycles)

B2 VELCADE+dexamethasone (4 cycles) followed by DCEP (2 cycles)

Randomization was stratified based on the initial  $\beta$ 2 microglobulin level ( $>$  or  $\leq$ 3 mg/l) and the presence of chromosome 13 abnormalities identified by fluorescence in situ hybridization (FISH) analysis. After induction treatment (Arms A1 and B1) or after consolidation treatment (Arms A2 and B2) all of the patients underwent AH SCT.

470 samples were sent to Illumina for genotyping on 2016 SNPs in 172 non-mitochondria genes. Out of the 470 samples, 29 samples are Hapmap control subjects, 3 samples are controls subjects from a Belgium family, and another 4 are samples from Example 1 for quality control. Therefore, there were totally 434 unique subjects from this study (103 in A1, 105 in A2, 111 in B1, 111 in B2 and 4 not treated).

The genotyping dataset contained 29 samples from Hapmap project as control for genotyping quality. Of the 1939 SNPs genotyped, 1934 had corresponding Hapmap data. Comparing the genotype calls, the 29 samples had an average concordance rate of 99.63%. However, a couple of SNPs (rs5699 and rs926103) had near 0% concordance between the Hapmap data and the dataset, indicating potential genotyping errors in these SNPs. To control data quality, 8 SNPs with  $<$ 90% concordance between the Hapmap data and treatment dataset were excluded from association analysis.

After the quality control and filtering, 212 VELCADE treated subjects were included in the association analysis on non-mtSNPs.

#### Example 3

SNPs with minor allele frequency (MAF) less than 0.01 were excluded from subsequent analysis, since the accuracy of the clustering algorithm used by to generate genotyping calls is relatively low for SNPs with very low minor allele frequencies. There were 11 SNPs in the entire analysis of Example 1 with less than a 90% call rate and these were excluded. Of the remaining SNPs, 26 SNPs had MAF less



than 0.01 and these were excluded. Hardy-Weinberg equilibrium (HWE) test was performed. Significant deviation from Hardy-Weinberg equilibrium may indicate potential genotyping errors in a homogenous population. However, moderate deviation from HWE may indicate positive associations with the study endpoints. For the Example 1 study, the HWE test was performed in the Caucasian subjects since they form the largest homogenous population of the study reported herein. SNPs that deviated from HWE with p-value less than 0.05/2000 were excluded from subsequent analysis. There were 5 SNPs from the Example 1 study that failed the HWE test and these were excluded. Appendix 1 lists the total set of SNPs tested, genotype status, call rate, MAF, P-value for HWE test, and the final statistical analysis status. After SNP level QC, 1885 non-mtSNPs were retained for the association analysis.

Out of the 2016 non-mtSNPs genotyped from subjects of Example 2 study, 1939 SNPs were successfully genotyped. There were 6 SNPs with less than 90% call rate and were excluded. Of the remaining SNPs, 11 SNPs had minor allele frequency (MAF) less than 0.01 and were excluded. There were 6 SNPs from the Example 2 study that failed the HWE test (P<sub>HWE</sub><0.05/2000) conducted on the 212 VELCADE treated white subjects and these were excluded. The annotation of the 2016 SNPs are listed in Appendix 1 together with the genotype status, call rate, MAF, P-value for HWE test, and the final statistical analysis status. After QC, 1908 non-mtSNPs were included in the association analysis.

For each non-mtSNP, three genomic models were tested during the association analysis: Additive, Dominant and Recessive. All the non-mtSNPs under study are bi-allelic SNPs with a major allele (A) and a minor allele (B). The Dominant model compares subjects with AA genotype with those with AB or BB genotype. The Recessive model compares subjects with AA or AB genotype with those with BB genotype. The Additive model compares subjects having 0 copy of B (AA) with those have 1 copy of B (AB), and those with 2 copy of B (BB). MAF greater than 1% was used as threshold to filter SNPs during the quality control process. Included in this analysis is the following: 1) for the Dominant model, only SNPs with at least 4 AB/BB subjects will be analyzed; 2) for the Recessive model, only SNPs with at least 4 BB subjects will be analyzed; 3) for the Additive model, only SNPs with at least 4 BB subjects, or those with at least 4 AB and 0 BB subjects, will be analyzed. After this filtration, a total of 1445 SNPs for analysis were included in the Additive model, 1885 SNPs were included in the Dominant model, and 1136 SNPs were included in the Recessive model. For Example 2 SNPs, three genomic models were tested during the association analysis and minor allele frequency greater than 1% was used as a threshold to filter SNPs during the quality control process. Under this condition, the minimum number of B alleles each SNP has is 5, since  $212 \times 2 \times 1\% = 4.24$ , which can be of either one of the three possible genotype distributions: 1) 207 AA, 5 AB, 0 BB; 2) 208 AA, 3AB, 1BB; 3) 209 AA, 1 AB, 2 BB. Included in this analysis is the following: 1) for the Dominant model, only SNPs with at least 5 AB/BB subjects will be analyzed; 2) for the Recessive model, only SNPs with at least 5 BB subjects will be analyzed; 3) for the Additive model, only SNPs with at least 5 BB subjects, or those with at least 5 AB and 0 BB subjects, will be analyzed. After this filtration, there were 1441 SNPs for analysis in additive model, 1908 SNPs for dominant model, and 1259 SNPs for recessive model.

All 64 tagging mtSNPs analyzed in Example 1 study had a >90% call rate. This genotype mtSNP genotype information was used to impute the genotype of other 80 common mtSNPs and 9 haplogroups following the method described

by Saxena and colleagues (Saxena et al. (2006), *American Journal of Human Genetics*, vol. 79, pages 54-61). After SNP level quality control and this filtering process, 62 mtSNPs were retained for association analysis. Note that a slightly higher MAF threshold was used for mtSNPs: 0.025 instead of 0.01 because the mtSNPs do not form heterozygous genotypes, and subjects with AA genotype against those with BB genotype were analyzed. The list of mtSNPs genotyped and imputed are listed in Appendix 1. Because there were no significant associations between the mitochondrial SNPs and peripheral neuropathy categories, they were not genotyped in the Example 2 dataset.

A quantile-quantile plot (Q-Q plot) is a graphical data analysis method for comparing ordered values of a statistic with quantiles of a specific theoretical distribution. In large-scale candidate gene association studies, Q-Q plots of p-values for association are often used for visualizing the result. In such plots, the  $-\log_{10}$  transformed p-values are ordered and then plotted against the  $-\log_{10}$  transformed quantiles of uniform distribution. Under the null hypothesis that there is no SNP associated with the endpoints of interest, the p-values should follow a uniform distribution and the Q-Q plot should fall right on the expected line. While deviation of the Q-Q plot from the expected line at the extreme right hand tail may indicate significant associations, deviation of a large portion of the Q-Q plot may indicate potential data errors, such as genotyping errors or population stratification. For each of the endpoints, an initial analysis was performed using  $\chi^2$  tests on the dominant model and the Q-Q plot was used to identify potential problems in the data.

For the 139 VELCADE™ treated Caucasian subjects in Example 1, Q-Q plots of the  $\chi^2$  tests on each of the three adverse events of interest (peripheral sensory neuropathy, peripheral neuropathy NEC, and neuralgia) using the dominant model on the 1885 non-mtSNPs showed no obvious genotyping problems in the data. The observed P-values are generally bigger (smaller in  $-\log_{10}$  scale) than the expected P-values but fall within the 95% confidence intervals of the expected P-values. But some observed P-values fall out of the lower boundary of 95% confidence interval on the  $-\log_{10}$  scale. This is consistent with small sample sizes using this analysis, which has relatively lower power.

Demographic and baseline characteristics of the 139 VELCADE treated Caucasian subjects in Example 1 are summarized in Tables 1 and 2. There were no significant differences in these baseline characteristics between the subset of 139 subjects included in the pharmacogenomics study and the 340 subjects in the VMP arm of the Example 1 study, except for “region” since non-Caucasian subjects were excluded in the Pharmacogenomic (PGx) cohort.

TABLE 1

Comparison of the Baseline Continuous Characteristic for VELCADE Treated Caucasian Subjects with the Clinical Study Cohort Treated with VELCADE.

Baseline Continuous Characteristic	Example 1 Study (N = 340) Median (range)	Example 1 PGx Subset (N = 139) Median (range)
Age (years)	71 (57-90)	72 (58-90)
Body Surface Area (m <sup>2</sup> )	1.8 (1.3-2.4)	1.8 (1.4-2.4)
Height (cm)	165 (139-187)	167 (145-187)
Weight (kg)	71 (40.3-127.9)	73.5 (47-125)
BMI	25.9 (15.6-49.2)	26 (17.1-39.6)

TABLE 2

Comparison of the Baseline Categorical Characteristic for VELCADE Treated Caucasian Subjects with the Clinical Study Cohort Treated with VELCADE.			
Baseline Categorical Characteristic		Example 1 Study (N = 340) No. of Patients (%)	Example 1 PGx Subset (N = 139) No. of Patients (%)
Sex	Female	168 (49.4)	61 (43.9)
	Male	172 (50.6)	78 (56.1)
Baseline b2-microglobulin	<2.5 mg/L	42 (12.4)	13 (9.4)
	2.5 to 5.5 mg/L	187 (55.0)	88 (63.3)
	>5.5 mg/L	111 (32.6)	38 (27.3)
Baseline Albumin	<3.5 g/dL	198 (58.2)	75 (54.0)
	>=3.5 g/dL	142 (41.8)	64 (46.0)
Region	Europe	266 (78.2)	117 (84.2)
	North America	32 (9.4)	22 (15.8)
	Other	42 (12.4)	0 (0.0)
	Sensory or Motor Neuropathy at Entry	37 (10.9)	17 (12.2)
Baseline Diabetes		39 (11.5)	19 (13.7)
Baseline Creatinine	<30 mL/min	19 (5.6)	8 (5.8)
Clearance Group	30-50 mL/min	92 (27.1)	33 (23.7)
	51-80 mL/min	167 (49.1)	70 (50.4)
	>80 mL/min	62 (18.2)	28 (20.1)

The demographics information and baseline characteristics of the 212 VELCADE™ treated subjects in Example 2 were compared with the 139 VELCADE™ treated white subjects in Example 1 as shown in Tables 3 and 4. Significant differences in subjects' age, height, BMI, baseline β-microglobulin, baseline albumin, baseline creatinine clearance, neuropathy and diabetes history were observed between the 139 subjects from Example 1 and the 212 subjects from Example 2.

TABLE 3

Comparison of the Baseline Continuous Characteristic.			
Baseline Continuous Characteristic	Example 1 PGx Subset (Vc-mp) (N = 139) Median (range)	Example 2 Study PGx Subset (B1 and B2 arms) (N = 212) Median (range)	P*
Age (years)	72 (58-90)	56 (31-65)	<0.0001
Body Surface Area (m <sup>2</sup> )	1.8 (1.4-2.4)	1.8 (1.3-2.5)	0.15
Height (cm)	167 (145-187)	170 (146-196)	0.02
Weight (kg)	73.5 (47-125)	72 (42-126)	0.78
BMI	26 (17.1-39.6)	24.9 (17.9-38.7)	0.03

\*P-values from two-sided t-tests.

TABLE 4

Comparison of the Baseline Categorical Characteristic				
Baseline Categorical Characteristic		Example 1 PGx Subset (Vc-mp) (N = 139) No. of Patients (%)	Example 2 PGx Subset (B1 and B2 arms) (N = 212) No. of Patients (%)	P*
Sex	Female	61 (43.9)	92 (43.4)	0.93
	Male	78 (56.1)	120 (56.6)	
Baseline b2-microglobulin	<2.5 mg/L	13 (9.4)	60 (28.3)	<0.0001
	2.5 to 5.5 mg/L	88 (63.3)	103 (48.6)	
	>5.5 mg/L	38 (27.3)	49 (23.1)	
Baseline	<3.5 g/dL	75 (54.0)	50 (23.6)	<0.0001

TABLE 4-continued

Comparison of the Baseline Categorical Characteristic				
Baseline Categorical Characteristic		Example 1 PGx Subset (Vc-mp) (N = 139) No. of Patients (%)	Example 2 PGx Subset (B1 and B2 arms) (N = 212) No. of Patients (%)	P*
Albumin	>=3.5 g/dL	64 (46.0)	162 (76.4)	
Region	Europe	117 (84.2)	NA	NA
	North America	22 (15.8)	NA	
	Other	0 (0.0)	NA	
Sensory or Motor Neuropathy at Entry		17 (12.2)	1 (0.5)	<0.0001
Baseline Diabetes		19 (13.7)	12 (5.7)	0.01
Baseline Creatinine	<30 mL/min	8 (5.8)	17 (8.0)	<0.0001
	30-50 mL/min	33 (23.7)	19 (9.0)	
Clearance	51-80 mL/min	70 (50.4)	62 (29.3)	
Group	>80 mL/min	28 (20.1)	114 (53.8)	

\*P-values from Chi-square tests.

All statistical tests were interpreted at the 5% significance level (2-tailed) unless otherwise specified. Multiple testing corrections were conducted using Bonferroni adjustment for single locus (SNP) association tests and random permutation (1000 times) for multi-loci (Haplotype) association tests.

Association of individual SNPs with VELCADE™ treatment-emergent peripheral neuropathy events was performed based on genotypic, dominant and recessive models using logistic regression in SAS (PROC LOGISTIC, SAS, v. 9.1). Samples within each peripheral neuropathy subgroup can be further stratified according to the number of AE incidences, the maximum NCI toxicity grade of the adverse event, the reversibility, and the duration of the adverse event. Baseline demographic data such as age, gender, race, country, baseline toxicity grade of neurological disease, and risk-factors for peripheral neuropathy determined in clinical study of adverse event of VELCADE™ were used as covariates. Multiple testing corrections were conducted using Bonferroni adjustment.

Haplotype association analysis was performed based on Haplotype Trend Regression using the Logistic Regression module in HelixTree (HelixTree, v. 6.2). Association of the haplotypes formed by 2 to 4 neighboring SNPs on the same chromosome with peripheral neuropathy was tested, with age, gender, race, country, and risk-factors for peripheral neuropathy determined in the ongoing VELCADE™ adverse event clinical study as covariates. Haplotype frequencies were estimated using the expectation maximization (EM) algorithm in HelixTree. Multiple testing corrections were performed by all-marker permutation (1000 times). During each permutation, the group label (e.g. with neuralgia, without neuralgia) for each sample was randomly permuted. The haplotype association test was performed based on the permuted group label. The frequency that a haplotype marker had a more significant P-value in the permuted dataset than the original dataset was used as the permutation adjusted P-value.

The primary endpoints included onset of each of the three adverse events of interest: peripheral sensory neuropathy (68 cases/71 controls), peripheral neuropathy NEC (72 cases/67 controls), Neuralgia (59 cases/80 controls), and any occurrence of any one of the three adverse events (AE3: 84 cases/55 controls). Patients were grouped into cases (those with any onset of the adverse events of interest) and controls (those without the adverse event of interest). As shown in Table 5, the frequencies of the onset of adverse events of

interest in the 139 selected subjects for the pharmacogenomics subset were similar to those in the VELCADE™ treated arm of Example 1.

TABLE 5

Comparison of the Frequency of Adverse Event of Interest for VELCADE Treated Caucasian Subjects Genotyped with the VELCADE Treated Clinical Trial Subjects.		
AE Cases of Interest	Study (VMP) No. of Patients (%) (N = 340)	PGx Subset (VMP) No. of Patients (%) (N = 139)
Peripheral Neuropathy NEC	159 (46.8)	72 (51.8)
Peripheral Sensory Neuropathy	151 (44.4)	68 (48.9)
Neuralgia	121 (35.6)	59 (42.4)
Any of the three AE	187 (55.0)	84 (60.4)

For consistency between Example 1 and Example 2, the regression model included all the predetermined covariates including: age, gender, baseline b2-microglobulin, baseline albumin, body surface area (BSA), body mass index (BMI), neuropathy status at entry (either sensory neuropathy or motor neuropathy), diabetes status at baseline, and creatinine clearance at baseline (categorized into 4 groups: <30 mL/min, ≥30 and ≤50 mL/min, >50 and ≤80 mL/min, >80 mL/min).

After Bonferroni correction for multiple testing using  $P=0.05/(1885+62)=2.57E-5$  as threshold, none of the 1885 non-mtSNPs and 62 mtSNPs showed any significant association with the onset of any of the adverse event endpoints tested in Example 1. Correction by False Discovery Rate (FDR)<0.05 was used as threshold for multiple testing and no SNPs showed significant association with the onset of any of the adverse events tested.

Haplotype association analysis was performed based on Haplotype Trend Regression using the Logistic Regression module in HelixTree (HelixTree v. 6.2). Association of the haplotypes formed by 2 to 4 neighboring non-mtSNPs on the same chromosome with peripheral neuropathy was tested. Haplotype frequencies were estimated using the expectation maximization (EM) algorithm in HelixTree. After multiple testing corrections using all-marker permutation (1000 times), none of the haplotypes tested showed any significant association (P-permutation<0.05) with any of the adverse event endpoints under study.

Association of individual SNPs with time of onset of VELCADE treatment-emergent peripheral neuropathy events was performed based on genotypic, dominant and recessive models using log rank test and Cox regression in SAS (PROC LIFETEST and PROC PHREG, SAS v. 9.1). Baseline demographic data such as age, gender, race, country, baseline toxicity grade of neurological disease, and risk-factors for peripheral neuropathy determined in the ongoing VELCADE™ adverse event clinical study were tested as covariates for the Cox proportional hazards model. Multiple testing corrections were conducted using Bonferroni adjustment.

The secondary end points tested included time to onset of any peripheral neuropathy (72 events/67 censored), time to onset of grade≥2 peripheral neuropathy (50 events/89 censored), and time to onset of grade≥3 peripheral neuropathy (21 events/118 censored). The same set of covariates used in the logistic regression were used as covariates for the Cox proportional hazards model for each of the end points.

After Bonferroni correction for multiple testing using  $P=0.05/(1885+62)=2.57E-5$  as threshold, one SNP

(rs4553808 from gene CTLA4) showed significant association (Wald Type 3 test  $P=1.68E-6$ , FDR=0.0019) with time to onset of Peripheral Neuropathy in recessive model. The proportionality test showed that the proportional assumption of Cox regression was not violated by this model. Patients with the homozygous genotype of the minor allele of rs4553808 (GG) tend to have earlier onset of Peripheral Neuropathy than those that contain only 1 or 0 copy of the minor allele (AA/AG); median time to onset for these subjects was 36 days compared to 89.5 days. There were only 6 patients who had the GG genotype in the dataset. All of them had some level of Peripheral Neuropathy during the Example 1 study: 2 subjects had maximum grade 1 peripheral neuropathy, 2 had maximum grade 2 peripheral neuropathy, and 2 subjects had maximum grade 3 peripheral neuropathy. None of the 5 subjects with the GG genotype of rs4553808 from the non-VELCADE treated arm had any onset of peripheral neuropathy during the trial.

The association of single markers with the cumulative dosage of VELCADE at the onset of peripheral neuropathy was tested. For this endpoint, rs4553808 showed a marginally significant association. Patients with homozygous genotype of the minor allele of rs4553808 (GG) tended to have onset of peripheral neuropathy at a lower cumulative dosage of VELCADE™ than those that contained only 1 or 0 copy of the minor allele (AA/AG): the median time to onset for these subjects was 8.45 mg/m<sup>2</sup> vs. 18.8 mg/m<sup>2</sup>.

One SNP, rs1474642 of gene PSMB1, showed significant associations with time to onset of level≥2 Peripheral neuropathy in recessive model after Bonferroni correction. If using FDR≤0.05 as threshold, another SNP, rs12568757 of CTSS, also showed a significant association. The proportionality test showed that the proportional assumption of Cox regression was not violated by this model.

Using the cumulative dosage of VELCADE to the onset of level≥2 Peripheral neuropathy as endpoint, rs1474642 and rs12568757 showed a marginally significant association. However, another SNP, rs916758 of DYNC111, showed a significant association with the cumulative dosage of VELCADE to onset of level≥2 peripheral neuropathy in the dominant model: Wald Type 3 test  $P=6.14E-6$ , FDR=0.012.

Patients with the homozygous genotype of the minor allele of rs1474642 (GG) tended to have earlier onset of level≥2 peripheral neuropathy than those that contained only 1 or 0 copies of the minor allele (AA/AG): the median time to onset for these subjects was 26 days vs. 109 days; whereas median cumulative dosage of VELCADE™ to time to onset was 6.9 mg/m<sup>2</sup> vs. 22.1 mg/m<sup>2</sup>. There were 4 patients with the homozygous GG genotype. Two of these subjects had maximum grade 3 peripheral neuropathy, one had grade 2 peripheral neuropathy, and one had no peripheral neuropathy during the study. In the MP-treated arm of Example 1 study, 6 of the 142 successfully genotyped MP-treated Caucasian subjects had GG genotype of rs1474642. None of these subjects had any onset of peripheral neuropathy during the trial.

Similarly, patients with the homozygous genotype of the minor allele of rs12568757 (GG) tended to have earlier onset of level≥Grade 2 peripheral neuropathy than those that contained only 1 or 0 copy of the minor allele (AA/AG); the median time to onset was 88 days vs. 113 days; whereas the median cumulative dosage of VELCADE™ to onset was 18.4 mg/m<sup>2</sup> vs. 23.2 mg/m<sup>2</sup>. There were 39 patients with the GG genotype: 10 with grade 3 peripheral neuropathy, 11 with grade 2, 6 with grade 1 and 12 with no peripheral neuropathy during the study. In the MP-treated arm of

Example 1 study, 39 of the 142 successfully genotyped MP-treated Caucasian subjects had GG genotype of rs12568757. But only two of them had peripheral neuropathy during the trial: one had grade 1, the other had grade 2.

Patients carrying 1 or 2 copies of the minor allele of rs916758 (AG/GG) tended to have earlier onset of level  $\geq 2$  peripheral neuropathy than those that contain 0 copies of the minor allele (AA): median time to onset was 75 days vs. 109 days; whereas median cumulative dosage of VELCADE to onset was 16.6 mg/m<sup>2</sup> vs. 23.2 mg/m<sup>2</sup>. There were 32 patients with AG/GG genotypes: 8 with grade 3 peripheral neuropathy, 9 with grade 2, 2 with grade 1 and 13 with no peripheral neuropathy during the study. In the MP-treated arm of Example 1 study, 33 of the 142 successfully genotyped MP-treated caucasian subjects had AG/GG genotypes of rs916758. But only two of them had grade 1 peripheral neuropathy during the trial.

No SNP showed a significant association with time to onset of level  $\geq$  Grade 3 peripheral neuropathy after Bonferroni correction. But using FDR < 0.05 as threshold, one SNP (rs11974610 of gene GJE1) showed a significant association. Using cumulative dosage of VELCADE™ to the onset of level  $\geq$  Grade 3 peripheral neuropathy as the endpoint, rs11974610 showed a marginally significant association. Patients with the homozygous genotype of the minor allele of rs11974610 (AA) tended to have an earlier onset of level  $\geq$  Grade 3 peripheral neuropathy than those that contain only 1 or 0 copies of the minor allele (GG/GA): median time to onset was 97 days vs. 113 days; whereas median cumulative dosage of VELCADE™ to onset was 17.6 mg/m<sup>2</sup> vs. 24.7 mg/m<sup>2</sup>. There were 6 patients with the AA genotypes. Four of them had maximum grade 3 peripheral neuropathy, and 2 had no peripheral neuropathy during the study. In the MP-treated arm of the Example 1 study, 5 of the 142 successfully genotyped MP-treated Caucasian subjects had AA genotype of rs11974610. Only one of them had grade 2 peripheral neuropathy during the trial.

The subjects who had the homozygous genotypes for the minor allele of rs4553808, rs1474642, and rs11974610, had no overlap. But among the 39 subjects who had GG genotype of rs12568757, 2 of them also had GG of rs4553808, 1 had GG of rs1474642, and 3 had AA of rs11974610. All 6 subjects who had two copies of the markers identified had onset of peripheral neuropathy during the Example 1 study. Among the 32 patients with AG/GG genotypes of rs916758, 16 of them also had GG of rs12568757 (11 of them had onset of peripheral neuropathy), 2 had both GG of rs4553808 and GG of rs12568757, 1 had GG of rs1474642 and GG of rs12568757, 1 had AA of rs11974610 and GG of rs12568757, and 1 had GG of rs1474642.

The 5 SNPs which either showed significant associations with time to onset of different levels of peripheral neuropathy or with cumulative dosage of VELCADE™ to the onset of peripheral neuropathy in Example 1 were validated with the Example 2 study. The onset rate of peripheral neuropathy event (including peripheral neuropathies, dysesthesia, and paraesthesia) is 44.8% in Example 2, comparable with the 51.8% in the Example 1 (P=0.24). The analysis results are summarized in Table 6. Based on the raw p-values for the

association tests, none of the significant associations identified in Example 1 were replicated in Example 2. However, rs4553808 showed the same trend in association with time to onset of peripheral neuropathy in the recessive model (Wald Type 3 P-value=0.138). Patients with homogenous genotype of the minor allele of rs4553808 (GG) tend to have earlier onset of peripheral neuropathy than those that contain only 1 or 0 copy of the minor allele (AA/AG): median time to onset was 68 days vs. 70 days. Even though rs916758 also had a relatively low P-value of association (Wald Type 3 P-value=0.113), the trend is opposite to what was observed in Example 1.

TABLE 6

Verification of Example 1 significant associations in Example 2.			
SNP ID	Endpoint	Genetic Model	P-value
rs4553808	time to onset of PN	Recessive	0.138
rs1474642	time to onset of level $\geq 2$ PN	Recessive	0.933
rs12568757	time to onset of level $\geq 2$ PN	Recessive	0.444
rs11974610	time to onset of level $\geq 3$ PN	Recessive	0.996
rs916758	cumulative dosage of VELCADE to level $\geq 2$ PN	Dominant	0.113

The association with time and cumulative dosage of VELCADE™ to the onset of different levels of peripheral neuropathy in all 1908 SNPs in Example 2 was tested. No significant associations was identified after multiple testing correction using Bonferroni (0.05/1908=2.62E-05). The primary endpoints in Example 2 were tested in all 1908 genotyped SNPs: peripheral sensory neuropathy (8 cases/204 controls), peripheral neuropathy NEC (44 cases/168 controls), Neuralgia (9 cases/203 controls), and any occurrence of any one of the three adverse events (AE3: 51 cases/161 controls). One SNP (rs1261134 of gene TCF4) showed significant association with the onset of any one of the adverse events of interest in the additive model after multiple testing correction by FDR adjustments.

The inventors have identified 4 SNPs (rs4553808 of CTLA4, rs1474642 of PSMB1, rs12568757 of CTSS, and rs11974610 of GJE1) which showed significant associations with time to onset of different levels of peripheral neuropathy in the recessive model. These SNPs also showed marginally significant associations with cumulative dosage of VELCADE™ to the onset of peripheral neuropathy in the recessive model. Another SNP, rs916758 of DYNC111, showed significant association with the cumulative dosage of VELCADE™ to onset of level  $\geq$  Grade 2 peripheral neuropathy in the dominant model in Example 1. However, it did not have significant association with time to onset of peripheral neuropathy. These associations are related to VELCADE™ treatment because subjects with the identified markers in the MP treated arm had zero or very low frequency of onset of peripheral neuropathy during the trial. None of these associations were replicated in Example 2. One SNP, rs4553808, showed the same trend of association with time to onset of peripheral neuropathy in Example 2 (P=0.138).

## APPENDIX 1

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs307370	36	1	1263141	127	DVL1	1855
rs307359	36	1	1269877	127	DVL1	1855
rs6695456	36	1	10193113	127	KIF1B	23095

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs11586485	36	1	10231613	127	KIF1B	23095
rs3748575	36	1	10264939	127	KIF1B	23095
rs3748576	36	1	10265216	127	KIF1B	23095
rs17397129	36	1	10268049	127	KIF1B	23095
rs8019	36	1	10289074	127	KIF1B	23095
rs17402390	36	1	10321547	127	KIF1B	23095
rs17034775	36	1	10321595	127	KIF1B	23095
rs12125492	36	1	10344465	127	KIF1B	23095
rs12403443	36	1	10346575	127	KIF1B	23095
rs1002076	36	1	10361479	127	KIF1B	23095
rs11121556	36	1	10365454	127	KIF1B	23095
rs1474868	36	1	11966751	127	MFN2	9927
rs6675934	36	1	11974992	127	MFN2	9927
rs1810563	36	1	11976617	127	MFN2	9927
rs2236057	36	1	11984792	127	MFN2	9927
rs183339	36	1	19536998	127	CAPZB	832
rs2268813	36	1	19539395	127	CAPZB	832
rs16862684	36	1	19546907	127	CAPZB	832
rs1535036	36	1	19549511	127	CAPZB	644075
rs214336	36	1	19551060	127	CAPZB	644075
rs214338	36	1	19552460	127	CAPZB	644075
rs761308	36	1	19552706	127	CAPZB	644075
rs127037	36	1	19552732	127	CAPZB	644075
rs17477654	36	1	19553131	127	CAPZB	644075
rs7533994	36	1	19553860	127	CAPZB	644075
rs214344	36	1	19554234	127	CAPZB	644075
rs10917432	36	1	19571448	127	CAPZB	832
rs17394154	36	1	19578972	127	CAPZB	832
rs4911987	36	1	19594090	127	CAPZB	644083
rs12030205	36	1	19612761	127	CAPZB	832
rs3829833	36	1	19620083	127	CAPZB	832
rs11586303	36	1	19637868	127	CAPZB	832
rs4911997	36	1	19638256	127	CAPZB	832
rs1472568	36	1	19639019	127	CAPZB	832
rs9651016	36	1	19641828	127	CAPZB	832
rs10458381	36	1	19641830	127	CAPZB	832
rs10917451	36	1	19641910	127	CAPZB	832
rs2088824	36	1	19657921	127	CAPZB	832
rs12401874	36	1	19662284	127	CAPZB	832
rs9887859	36	1	19664676	127	CAPZB	832
rs10799815	36	1	19668262	127	CAPZB	832
rs16862800	36	1	19668729	127	CAPZB	832
rs4912104	36	1	19672216	127	CAPZB	832
rs10799817	36	1	19678584	127	CAPZB	832
rs6664461	36	1	19681758	127	CAPZB	832
rs10917461	36	1	19682345	127	CAPZB	832
rs1995309	36	1	19691836	127	CAPZB	832
rs16822407	36	1	19693956	127	CAPZB	832
rs1474646	36	1	22314612	127	WNT4	54361
rs2235530	36	1	22316347	127	WNT4	54361
rs12756110	36	1	22319735	127	WNT4	54361
rs3765350	36	1	22319903	127	WNT4	54361
rs12131703	36	1	22320804	127	WNT4	54361
rs6678992	36	1	22326429	127	WNT4	54361
rs10917158	36	1	22326960	127	WNT4	54361
rs7544210	36	1	22327729	127	WNT4	54361
rs12042083	36	1	22345319	127	WNT4	54361
rs7542242	36	1	22350080	127	WNT4	54361
rs1042114	36	1	29011562	127	OPRD1	4985
rs2236861	36	1	29012343	127	OPRD1	4985
rs678849	36	1	29017775	127	OPRD1	4985
rs4654322	36	1	29023832	127	OPRD1	4985
rs2236855	36	1	29034586	127	OPRD1	4985
rs6697423	36	1	29043082	127	OPRD1	4985
rs529520	36	1	29047533	127	OPRD1	4985
rs581111	36	1	29047960	127	OPRD1	4985
rs508448	36	1	29054112	127	OPRD1	4985
rs204069	36	1	29067405	127	OPRD1	4985
rs16866009	36	1	33013876	127	YARS	8565
rs699005	36	1	33018389	127	YARS	8565
rs2282294	36	1	33018764	127	YARS	8565
rs881393	36	1	33029232	127	YARS	8565
rs10753265	36	1	33036599	127	YARS	8565
rs10798918	36	1	33048568	127	YARS	8565

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs6677618	36	1	33053704	127	YARS	8565
rs1741969	36	1	35028712	127	GJB3	2701
rs6668196	36	1	35841791	127	PSMB2	5690
rs676614	36	1	35880097	127	PSMB2	5690
rs959	36	1	71090849	127	PTGER3	5733
rs6656853	36	1	71097887	127	PTGER3	5733
rs6672081	36	1	71097928	127	PTGER3	5733
rs7533733	36	1	71100822	127	PTGER3	5733
rs17131465	36	1	71102044	127	PTGER3	5733
rs5702	36	1	71104018	127	PTGER3	5733
rs1409986	36	1	71104086	127	PTGER3	5733
rs11209706	36	1	71105576	127	PTGER3	5733
rs1327449	36	1	71110513	127	PTGER3	5733
rs11804767	36	1	71124792	127	PTGER3	5733
rs4147114	36	1	71129253	127	PTGER3	5733
rs1409165	36	1	71136693	127	PTGER3	5733
rs11209710	36	1	71137606	127	PTGER3	5733
rs1359835	36	1	71138082	127	PTGER3	5733
rs4650094	36	1	71138571	127	PTGER3	5733
rs6659643	36	1	71139087	127	PTGER3	5733
rs942976	36	1	71140159	127	PTGER3	5733
rs17541722	36	1	71146509	127	PTGER3	5733
rs1327466	36	1	71146695	127	PTGER3	5733
rs17542063	36	1	71156823	127	PTGER3	5733
rs6424410	36	1	71157268	127	PTGER3	5733
rs602383	36	1	71164234	127	PTGER3	5733
rs499641	36	1	71185970	127	PTGER3	5733
rs650194	36	1	71187451	127	PTGER3	5733
rs7541936	36	1	71188185	127	PTGER3	5733
rs5699	36	1	71191040	127	PTGER3	5733
rs977214	36	1	71198848	127	PTGER3	5733
rs626398	36	1	71205572	127	PTGER3	5733
rs3819790	36	1	71215723	127	PTGER3	5733
rs2050066	36	1	71227723	127	PTGER3	5733
rs6424414	36	1	71228058	127	PTGER3	5733
rs2300167	36	1	71230750	127	PTGER3	5733
rs10789314	36	1	71237136	127	PTGER3	5733
rs5693	36	1	71247370	127	PTGER3	5733
rs5675	36	1	71250127	127	PTGER3	5733
rs5673	36	1	71250429	127	PTGER3	5733
rs8179390	36	1	71266953	127	PTGER3	5733
rs2817864	36	1	71275693	127	PTGER3	5733
rs2744902	36	1	71280129	127	PTGER3	5733
rs2817869	36	1	71294992	127	PTGER3	9406
rs2488787	36	1	112807331	127	WNT2B	55917
rs11102479	36	1	112808327	127	WNT2B	7482
rs1175649	36	1	112820800	127	WNT2B	7482
rs1175650	36	1	112821097	127	WNT2B	7482
rs10776751	36	1	112821821	127	WNT2B	7482
rs1759693	36	1	112824815	127	WNT2B	7482
rs974442	36	1	112829794	127	WNT2B	7482
rs351359	36	1	112841800	127	WNT2B	7482
rs11807828	36	1	112844072	127	WNT2B	7482
rs351364	36	1	112846584	127	WNT2B	7482
rs3790606	36	1	112853709	127	WNT2B	7482
rs351370	36	1	112856182	127	WNT2B	7482
rs12138754	36	1	112857176	127	WNT2B	7482
rs910697	36	1	112864648	127	WNT2B	7482
rs2273368	36	1	112865294	127	WNT2B	7482
rs11102489	36	1	112865873	127	WNT2B	7482
rs11102516	36	1	112962873	127	CAPZA1	54879
rs7550315	36	1	112993391	127	CAPZA1	829
rs1238	36	1	113015620	127	CAPZA1	829
rs6537748	36	1	113015904	127	CAPZA1	829
rs6330	36	1	115630836	127	NGFB	4803
rs6328	36	1	115631466	127	NGFB	4803
rs2268793	36	1	115633306	127	NGFB	4803
rs2268792	36	1	115634405	127	NGFB	4803
rs17033622	36	1	115635714	127	NGFB	4803
rs2239622	36	1	115639232	127	NGFB	4803
rs2856811	36	1	115639805	127	NGFB	4803
rs6678788	36	1	115641194	127	NGFB	4803
rs11102920	36	1	115642633	127	NGFB	4803
rs6686615	36	1	115646569	127	NGFB	4803

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs12058927	36	1	115647744	127	NGFB	4803
rs12402406	36	1	115649911	127	NGFB	4803
rs4644491	36	1	115654507	127	NGFB	4803
rs7555016	36	1	115656670	127	NGFB	4803
rs10858073	36	1	115657510	127	NGFB	4803
rs10776798	36	1	115663777	127	NGFB	4803
rs7530686	36	1	115665423	127	NGFB	4803
rs4839436	36	1	115670612	127	NGFB	4803
rs10858074	36	1	115671833	127	NGFB	4803
rs11102925	36	1	115672877	127	NGFB	4803
rs4839028	36	1	115673789	127	NGFB	4803
rs4320778	36	1	115676454	127	NGFB	4803
rs10745349	36	1	115676717	127	NGFB	4803
rs11102929	36	1	115678026	127	NGFB	4803
rs17033706	36	1	115679147	127	NGFB	4803
rs4634908	36	1	115681344	127	NGFB	4803
rs17540656	36	1	115681655	127	NGFB	4803
rs10776801	36	1	115684064	127	NGFB	4803
rs11583020	36	1	115685317	127	NGFB	4803
rs11102932	36	1	115687606	127	NGFB	4803
rs4310443	36	1	115688564	127	NGFB	4803
rs4073110	36	1	115688850	127	NGFB	4803
rs10776802	36	1	115690449	127	NGFB	4803
rs10858078	36	1	115690525	127	NGFB	4803
rs11576175	36	1	148994018	127	CTSS	1520
rs10888390	36	1	148994163	127	CTSS	1520
rs12568757	36	1	148996417	127	CTSS	1520
rs7172	36	1	149638762	127	PSMB4	5692
rs4603	36	1	149640649	127	PSMB4	5692
rs2485662	36	1	154350092	127	LMNA	4000
rs6686943	36	1	154359615	127	LMNA	4000
rs9427236	36	1	154360030	127	LMNA	4000
rs505058	36	1	154372809	127	LMNA	4000
rs4641	36	1	154374158	127	LMNA	4000
rs6669212	36	1	154376937	127	LMNA	4000
rs7544967	36	1	155048992	127	NTRK1	9047
rs926103	36	1	155051606	127	NTRK1	9047
rs2150906	36	1	155051980	127	NTRK1	4914
rs1800601	36	1	155052241	127	NTRK1	4914
rs4661222	36	1	155061630	127	NTRK1	9047
rs2768747	36	1	155067388	127	NTRK1	3645
rs1998977	36	1	155070745	127	NTRK1	3645
rs6674412	36	1	155071605	127	NTRK1	3645
rs11812062	36	1	155072321	127	NTRK1	3645
rs4661229	36	1	155075830	127	NTRK1	3645
rs12145540	36	1	155084568	127	NTRK1	3645
rs4661063	36	1	155091425	127	NTRK1	3645
rs11264577	36	1	155103591	127	NTRK1	4914
rs1800879	36	1	155104765	127	NTRK1	4914
rs12132885	36	1	155108960	127	NTRK1	4914
rs6334	36	1	155112857	127	NTRK1	4914
rs2644604	36	1	155114730	127	NTRK1	4914
rs2768755	36	1	155114744	127	NTRK1	4914
rs6336	36	1	155115542	127	NTRK1	4914
rs2644596	36	1	155118938	127	NTRK1	4914
rs943551	36	1	155122121	127	NTRK1	4914
rs4657015	36	1	159539065	127	MPZ	4359
rs4657016	36	1	159539150	127	MPZ	4359
rs7532602	36	1	159540935	127	MPZ	4359
rs16832786	36	1	159541529	127	MPZ	4359
rs7531561	36	1	159545854	127	MPZ	4359
rs11579939	36	1	159546142	127	MPZ	4359
rs3813630	36	1	159546873	127	MPZ	4359
rs4131826	36	1	159549008	127	MPZ	6391
rs11265589	36	1	159550921	127	MPZ	6391
rs16832809	36	1	159551916	127	MPZ	6391
rs7734	36	1	180619244	127	GLUL	2752
rs9347	36	1	180619821	127	GLUL	2752
rs17462824	36	1	180622870	127	GLUL	2752
rs1058111	36	1	180623022	127	GLUL	2752
rs12136955	36	1	180625567	127	GLUL	2752
rs12403634	36	1	180626938	127	GLUL	2752
rs12756106	36	1	180631766	127	GLUL	127670
rs1925829	36	1	180637397	127	GLUL	127670

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs689470	36	1	184907681	127	PTGS2	5743
rs2206593	36	1	184909052	127	PTGS2	5743
rs5275	36	1	184909681	127	PTGS2	5743
rs5277	36	1	184914820	127	PTGS2	5743
rs4648261	36	1	184915627	127	PTGS2	5743
rs2745557	36	1	184915844	127	PTGS2	5743
rs689466	36	1	184917374	127	PTGS2	5743
rs12042763	36	1	184918499	127	PTGS2	5743
rs10911907	36	1	184923125	127	PTGS2	5743
rs1009658	36	1	226170404	127	WNT9A	7483
rs12748472	36	1	226170998	127	WNT9A	7483
rs3820623	36	1	226173885	127	WNT9A	7483
rs8192633	36	1	226176094	127	WNT9A	7483
rs10127943	36	1	226176687	127	WNT9A	7483
rs12046421	36	1	226177357	127	WNT9A	7483
rs2527614	36	1	226193093	127	WNT9A	7483
rs680997	36	1	226193850	127	WNT9A	7483
rs697763	36	1	226259245	127	WNT3A	89780
rs708122	36	1	226283620	127	WNT3A	89780
rs10916258	36	1	226286505	127	WNT3A	89780
rs752107	36	1	226313974	127	WNT3A	89780
rs7536290	36	1	228903325	127	AGT	183
rs11122574	36	1	228904431	127	AGT	183
rs7079	36	1	228904954	127	AGT	183
rs2478523	36	1	228908132	127	AGT	183
rs3789664	36	1	228910047	127	AGT	183
rs2493131	36	1	228910128	127	AGT	183
rs6687360	36	1	228911615	127	AGT	183
rs11568054	36	1	228912178	127	AGT	183
rs699	36	1	228912417	127	AGT	183
rs4762	36	1	228912600	127	AGT	183
rs2004776	36	1	228915325	127	AGT	183
rs3789678	36	1	228916105	127	AGT	183
rs5050	36	1	228916509	127	AGT	183
rs2071406	36	1	228917264	127	AGT	183
rs2493137	36	1	228918739	127	AGT	183
rs1326886	36	1	228926383	127	AGT	183
rs6746378	36	2	43851116	127	DYNC2LI1	130271
rs7606529	36	2	43854289	127	DYNC2LI1	51626
rs2288709	36	2	43857514	127	DYNC2LI1	51626
rs17031514	36	2	43860159	127	DYNC2LI1	51626
rs3815995	36	2	43864124	127	DYNC2LI1	51626
rs11695056	36	2	43868913	127	DYNC2LI1	51626
rs9309107	36	2	43875330	127	DYNC2LI1	51626
rs10208317	36	2	43880895	127	DYNC2LI1	51626
rs11556157	36	2	43881517	127	DYNC2LI1	51626
rs17343939	36	2	54614833	127	SPTBN1	56969
rs9309255	36	2	54627345	127	SPTBN1	6711
rs11892788	36	2	54637612	127	SPTBN1	6711
rs4671961	36	2	54652100	127	SPTBN1	6711
rs10204932	36	2	54652631	127	SPTBN1	6711
rs2229506	36	2	54698294	127	SPTBN1	6711
rs6715538	36	2	54701438	127	SPTBN1	6711
rs2971886	36	2	54704804	127	SPTBN1	6711
rs12624153	36	2	54711305	127	SPTBN1	6711
rs1052788	36	2	54712015	127	SPTBN1	6711
rs2229503	36	2	54712168	127	SPTBN1	6711
rs2941579	36	2	54715329	127	SPTBN1	6711
rs6760298	36	2	54719324	127	SPTBN1	6711
rs6748715	36	2	54719998	127	SPTBN1	6711
rs2941584	36	2	54735125	127	SPTBN1	6711
rs17344343	36	2	54735795	127	SPTBN1	6711
rs17416242	36	2	54737289	127	SPTBN1	6711
rs17416291	36	2	54740732	127	SPTBN1	6711
rs17046097	36	2	54741579	127	SPTBN1	6711
rs2941587	36	2	54742001	127	SPTBN1	6711
rs2971879	36	2	54742037	127	SPTBN1	6711
rs2971878	36	2	54742282	127	SPTBN1	6711
rs1047465	36	2	54742519	127	SPTBN1	6711
rs2971877	36	2	54742640	127	SPTBN1	6711
rs10528	36	2	54742653	127	SPTBN1	6711
rs1047499	36	2	54742894	127	SPTBN1	6711
rs3771748	36	2	74460295	127	DCTN1	1639
rs2229169	36	2	96144443	127	ADRA2B	151



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rs11692435	36	2	97641786	127	ACTR1B	10120
rs10496323	36	2	97656271	127	ACTR1B	728537
rs6745653	36	2	97656429	127	ACTR1B	728537
rs9711882	36	2	149508149	127	KIF5C	727742
rs9711441	36	2	149508356	127	KIF5C	727742
rs9288721	36	2	149508624	127	KIF5C	727742
rs9711454	36	2	149508669	127	KIF5C	727742
rs9711815	36	2	149512294	127	KIF5C	727742
rs11893617	36	2	149513319	127	KIF5C	727742
rs9287841	36	2	149513821	127	KIF5C	727742
rs9679707	36	2	149513954	127	KIF5C	727742
rs9679278	36	2	149514117	127	KIF5C	727742
rs4459700	36	2	149517344	127	KIF5C	727742
rs6751242	36	2	149517518	127	KIF5C	727742
rs7569536	36	2	149519120	127	KIF5C	727742
rs6722730	36	2	149520062	127	KIF5C	727742
rs4130557	36	2	149520882	127	KIF5C	727742
rs6710001	36	2	149525164	127	KIF5C	727742
rs11885746	36	2	149525475	127	KIF5C	727742
rs11885858	36	2	149525687	127	KIF5C	727742
rs6730426	36	2	149530152	127	KIF5C	727742
rs7564570	36	2	149535222	127	KIF5C	727742
rs6717088	36	2	149535880	127	KIF5C	727742
rs6738453	36	2	149539156	127	KIF5C	727742
rs6755213	36	2	149539190	127	KIF5C	727742
rs11901442	36	2	149546378	127	KIF5C	727742
rs7573156	36	2	149558655	127	KIF5C	727742
rs6738277	36	2	149562206	127	KIF5C	727742
rs6736802	36	2	149566980	127	KIF5C	727742
rs6721330	36	2	149567152	127	KIF5C	727742
rs6435220	36	2	149569925	127	KIF5C	727742
rs4667372	36	2	149570507	127	KIF5C	727742
rs4452104	36	2	149571652	127	KIF5C	727742
rs6435387	36	2	149573496	127	KIF5C	727742
rs7577450	36	2	149584207	127	KIF5C	727742
rs1568853	36	2	149594837	127	KIF5C	130576
rs10933498	36	2	149595915	127	KIF5C	130576
rs17347194	36	2	149596430	127	KIF5C	130576
rs7574918	36	2	165647425	127	SCN3A	6328
rs2165208	36	2	165658095	127	SCN3A	6328
rs1347992	36	2	165670111	127	SCN3A	6328
rs1158135	36	2	165688559	127	SCN3A	6328
rs17829560	36	2	165689591	127	SCN3A	6328
rs1439806	36	2	165700012	127	SCN3A	6328
rs1946892	36	2	165704353	127	SCN3A	6328
rs16850131	36	2	165711725	127	SCN3A	6328
rs4667792	36	2	165726600	127	SCN3A	6328
rs4145346	36	2	165739570	127	SCN3A	6328
rs11894144	36	2	165742551	127	SCN3A	6328
rs2390165	36	2	165768165	127	SCN3A	6328
rs6719780	36	2	165774518	127	SCN3A	6328
rs6727857	36	2	165776529	127	SCN3A	6328
rs17804037	36	2	166761274	127	SCN9A	6335
rs16851751	36	2	166761632	127	SCN9A	6335
rs7582791	36	2	166777500	127	SCN9A	6335
rs7600169	36	2	166789225	127	SCN9A	6335
rs16851799	36	2	166794660	127	SCN9A	6335
rs10170041	36	2	166795107	127	SCN9A	6335
rs6746030	36	2	166807404	127	SCN9A	6335
rs2155879	36	2	166808492	127	SCN9A	6335
rs4426541	36	2	166829202	127	SCN9A	6335
rs4453709	36	2	166834700	127	SCN9A	6335
rs12477229	36	2	166843902	127	SCN9A	6335
rs6706811	36	2	166849948	127	SCN9A	6335
rs9917250	36	2	166851501	127	SCN9A	6335
rs6747673	36	2	166853220	127	SCN9A	6335
rs13402180	36	2	166853241	127	SCN9A	6335
rs12620053	36	2	166866532	127	SCN9A	6335
rs13017637	36	2	166868192	127	SCN9A	6335
rs12994338	36	2	166868275	127	SCN9A	6335
rs4605385	36	2	166869844	127	SCN9A	6335
rs10171225	36	2	166870895	127	SCN9A	6335

## APPENDIX 1-continued

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rs4455169	36	2	166886401	127	SCN9A	6335
rs2138349	36	2	172251643	127	DYNC1I2	1781
rs312924	36	2	172272267	127	DYNC1I2	1781
rs10185633	36	2	172286107	127	DYNC1I2	1781
rs13000153	36	2	172294313	127	DYNC1I2	1781
rs2292816	36	2	172294960	127	DYNC1I2	1781
rs2001350	36	2	177808671	127	NFE2L2	4780
rs1806649	36	2	177826398	127	NFE2L2	4780
rs13005431	36	2	177829358	127	NFE2L2	4780
rs2364722	36	2	177833033	127	NFE2L2	4780
rs2364725	36	2	177841234	127	NFE2L2	4780
rs16865105	36	2	177844875	127	NFE2L2	4780
rs10202963	36	2	201950152	127	TRAK2	66008
rs10931943	36	2	201951206	127	TRAK2	66008
rs3795966	36	2	201953489	127	TRAK2	66008
rs2244438	36	2	201960784	127	TRAK2	66008
rs13022344	36	2	201972401	127	TRAK2	66008
rs2540334	36	2	201979592	127	TRAK2	66008
rs12473209	36	2	201988178	127	TRAK2	729191
rs1009276	36	2	202031201	127	TRAK2	55437
rs733618	36	2	204439189	127	CTLA4	1493
rs4553808	36	2	204439250	127	CTLA4	1493
rs11571316	36	2	204439334	127	CTLA4	1493
rs11571317	36	2	204440253	127	CTLA4	1493
rs5742909	36	2	204440592	127	CTLA4	1493
rs231775	36	2	204440959	127	CTLA4	1493
rs7596898	36	2	219427976	127	WNT6	7475
rs11695967	36	2	219429434	127	WNT6	7475
rs6747776	36	2	219433562	127	WNT6	7475
rs6754599	36	2	219440386	127	WNT6	7475
rs3806557	36	2	219452118	127	WNT10A; WNT6	80326
rs7349332	36	2	219464627	127	WNT10A	80326
rs4574113	36	2	219470906	127	WNT10A	80326
rs755302	36	2	241301068	127	KIF1A	547
rs4613	36	2	241301960	127	KIF1A	547
rs3732341	36	2	241304217	127	KIF1A	547
rs3772050	36	2	241321413	127	KIF1A	547
rs10174559	36	2	241325449	127	KIF1A	547
rs7578279	36	2	241325937	127	KIF1A	547
rs3772054	36	2	241327201	127	KIF1A	547
rs10196604	36	2	241334748	127	KIF1A	547
rs7598218	36	2	241346971	127	KIF1A	547
rs3821345	36	2	241352633	127	KIF1A	547
rs11681427	36	2	241354900	127	KIF1A	547
rs2288750	36	2	241371118	127	KIF1A	547
rs4676366	36	2	241382335	127	KIF1A	547
rs734586	36	2	241383427	127	KIF1A	547
rs3755539	36	2	241387890	127	KIF1A	547
rs4455151	36	2	241393045	127	KIF1A	547
rs13416949	36	2	241399871	127	KIF1A	547
rs4499423	36	2	241411841	127	KIF1A	547
rs12329123	36	2	241414545	127	KIF1A	547
rs11720627	36	3	13830351	127	WNT7A	7476
rs3762725	36	3	13832578	127	WNT7A	7476
rs1124479	36	3	13832859	127	WNT7A	7476
rs1124480	36	3	13832970	127	WNT7A	7476
rs1946620	36	3	13833800	127	WNT7A	7476
rs3796314	36	3	13834333	127	WNT7A	7476
rs9840696	36	3	13840076	127	WNT7A	7476
rs867606	36	3	13844302	127	WNT7A	7476
rs934453	36	3	13845053	127	WNT7A	7476
rs11711182	36	3	13851910	127	WNT7A	7476
rs12634112	36	3	13853890	127	WNT7A	7476
rs17038695	36	3	13854204	127	WNT7A	7476
rs934450	36	3	13862730	127	WNT7A	7476
rs1433355	36	3	13865845	127	WNT7A	7476
rs4257529	36	3	13869117	127	WNT7A	7476
rs1433354	36	3	13872246	127	WNT7A	7476
rs9849631	36	3	13877001	127	WNT7A	7476
rs7641735	36	3	13878475	127	WNT7A	7476
rs9864031	36	3	13883072	127	WNT7A	7476
rs12635960	36	3	13887489	127	WNT7A	7476
rs4685042	36	3	13888278	127	WNT7A	7476

## APPENDIX 1-continued

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SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
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rs1991850	36	3	13897995	127	WNT7A	7476
rs1077524	36	3	13905134	127	WNT7A	7476
rs6768050	36	3	13905491	127	WNT7A	7476
rs6782149	36	3	32544100	127	DYNC1LI1	51143
rs2303857	36	3	32553509	127	DYNC1LI1	51143
rs7621564	36	3	32572011	127	DYNC1LI1	51143
rs342729	36	3	32572136	127	DYNC1LI1	51143
rs9867284	36	3	32574240	127	DYNC1LI1	51143
rs3853720	36	3	32590673	127	DYNC1LI1	51143
rs11564445	36	3	41242756	127	CTNNB1	1499
rs11564447	36	3	41243358	127	CTNNB1	1499
rs4135385	36	3	41254444	127	CTNNB1	1499
rs2953	36	3	41256392	127	CTNNB1	1499
rs11706227	36	3	55471300	127	WNT5A	7474
rs597437	36	3	55471449	127	WNT5A	7474
rs11710229	36	3	55472993	127	WNT5A	7474
rs590386	36	3	55474447	127	WNT5A	7474
rs1829556	36	3	55476215	127	WNT5A	7474
rs7622120	36	3	55479770	127	WNT5A	7474
rs11918967	36	3	55480430	127	WNT5A	7474
rs648872	36	3	55494897	127	WNT5A	7474
rs566926	36	3	55495818	127	WNT5A	7474
rs506611	36	3	55497809	127	WNT5A	7474
rs557077	36	3	55506307	127	WNT5A	7474
rs2472671	36	3	120985735	127	NR1I2	8856
rs10934498	36	3	120987071	127	NR1I2	8856
rs1357459	36	3	120997246	127	NR1I2	8856
rs2461822	36	3	121002855	127	NR1I2	8856
rs7643645	36	3	121008187	127	NR1I2	8856
rs2472681	36	3	121012379	127	NR1I2	8856
rs3732359	36	3	121019119	127	NR1I2	8856
rs10511395	36	3	121019249	127	NR1I2	8856
rs3732360	36	3	121019271	127	NR1I2	8856
rs1054190	36	3	121019408	127	NR1I2	8856
rs1054191	36	3	121019587	127	NR1I2	8856
rs3814057	36	3	121019944	127	NR1I2	8856
rs3814058	36	3	121019981	127	NR1I2	8856
rs3108749	36	3	121077178	127	GSK3B	2932
rs6438553	36	3	121122719	127	GSK3B	2932
rs2199503	36	3	121261179	127	GSK3B	2932
rs334555	36	3	121286826	127	GSK3B	2932
rs3755557	36	3	121297647	127	GSK3B	2932
rs17811013	36	3	121299676	127	GSK3B	2932
rs17471	36	3	121300363	127	GSK3B	2932
rs13082681	36	3	123257824	127	CD86	942
rs2715277	36	3	123263840	127	CD86	942
rs6786977	36	3	123265496	127	CD86	942
rs4308217	36	3	123275877	127	CD86	942
rs17203439	36	3	123278196	127	CD86	942
rs9282641	36	3	123279458	127	CD86	942
rs2681422	36	3	123282244	127	CD86	942
rs9831894	36	3	123283177	127	CD86	942
rs11717893	36	3	123289515	127	CD86	942
rs9836399	36	3	123294501	127	CD86	942
rs13064913	36	3	123297201	127	CD86	942
rs1915092	36	3	123306065	127	CD86	942
rs3804588	36	3	123306847	127	CD86	942
rs2681417	36	3	123307887	127	CD86	942
rs2254911	36	3	123311527	127	CD86	942
rs9848900	36	3	123314187	127	CD86	942
rs1129055	36	3	123321009	127	CD86	942
rs1915087	36	3	123321481	127	CD86	942
rs17281995	36	3	123322331	127	CD86	942
rs2715272	36	3	123325931	127	CD86	942
rs2638363	36	3	149901883	127	AGTR1	185
rs2131127	36	3	149906833	127	AGTR1	185
rs4681443	36	3	149915159	127	AGTR1	185
rs12721241	36	3	149924310	127	AGTR1	185
rs379600	36	3	149927175	127	AGTR1	185
rs12721331	36	3	149927683	127	AGTR1	185
rs388915	36	3	149930446	127	AGTR1	185
rs12695902	36	3	149931108	127	AGTR1	185
rs385338	36	3	149931846	127	AGTR1	185

## APPENDIX 1-continued

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rs6801836	36	3	149938227	127	AGTR1	185
rs5182	36	3	149942085	127	AGTR1	185
rs5183	36	3	149942574	127	AGTR1	185
rs275645	36	3	149947144	127	AGTR1	185
rs12639531	36	3	149948041	127	AGTR1	185
rs275643	36	3	149948294	127	AGTR1	185
rs4912527	36	3	185352567	127	DVL3	440991
rs2175525	36	3	185369639	127	DVL3	1857
rs11919795	36	3	185373562	127	DVL3	1857
rs1976700	36	3	185375965	127	DVL3	1173
rs843346	36	3	185376213	127	DVL3	1173
rs17011297	36	4	87152084	127	MAPK10	5602
rs2589523	36	4	87152226	127	MAPK10	5602
rs7677101	36	4	87154441	127	MAPK10	5602
rs2575675	36	4	87154914	127	MAPK10	5602
rs7699978	36	4	87155080	127	MAPK10	5602
rs1201	36	4	87155492	127	MAPK10	5602
rs2589515	36	4	87156612	127	MAPK10	5602
rs958	36	4	87156898	127	MAPK10	5602
rs3775173	36	4	87173891	127	MAPK10	5602
rs1469870	36	4	87178920	127	MAPK10	5602
rs1436522	36	4	87183196	127	MAPK10	5602
rs6815306	36	4	87185351	127	MAPK10	5602
rs9307015	36	4	87188538	127	MAPK10	5602
rs1436529	36	4	87198106	127	MAPK10	5602
rs3775182	36	4	87198607	127	MAPK10	5602
rs4235078	36	4	87248342	127	MAPK10	5602
rs6821745	36	4	87257235	127	MAPK10	5602
rs4560400	36	4	87290185	127	MAPK10	5602
rs6822478	36	4	87295384	127	MAPK10	5602
rs17011419	36	4	87321398	127	MAPK10	5602
rs1460767	36	4	87326932	127	MAPK10	5602
rs12513237	36	4	87334679	127	MAPK10	5602
rs12650052	36	4	87357762	127	MAPK10	5602
rs1460769	36	4	87361272	127	MAPK10	5602
rs17011590	36	4	87388494	127	MAPK10	5602
rs6817452	36	4	87390273	127	MAPK10	5602
rs10516771	36	4	87390302	127	MAPK10	5602
rs1460757	36	4	87401134	127	MAPK10	5602
rs6531914	36	4	87403238	127	MAPK10	5602
rs6855169	36	4	87409854	127	MAPK10	5602
rs12640392	36	4	87417227	127	MAPK10	5602
rs17011659	36	4	87427125	127	MAPK10	5602
rs4693761	36	4	87430495	127	MAPK10	5602
rs17449015	36	4	87440851	127	MAPK10	5602
rs7654796	36	4	87450588	127	MAPK10	5602
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rs769378	36	4	87458788	127	MAPK10	5602
rs6531915	36	4	87459044	127	MAPK10	5602
rs17409687	36	4	87469460	127	MAPK10	5602
rs7677400	36	4	87471821	127	MAPK10	5602
rs4611890	36	4	87478030	127	MAPK10	5602
rs2904100	36	4	87486850	127	MAPK10	5602
rs2869433	36	4	87498120	127	MAPK10	5602
rs17011843	36	4	87516818	127	MAPK10	5602
rs17418221	36	4	87570385	127	MAPK10	5602
rs12507758	36	4	87570764	127	MAPK10	5602
rs4488910	36	4	87581858	127	MAPK10	5602
rs17452273	36	4	87591032	127	MAPK10	5602
rs7675845	36	4	87602300	127	MAPK10	5602
rs10015565	36	4	175800806	127	GLRA3	8001
rs4695940	36	4	175804386	127	GLRA3	8001
rs4334734	36	4	175804733	127	GLRA3	8001
rs12511536	36	4	175816017	127	GLRA3	8001
rs7686453	36	4	175822378	127	GLRA3	8001
rs7697737	36	4	175827908	127	GLRA3	8001
rs7700002	36	4	175831882	127	GLRA3	8001
rs12648678	36	4	175834855	127	GLRA3	8001
rs11939284	36	4	175840333	127	GLRA3	8001
rs1352058	36	4	175842980	127	GLRA3	8001
rs1471817	36	4	175847125	127	GLRA3	8001
rs17363787	36	4	175868255	127	GLRA3	8001
rs4695954	36	4	175868561	127	GLRA3	8001

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs9993143	36	4	175873951	127	GLRA3	8001
rs4594702	36	4	175878481	127	GLRA3	8001
rs17060810	36	4	175885544	127	GLRA3	8001
rs9312559	36	4	175886691	127	GLRA3	8001
rs12509729	36	4	175891718	127	GLRA3	8001
rs6553812	36	4	175894999	127	GLRA3	8001
rs13146324	36	4	175895830	127	GLRA3	8001
rs6850542	36	4	175898418	127	GLRA3	8001
rs1485935	36	4	175907193	127	GLRA3	8001
rs17060835	36	4	175907746	127	GLRA3	8001
rs17060847	36	4	175910652	127	GLRA3	8001
rs7689368	36	4	175916231	127	GLRA3	8001
rs2332940	36	4	175929528	127	GLRA3	8001
rs6855717	36	4	175931605	127	GLRA3	8001
rs10021711	36	4	175948375	127	GLRA3	8001
rs4695963	36	4	175949853	127	GLRA3	8001
rs1994313	36	4	175953201	127	GLRA3	8001
rs4695791	36	4	175960272	127	GLRA3	8001
rs6820174	36	4	175963278	127	GLRA3	8001
rs6851555	36	4	175966282	127	GLRA3	8001
rs7437645	36	4	175990446	127	GLRA3	8001
rs6834798	36	4	175996510	127	GLRA3	8001
rs4695965	36	4	175996696	127	GLRA3	8001
rs4133101	36	5	40715324	127	PTGER4	5734
rs2228058	36	5	40717011	127	PTGER4	5734
rs11957406	36	5	40719324	127	PTGER4	5734
rs4957343	36	5	40730827	127	PTGER4	5734
rs1882619	36	5	112106681	127	APC	324
rs396321	36	5	112141634	127	APC	728217
rs2439595	36	5	112146237	127	APC	324
rs1734242	36	5	112153318	127	APC	324
rs11953943	36	5	112183659	127	APC	324
rs2229992	36	5	112190753	127	APC	324
rs351771	36	5	112192460	127	APC	324
rs13167522	36	5	112195207	127	APC	324
rs41115	36	5	112203669	127	APC	324
rs42427	36	5	112204224	127	APC	324
rs866006	36	5	112204458	127	APC	324
rs459552	36	5	112204655	127	APC	324
rs465899	36	5	112205070	127	APC	324
rs2229995	36	5	112206694	127	APC	324
rs11242126	36	5	132058313	127	KIF3A	11127
rs17690965	36	5	132058566	127	KIF3A	11127
rs1468216	36	5	132064151	127	KIF3A	11127
rs3798130	36	5	132070045	127	KIF3A	11127
rs17691077	36	5	132071250	127	KIF3A	11127
rs3756752	36	5	132101772	127	KIF3A	11127
rs10041787	36	5	137447393	127	WNT8A	7478
rs10036244	36	5	137447624	127	WNT8A	7478
rs6596422	36	5	137454346	127	WNT8A	7478
rs17109205	36	5	148356356	127	SH3TC2	79628
rs11168078	36	5	148357775	127	SH3TC2	79628
rs11168079	36	5	148358031	127	SH3TC2	79628
rs17109208	36	5	148358668	127	SH3TC2	79628
rs1432795	36	5	148358977	127	SH3TC2	79628
rs6885467	36	5	148359748	127	SH3TC2	79628
rs3763022	36	5	148361271	127	SH3TC2	79628
rs1045942	36	5	148361390	127	SH3TC2	79628
rs3763020	36	5	148361511	127	SH3TC2	79628
rs998304	36	5	148362558	127	SH3TC2	79628
rs11740300	36	5	148384113	127	SH3TC2	79628
rs17708342	36	5	148385575	127	SH3TC2	79628
rs6875902	36	5	148388086	127	SH3TC2	79628
rs1432793	36	5	148388294	127	SH3TC2	79628
rs10074456	36	5	148390699	127	SH3TC2	79628
rs2304034	36	5	148391113	127	SH3TC2	79628
rs17109268	36	5	148396298	127	SH3TC2	79628
rs17795259	36	5	148397145	127	SH3TC2	79628
rs17722293	36	5	148402467	127	SH3TC2	79628
rs28173	36	5	148403766	127	SH3TC2	79628
rs36076	36	5	148412254	127	SH3TC2	79628
rs36044	36	5	148421321	127	SH3TC2	79628
rs2915806	36	5	148431108	127	SH3TC2	255187
rs252160	36	5	150067438	127	DCTN4	51164

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs3733925	36	5	150070537	127	DCTN4	51164
rs11954652	36	5	150078076	127	DCTN4	51164
rs9605	36	5	179595857	127	MAPK9	5601
rs6895740	36	5	179600539	127	MAPK9	5601
rs4601008	36	5	179603122	127	MAPK9	5601
rs4362908	36	5	179605431	127	MAPK9	5601
rs4147385	36	5	179610123	127	MAPK9	5601
rs6863088	36	5	179612366	127	MAPK9	5601
rs6868333	36	5	179620378	127	MAPK9	5601
rs13185784	36	5	179626674	127	MAPK9	5601
rs3111515	36	5	179627958	127	MAPK9	5601
rs9968653	36	5	179632110	127	MAPK9	5601
rs2112593	36	5	179633209	127	MAPK9	5601
rs3812066	36	5	179641502	127	MAPK9	5601
rs6867398	36	5	179644666	127	MAPK9	5601
rs915654	36	6	31646476	127	TNF	4049
rs2071590	36	6	31647747	127	TNF	4049
rs909253	36	6	31648292	127	TNF	4049
rs1799964	36	6	31650287	127	TNF	4049
rs1800630	36	6	31650455	127	TNF	4049
rs1800629	36	6	31651010	127	TNF	7124
rs3093661	36	6	31651737	127	TNF	7124
rs3093662	36	6	31652168	127	TNF	7124
rs4645843	36	6	31652541	127	TNF	7124
rs769178	36	6	31655493	127	TNF	4050
rs241429	36	6	32911818	127	PSMB8	6891
rs3819715	36	6	32912197	127	PSMB8	6891
rs241426	36	6	32912531	127	PSMB8	6891
rs3819720	36	6	32912548	127	PSMB8	6891
rs17583244	36	6	32912665	127	PSMB8	6891
rs3819721	36	6	32912776	127	PSMB8	6891
rs1871665	36	6	32912857	127	PSMB8	6891
rs241424	36	6	32912912	127	PSMB8	6891
rs2239701	36	6	32913027	127	PSMB8	6891
rs4713598	36	6	32914764	127	PSMB8	6891
rs3763366	36	6	32915424	127	PSMB8	6891
rs2071543	36	6	32919607	127	PSMB8	5696
rs2071542	36	6	32919623	127	PSMB8	5696
rs2071463	36	6	32920506	127	PSMB8; PSMB9	5696
rs2071541	36	6	32920836	127	PSMB8; PSMB9	6890
rs9469283	36	6	32921734	127	PSMB8; PSMB9	6890
rs2071482	36	6	32924678	127	PSMB8; PSMB9	6890
rs241423	36	6	32925988	127	PSMB8; PSMB9	6890
rs2071538	36	6	32926656	127	PSMB8; PSMB9	6890
rs4148879	36	6	32927456	127	PSMB8; PSMB9	6890
rs991760	36	6	32931545	127	PSMB9	5698
rs17587	36	6	32933068	127	PSMB9	5698
rs9276831	36	6	32940011	127	PSMB9	5698
rs851027	36	6	36098853	127	MAPK14	116369
rs13196204	36	6	36106754	127	MAPK14	1432
rs3804454	36	6	36114976	127	MAPK14	1432
rs2237094	36	6	36116122	127	MAPK14	1432
rs12211012	36	6	36146186	127	MAPK14	1432
rs9357207	36	6	36147131	127	MAPK14	1432
rs851006	36	6	36173163	127	MAPK14	1432
rs6457878	36	6	36184258	127	MAPK14	1432
rs3804452	36	6	36184912	127	MAPK14	1432
rs3804451	36	6	36185939	127	MAPK14	1432
rs6922865	36	6	36202166	127	MAPK13	5603
rs3761977	36	6	36204425	127	MAPK13	5603
rs1059227	36	6	36206388	127	MAPK13	5603
rs2071864	36	6	36208710	127	MAPK13	5603
rs2252430	36	6	36211899	127	MAPK13	5603
rs2071863	36	6	36215150	127	MAPK13	5603
rs13212041	36	6	78227843	127	HTR1B	3351
rs6297	36	6	78228660	127	HTR1B	3351
rs6296	36	6	78228979	127	HTR1B	3351
rs6298	36	6	78229711	127	HTR1B	3351
rs130058	36	6	78230000	127	HTR1B	3351
rs4140535	36	6	78231771	127	HTR1B	3351
rs2226183	36	6	78233257	127	HTR1B	3351
rs1213369	36	6	78234976	127	HTR1B	3351
rs1213370	36	6	78235516	127	HTR1B	3351
rs9400317	36	6	110114340	127	FIG4	221264

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs4947012	36	6	110118967	127	FIG4	221264
rs3823234	36	6	110130366	127	FIG4	9896
rs9398215	36	6	110146535	127	FIG4	9896
rs4947015	36	6	110159208	127	FIG4	9896
rs6568602	36	6	110159969	127	FIG4	9896
rs11964533	36	6	110165693	127	FIG4	9896
rs2295837	36	6	110171621	127	FIG4	9896
rs17612758	36	6	110172123	127	FIG4	9896
rs13191444	36	6	110190757	127	FIG4	9896
rs17613127	36	6	110205619	127	FIG4	9896
rs11153219	36	6	110209321	127	FIG4	9896
rs10499054	36	6	110212927	127	FIG4	9896
rs9885672	36	6	110214210	127	FIG4	9896
rs4499962	36	6	110225279	127	FIG4	9896
rs4473902	36	6	110226960	127	FIG4	9896
rs4495300	36	6	110231221	127	FIG4	9896
rs13220781	36	6	110233086	127	FIG4	9896
rs17070984	36	6	110233524	127	FIG4	9896
rs9398218	36	6	110252996	127	FIG4	9896
rs3757070	36	6	153111414	127	VIP	7432
rs12212849	36	6	153111896	127	VIP	7432
rs1407267	36	6	153112144	127	VIP	7432
rs3823082	36	6	153116015	127	VIP	7432
rs12201030	36	6	153118482	127	VIP	7432
rs688136	36	6	153121754	127	VIP	7432
rs664368	36	6	153125119	127	VIP	7432
rs671330	36	6	153126927	127	VIP	7432
rs6912029	36	6	154402201	127	OPRM1	4988
rs1799971	36	6	154402490	127	OPRM1	4988
rs557748	36	6	154405995	127	OPRM1	4988
rs4870266	36	6	154410691	127	OPRM1	4988
rs610231	36	6	154420170	127	OPRM1	4988
rs3823010	36	6	154420845	127	OPRM1	4988
rs589046	36	6	154434831	127	OPRM1	4988
rs483021	36	6	154439021	127	OPRM1	4988
rs563649	36	6	154449660	127	OPRM1	4988
rs2075572	36	6	154453697	127	OPRM1	4988
rs510587	36	6	154455121	127	OPRM1	4988
rs540825	36	6	154456139	127	OPRM1	4988
rs675026	36	6	154456256	127	OPRM1	4988
rs562859	36	6	154456266	127	OPRM1	4988
rs3798683	36	6	154460107	127	OPRM1	4988
rs599548	36	6	154460254	127	OPRM1	4988
rs511420	36	6	154465725	127	OPRM1	4988
rs512053	36	6	154481209	127	OPRM1	4988
rs10485058	36	6	154486907	127	OPRM1	4988
rs538174	36	6	154494229	127	OPRM1	4988
rs13193545	36	6	154503514	127	OPRM1	26034
rs9397687	36	6	154503778	127	OPRM1	26034
rs518596	36	6	154504070	127	OPRM1	26034
rs10223804	36	6	154504084	127	OPRM1	26034
rs483481	36	6	154505660	127	OPRM1	26034
rs569284	36	6	154506022	127	OPRM1	26034
rs6904856	36	6	154508824	127	OPRM1	26034
rs9371778	36	6	154515517	127	OPRM1	26034
rs9383693	36	6	154516563	127	OPRM1	26034
rs17277929	36	6	154519605	127	OPRM1	26034
rs2236257	36	6	154520259	127	OPRM1	26034
rs12199124	36	6	154527332	127	OPRM1	26034
rs7755635	36	6	154528053	127	OPRM1	26034
rs9397692	36	6	154529007	127	OPRM1	26034
rs2281617	36	6	154529113	127	OPRM1	26034
rs6939625	36	6	154529487	127	OPRM1	26034
rs12207621	36	6	154543952	127	OPRM1	26034
rs9479779	36	6	154544380	127	OPRM1	26034
rs1040822	36	6	154560330	127	OPRM1	26034
rs17085185	36	6	154561292	127	OPRM1	26034
rs9322451	36	6	154564353	127	OPRM1	26034
rs950808	36	6	154564963	127	OPRM1	26034
rs9397182	36	6	154568777	127	OPRM1	26034
rs9479791	36	6	154571206	127	OPRM1	26034
rs6913456	36	6	154572672	127	OPRM1	26034
rs6921548	36	6	154582015	127	OPRM1	26034
rs12212773	36	6	154592810	127	OPRM1	26034

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs9371781	36	6	154593899	127	OPRM1	26034
rs17292684	36	6	154596299	127	OPRM1	26034
rs6935927	36	6	154602029	127	OPRM1	26034
rs11155954	36	6	154608434	127	OPRM1	26034
rs9397698	36	6	154609054	127	OPRM1	26034
rs17214592	36	6	154612099	127	OPRM1	26034
rs7738233	36	6	154612240	127	OPRM1	26034
rs1474644	36	6	170690820	127	PSMB1	5689
rs2056970	36	6	170691401	127	PSMB1	5689
rs1474642	36	6	170694486	127	PSMB1	5689
rs9356664	36	6	170702320	127	PSMB1	5689
rs2206286	36	6	170703760	127	PSMB1	5689
rs12210583	36	6	170703954	127	PSMB1	5689
rs12717	36	6	170704225	127	PSMB1	5689
rs12210836	36	6	170704381	127	PSMB1	5689
rs2179373	36	6	170705298	127	PSMB1	6908
rs6456230	36	6	170709501	127	PSMB1	6908
rs852432	36	7	5529266	127	ACTB	60
rs13447427	36	7	5531960	127	ACTB	60
rs852392	36	7	5538658	127	ACTB	60
rs6463491	36	7	5545045	127	ACTB	60
rs12700386	36	7	22729534	127	IL6	3569
rs2069824	36	7	22731757	127	IL6	3569
rs1474348	36	7	22734433	127	IL6	3569
rs1524107	36	7	22734744	127	IL6	3569
rs2069840	36	7	22735097	127	IL6	3569
rs2069860	36	7	22737563	127	IL6	3569
rs2069849	36	7	22737681	127	IL6	3569
rs2069861	36	7	22738179	127	IL6	3569
rs10242595	36	7	22740756	127	IL6	3569
rs11766273	36	7	22742188	127	IL6	3569
rs7800861	36	7	24287185	127	NPY	4852
rs12700524	36	7	24287939	127	NPY	4852
rs3857723	36	7	24288352	127	NPY	4852
rs16139	36	7	24291404	127	NPY	4852
rs9785023	36	7	24291534	127	NPY	4852
rs16135	36	7	24294445	127	NPY	4852
rs5574	36	7	24295658	127	NPY	4852
rs16475	36	7	24298011	127	NPY	4852
rs16473	36	7	24300176	127	NPY	4852
rs16472	36	7	24300594	127	NPY	4852
rs2529439	36	7	30610273	127	GARS	2617
rs3807632	36	7	30611474	127	GARS	2617
rs728539	36	7	30614576	127	GARS	2617
rs1986756	36	7	30618463	127	GARS	2617
rs10951271	36	7	30627463	127	GARS	2617
rs2709778	36	7	30633958	127	GARS	2617
rs1859644	36	7	30641184	127	GARS	2617
rs2908200	36	7	75766731	127	HSPB1	3315
rs2868370	36	7	75768736	127	HSPB1	3315
rs7459185	36	7	75772576	127	HSPB1	3315
rs17773605	36	7	94762474	127	PON1	55607
rs8491	36	7	94763550	127	PON1	55607
rs3735590	36	7	94765431	127	PON1	5444
rs854551	36	7	94765613	127	PON1	5444
rs854552	36	7	94765860	127	PON1	5444
rs854555	36	7	94768327	127	PON1	5444
rs3917550	36	7	94772509	127	PON1	5444
rs3917594	36	7	94775375	127	PON1	5444
rs662	36	7	94775382	127	PON1	5444
rs3917541	36	7	94775560	127	PON1	5444
rs2299257	36	7	94780701	127	PON1	5444
rs854561	36	7	94784953	127	PON1	5444
rs2074351	36	7	94785735	127	PON1	5444
rs2272365	36	7	94786562	127	PON1	5444
rs3917490	36	7	94786777	127	PON1	5444
rs2049649	36	7	94787265	127	PON1	5444
rs2299260	36	7	94787473	127	PON1	5444
rs2299261	36	7	94787599	127	PON1	5444
rs854568	36	7	94787737	127	PON1	5444
rs2299262	36	7	94787864	127	PON1	5444
rs854569	36	7	94787991	127	PON1	5444
rs2237583	36	7	94788113	127	PON1	5444
rs2237584	36	7	94788773	127	PON1	5444



## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs854572	36	7	94792632	127	PON1	5444
rs854573	36	7	94792799	127	PON1	5444
rs17166818	36	7	94796564	127	PON1	5444
rs13228784	36	7	94798761	127	PON1	5444
rs4729205	36	7	95237165	127	DYNC111	1780
rs983350	36	7	95242854	127	DYNC111	1780
rs7798435	36	7	95250879	127	DYNC111	1780
rs1478983	36	7	95250893	127	DYNC111	1780
rs4729206	36	7	95258613	127	DYNC111	1780
rs6962547	36	7	95258858	127	DYNC111	1780
rs2706888	36	7	95262393	127	DYNC111	1780
rs11767450	36	7	95274371	127	DYNC111	1780
rs940424	36	7	95274841	127	DYNC111	1780
rs1922332	36	7	95279286	127	DYNC111	1780
rs2690294	36	7	95283196	127	DYNC111	1780
rs1227514	36	7	95298252	127	DYNC111	1780
rs11769486	36	7	95332678	127	DYNC111	1780
rs3757697	36	7	95337170	127	DYNC111	1780
rs6967902	36	7	95347742	127	DYNC111	1780
rs10249566	36	7	95350562	127	DYNC111	1780
rs4727329	36	7	95360863	127	DYNC111	1780
rs7809646	36	7	95364235	127	DYNC111	1780
rs984862	36	7	95367092	127	DYNC111	1780
rs4357216	36	7	95369751	127	DYNC111	1780
rs4729224	36	7	95384055	127	DYNC111	1780
rs10243540	36	7	95384186	127	DYNC111	1780
rs6952893	36	7	95384689	127	DYNC111	1780
rs319328	36	7	95387648	127	DYNC111	1780
rs319314	36	7	95394566	127	DYNC111	1780
rs6950190	36	7	95396294	127	DYNC111	1780
rs2860011	36	7	95397030	127	DYNC111	1780
rs319312	36	7	95397227	127	DYNC111	1780
rs17775819	36	7	95397951	127	DYNC111	1780
rs1488516	36	7	95401327	127	DYNC111	1780
rs2239954	36	7	95415377	127	DYNC111	1780
rs319345	36	7	95415761	127	DYNC111	1780
rs12155036	36	7	95416050	127	DYNC111	1780
rs4729228	36	7	95419185	127	DYNC111	1780
rs13237676	36	7	95430998	127	DYNC111	1780
rs1548399	36	7	95435367	127	DYNC111	1780
rs12537028	36	7	95437211	127	DYNC111	1780
rs13231718	36	7	95438304	127	DYNC111	1780
rs319301	36	7	95442487	127	DYNC111	1780
rs1488517	36	7	95446689	127	DYNC111	1780
rs17705297	36	7	95447233	127	DYNC111	1780
rs319322	36	7	95447893	127	DYNC111	1780
rs2073984	36	7	95452403	127	DYNC111	1780
rs17705339	36	7	95454245	127	DYNC111	1780
rs1685818	36	7	95454893	127	DYNC111	1780
rs2299269	36	7	95457313	127	DYNC111	1780
rs12704828	36	7	95461843	127	DYNC111	1780
rs1488514	36	7	95465707	127	DYNC111	1780
rs756860	36	7	95467014	127	DYNC111	1780
rs81018	36	7	95467762	127	DYNC111	1780
rs4727332	36	7	95468537	127	DYNC111	1780
rs1488515	36	7	95469132	127	DYNC111	1780
rs739513	36	7	95473084	127	DYNC111	1780
rs7780260	36	7	95478193	127	DYNC111	1780
rs13241648	36	7	95483235	127	DYNC111	1780
rs319319	36	7	95484060	127	DYNC111	1780
rs319318	36	7	95486023	127	DYNC111	1780
rs1994506	36	7	95486102	127	DYNC111	1780
rs319290	36	7	95491815	127	DYNC111	1780
rs7782220	36	7	95496227	127	DYNC111	1780
rs2214097	36	7	95497816	127	DYNC111	1780
rs2299278	36	7	95504398	127	DYNC111	1780
rs1048666	36	7	95506600	127	DYNC111	1780
rs13227274	36	7	95533741	127	DYNC111	1780
rs7796347	36	7	95539385	127	DYNC111	1780
rs42084	36	7	95547259	127	DYNC111	1780
rs2299287	36	7	95550618	127	DYNC111	1780
rs42065	36	7	95556515	127	DYNC111	1780
rs452	36	7	95559946	127	DYNC111	1780
rs17776584	36	7	95563294	127	DYNC111	1780

## APPENDIX 1-continued

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rs7794344	36	7	95564950	127	DYNC1I1	1780
rs6966540	36	7	95565903	127	DYNC1I1	1780
rs12670075	36	7	95569095	127	DYNC1I1	1780
rs6956305	36	7	99079246	127	CYP3A5	1577
rs15524	36	7	99083850	127	CYP3A5	1577
rs4646450	36	7	99104254	127	CYP3A5	1577
rs776746	36	7	99108475	127	CYP3A5	1577
rs12333983	36	7	99192050	127	CYP3A4	1576
rs4986910	36	7	99196460	127	CYP3A4	1576
rs4646437	36	7	99203019	127	CYP3A4	1576
rs2740574	36	7	99220032	127	CYP3A4	1576
rs2571992	36	7	99357852	127	GJE1	349149
rs2527908	36	7	99358499	127	GJE1	349149
rs11977827	36	7	99364252	127	GJE1	349149
rs11974610	36	7	99365913	127	GJE1	349149
rs2525549	36	7	99371047	127	GJE1	349149
rs41796	36	7	116297475	127	CAPZA2	830
rs12537143	36	7	116304161	127	CAPZA2	830
rs4808	36	7	116315476	127	CAPZA2	830
rs3173936	36	7	116345175	127	CAPZA2	830
rs1049618	36	7	116345952	127	CAPZA2	830
rs1978105	36	7	116350167	127	CAPZA2	830
rs887574	36	7	116703248	127	WNT2	7472
rs887575	36	7	116703464	127	WNT2	7472
rs4730775	36	7	116704354	127	WNT2	7472
rs2024233	36	7	116704663	127	WNT2	7472
rs2228946	36	7	116705321	127	WNT2	7472
rs733153	36	7	116706028	127	WNT2	7472
rs2896218	36	7	116707214	127	WNT2	7472
rs3779547	36	7	116718198	127	WNT2	7472
rs10227271	36	7	116727284	127	WNT2	7472
rs39306	36	7	116728472	127	WNT2	7472
rs2285544	36	7	116731519	127	WNT2	7472
rs1989836	36	7	116734432	127	WNT2	7472
rs2285545	36	7	116735407	127	WNT2	7472
rs39312	36	7	116742021	127	WNT2	7472
rs739517	36	7	116742935	127	WNT2	7472
rs39321	36	7	116756145	127	WNT2	7472
rs6961545	36	7	116759067	127	WNT2	7472
rs3757552	36	7	120751201	127	WNT16	51384
rs2908004	36	7	120757005	127	WNT16	51384
rs3801387	36	7	120762001	127	WNT16	51384
rs2707471	36	7	120763913	127	WNT16	51384
rs3801385	36	7	120764779	127	WNT16	51384
rs13225343	36	7	133772980	127	AKR1B1	231
rs10252030	36	7	133774414	127	AKR1B1	231
rs17167841	36	7	133775472	127	AKR1B1	231
rs2734649	36	7	133786291	127	AKR1B1	231
rs1790998	36	7	133788920	127	AKR1B1	231
rs17188118	36	7	133792608	127	AKR1B1	231
rs5053	36	7	133794403	127	AKR1B1	231
rs1708403	36	7	133802904	127	AKR1B1	231
rs11489454	36	7	149570491	127	ARP11	653857
rs2530976	36	7	149586818	127	ARP11	653857
rs17134508	36	7	149601156	127	ARP11	653857
rs17835738	36	7	149623031	127	ARP11	653857
rs2976441	36	8	24863702	127	NEFL	4747
rs2979704	36	8	24864984	127	NEFL	4747
rs17052849	36	8	24865862	127	NEFL	4747
rs1059111	36	8	24866005	127	NEFL	4747
rs2979687	36	8	24870320	127	NEFL	4747
rs3757985	36	8	24872354	127	NEFL	4747
rs17830286	36	8	24873062	127	NEFL	4747
rs17830392	36	8	24874818	127	NEFL	4747
rs2976423	36	8	24877933	127	NEFL	4747
rs2614082	36	8	28226449	127	PNOC	5368
rs2722894	36	8	28227458	127	PNOC	5368
rs12677384	36	8	28228417	127	PNOC	5368
rs3808366	36	8	28229670	127	PNOC	5368
rs17058952	36	8	28230273	127	PNOC	5368
rs1563945	36	8	28230805	127	PNOC	5368
rs11779594	36	8	28237674	127	PNOC	5368
rs7840629	36	8	28238368	127	PNOC	5368

## APPENDIX 1-continued

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rs2614108	36	8	28244552	127	PNOC	5368
rs189509	36	8	28247625	127	PNOC	5368
rs3735736	36	8	28250016	127	PNOC	5368
rs351784	36	8	28253666	127	PNOC	5368
rs17058985	36	8	28254863	127	PNOC	5368
rs904053	36	8	28258855	127	PNOC	55893
rs351779	36	8	28260183	127	PNOC	55893
rs4733400	36	8	30132056	127	DCTN6	10671
rs7829853	36	8	30143082	127	DCTN6	10671
rs16876610	36	8	30149412	127	DCTN6	10671
rs2242457	36	8	30162200	127	DCTN6	10671
rs7839445	36	8	54303000	127	OPRK1	4986
rs7843295	36	8	54303951	127	OPRK1	4986
rs963549	36	8	54304377	127	OPRK1	4986
rs16918875	36	8	54304707	127	OPRK1	4986
rs702764	36	8	54304710	127	OPRK1	4986
rs16918909	36	8	54312587	127	OPRK1	4986
rs1365098	36	8	54315236	127	OPRK1	4986
rs6473799	36	8	54315676	127	OPRK1	4986
rs17272364	36	8	54318360	127	OPRK1	4986
rs7836120	36	8	54320092	127	OPRK1	4986
rs6985606	36	8	54323669	127	OPRK1	4986
rs12677359	36	8	54333799	127	OPRK1	4986
rs4738450	36	8	75426887	127	GDAP1	54332
rs6472842	36	8	75441012	127	GDAP1	54332
rs10504580	36	8	75441371	127	GDAP1	54332
rs7844272	36	8	134314989	127	NDRG1	10397
rs2929975	36	8	134315900	127	NDRG1	10397
rs1049697	36	8	134319347	127	NDRG1	10397
rs3779945	36	8	134321914	127	NDRG1	10397
rs17641864	36	8	134322616	127	NDRG1	10397
rs2929978	36	8	134323979	127	NDRG1	10397
rs11784952	36	8	134324460	127	NDRG1	10397
rs2977557	36	8	134326285	127	NDRG1	10397
rs2233339	36	8	134327893	127	NDRG1	10397
rs2233336	36	8	134330130	127	NDRG1	10397
rs10956698	36	8	134332521	127	NDRG1	10397
rs3779939	36	8	134332635	127	NDRG1	10397
rs7018287	36	8	134333236	127	NDRG1	10397
rs3779936	36	8	134334930	127	NDRG1	10397
rs2272650	36	8	134336152	127	NDRG1	10397
rs1011460	36	8	134339120	127	NDRG1	10397
rs2929984	36	8	134340069	127	NDRG1	10397
rs2233329	36	8	134340511	127	NDRG1	10397
rs2233327	36	8	134340688	127	NDRG1	10397
rs7839335	36	8	134340830	127	NDRG1	10397
rs2929985	36	8	134341389	127	NDRG1	10397
rs7825728	36	8	134341479	127	NDRG1	10397
rs4736442	36	8	134343050	127	NDRG1	10397
rs2929989	36	8	134346995	127	NDRG1	10397
rs3779932	36	8	134348162	127	NDRG1	10397
rs2929994	36	8	134354866	127	NDRG1	10397
rs2929995	36	8	134354989	127	NDRG1	10397
rs10956699	36	8	134357765	127	NDRG1	10397
rs4504614	36	8	134367674	127	NDRG1	10397
rs2004066	36	8	134368101	127	NDRG1	10397
rs3802254	36	8	134369548	127	NDRG1	10397
rs3802253	36	8	134373063	127	NDRG1	10397
rs10108354	36	8	134378316	127	NDRG1	10397
rs4373502	36	8	134384423	127	NDRG1	10397
rs7007149	36	8	134386997	127	NDRG1	10397
rs3808870	36	9	34611238	127	DCTN3	138715
rs3808869	36	9	34612389	127	DCTN3	138715
rs10814129	36	9	34613718	127	DCTN3	138715
rs10972175	36	9	34615409	127	DCTN3	138715
rs17589865	36	9	93829611	127	SPTLC1	10558
rs6479399	36	9	93831953	127	SPTLC1	10558
rs7027257	36	9	93840128	127	SPTLC1	10558
rs10992216	36	9	93855978	127	SPTLC1	10558
rs10820936	36	9	93870795	127	SPTLC1	10558
rs17749165	36	9	93900718	127	SPTLC1	10558
rs2297568	36	9	93914472	127	SPTLC1	10558
rs7858974	36	9	93919931	127	SPTLC1	10558

## APPENDIX 1-continued

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rs7024547	36	9	93922309	127	SPTLC1	10558
rs7872727	36	9	110665911	127	IKBKAP	10881
rs10979572	36	9	110668010	127	IKBKAP	8518
rs3763646	36	9	110671791	127	IKBKAP	8518
rs2027433	36	9	110677125	127	IKBKAP	8518
rs4978753	36	9	110677292	127	IKBKAP	8518
rs10435834	36	9	110680452	127	IKBKAP	8518
rs10435835	36	9	110680488	127	IKBKAP	8518
rs1538660	36	9	110681646	127	IKBKAP	8518
rs7874280	36	9	110682356	127	IKBKAP	8518
rs2185330	36	9	110683298	127	IKBKAP	8518
rs3204145	36	9	110691441	127	IKBKAP	8518
rs1063110	36	9	110693395	127	IKBKAP	8518
rs947196	36	9	110695753	127	IKBKAP	8518
rs10979597	36	9	110696853	127	IKBKAP	8518
rs2275626	36	9	110698842	127	IKBKAP	8518
rs10979599	36	9	110699098	127	IKBKAP	8518
rs2230793	36	9	110699304	127	IKBKAP	8518
rs10979601	36	9	110700672	127	IKBKAP	8518
rs10979604	36	9	110703575	127	IKBKAP	8518
rs10979605	36	9	110703614	127	IKBKAP	8518
rs838827	36	9	110708473	127	IKBKAP	-99
rs1759852	36	9	110709877	127	IKBKAP	8518
rs725036	36	9	110710078	127	IKBKAP	8518
rs838824	36	9	110710528	127	IKBKAP	8518
rs838821	36	9	110712549	127	IKBKAP	8518
rs11791215	36	9	110713401	127	IKBKAP	8518
rs2297579	36	9	110713665	127	IKBKAP	8518
rs754333	36	9	110726717	127	IKBKAP	8518
rs10979614	36	9	110727627	127	IKBKAP	8518
rs2275639	36	9	110735980	127	IKBKAP	8518
rs2275641	36	9	110736210	127	IKBKAP	8518
rs838819	36	9	110740986	127	IKBKAP	54942
rs13299328	36	9	110743382	127	IKBKAP	54942
rs16911652	36	9	124168568	127	PTGS1	5742
rs1236913	36	9	124173300	127	PTGS1	5742
rs3842787	36	9	124173328	127	PTGS1	5742
rs1213266	36	9	124176705	127	PTGS1	5742
rs10306135	36	9	124177516	127	PTGS1	5742
rs3842788	36	9	124180027	127	PTGS1	5742
rs2282169	36	9	124180517	127	PTGS1	5742
rs5788	36	9	124183613	127	PTGS1	5742
rs5789	36	9	124183794	127	PTGS1	5742
rs4273915	36	9	124185150	127	PTGS1	5742
rs12238505	36	9	124191705	127	PTGS1	5742
rs5794	36	9	124192442	127	PTGS1	5742
rs1330811	36	9	126157167	127	PSMB7	5695
rs16927388	36	9	126159263	127	PSMB7	5695
rs11789637	36	9	126163122	127	PSMB7	5695
rs3780199	36	9	126190892	127	PSMB7	5695
rs12344916	36	9	126203444	127	PSMB7	5695
rs4574	36	9	126216982	127	PSMB7	5695
rs12343206	36	9	126223888	127	PSMB7	5695
rs599924	36	9	135208412	127	SURF1	6834
rs2051680	36	9	135212610	127	SURF1	6834
rs2296809	36	9	135216838	127	SURF1	6835
rs1059773	36	9	135218686	127	SURF1	6836
rs7025557	36	9	139887566	127	CACNA1B	774
rs11137292	36	9	139900026	127	CACNA1B	774
rs11137293	36	9	139902442	127	CACNA1B	774
rs4076712	36	9	139906739	127	CACNA1B	774
rs11137300	36	9	139921333	127	CACNA1B	774
rs12236550	36	9	139957854	127	CACNA1B	774
rs4077399	36	9	139968839	127	CACNA1B	774
rs12352971	36	9	139986647	127	CACNA1B	774
rs7028989	36	9	140031491	127	CACNA1B	774
rs7865887	36	9	140059617	127	CACNA1B	774
rs11137351	36	9	140059949	127	CACNA1B	774
rs1547503	36	9	140061934	127	CACNA1B	774
rs11137363	36	9	140089212	127	CACNA1B	774
rs936249	36	9	140091136	127	CACNA1B	774
rs10867105	36	9	140094586	127	CACNA1B	774
rs7357733	36	9	140123767	127	CACNA1B	774

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rs766374	36	9	140125835	127	CACNA1B	774
rs2229948	36	9	140128697	127	CACNA1B	774
rs4876928	36	9	140128836	127	CACNA1B	774
rs2739257	36	9	140130278	127	CACNA1B	774
rs2606356	36	9	140131345	127	CACNA1B	774
rs2606357	36	9	140131402	127	CACNA1B	774
rs2606358	36	9	140131592	127	CACNA1B	774
rs2278971	36	9	140134840	127	CACNA1B	774
rs211376	36	10	32346878	127	KIF5B	3799
rs2286746	36	10	32348400	127	KIF5B	3799
rs11594506	36	10	32379798	127	KIF5B	3799
rs17409410	36	10	32383111	127	KIF5B	3799
rs11101312	36	10	49277756	127	MAPK8	5599
rs10857561	36	10	49278644	127	MAPK8	5599
rs17698002	36	10	49279184	127	MAPK8	5599
rs7075976	36	10	49284283	127	MAPK8	5599
rs17010447	36	10	49294715	127	MAPK8	5599
rs11101318	36	10	49295589	127	MAPK8	5599
rs2289805	36	10	49297918	127	MAPK8	5599
rs17780725	36	10	49300893	127	MAPK8	5599
rs1509964	36	10	64237370	127	EGR2	84890
rs1509963	36	10	64240417	127	EGR2	1959
rs224277	36	10	64250067	127	EGR2	1959
rs10995317	36	10	64252772	127	EGR2	1959
rs224285	36	10	64254816	127	EGR2	1959
rs3793772	36	10	102212815	127	WNT8B	7479
rs3793771	36	10	102212947	127	WNT8B	7479
rs2970	36	10	102236502	127	WNT8B	25956
rs3740409	36	10	104226635	127	ACTR1A	79847
rs5870	36	10	104229090	127	ACTR1A	10121
rs13287	36	10	104230428	127	ACTR1A	10121
rs17709610	36	10	104240268	127	ACTR1A	10121
rs3842748	36	11	2137971	127	TH	3630
rs2070762	36	11	2142911	127	TH	7054
rs6356	36	11	2147527	127	TH	7054
rs10840490	36	11	2150393	127	TH	7054
rs10770141	36	11	2150416	127	TH	7054
rs10743149	36	11	2150751	127	TH	7054
rs10840491	36	11	2150966	127	TH	7054
rs4929966	36	11	2154012	127	TH	7054
rs11564710	36	11	2156905	127	TH	7054
rs6578993	36	11	2157739	127	TH	7054
rs11564709	36	11	2157914	127	TH	7054
rs1045634	36	11	9757026	127	SBF2	81846
rs3829252	36	11	9758027	127	SBF2	81846
rs3751000	36	11	9758501	127	SBF2	81846
rs634680	36	11	9775465	127	SBF2	81846
rs438151	36	11	9781441	127	SBF2	81846
rs421752	36	11	9783597	127	SBF2	81846
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rs12574508	36	11	9810353	127	SBF2	81846
rs7483882	36	11	9817585	127	SBF2	81846
rs9645624	36	11	9820503	127	SBF2	81846
rs11603291	36	11	9822432	127	SBF2	81846
rs11042510	36	11	9825416	127	SBF2	81846
rs11042511	36	11	9827198	127	SBF2	81846
rs2649049	36	11	9829859	127	SBF2	81846
rs360166	36	11	9834085	127	SBF2	81846
rs7102464	36	11	9836414	127	SBF2	81846
rs780382	36	11	9838051	127	SBF2	81846
rs4910067	36	11	9842425	127	SBF2	81846
rs1546542	36	11	9857034	127	SBF2	81846
rs10500711	36	11	9857911	127	SBF2	81846
rs11042524	36	11	9858687	127	SBF2	81846
rs17354870	36	11	9860504	127	SBF2	81846
rs10840318	36	11	9873179	127	SBF2	81846
rs7936793	36	11	9873798	127	SBF2	81846
rs17355751	36	11	9877034	127	SBF2	81846
rs7130923	36	11	9890931	127	SBF2	81846

## APPENDIX 1-continued

SNPs genotyped						
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rs7939451	36	11	9917655	127	SBF2	81846
rs10840331	36	11	9929055	127	SBF2	81846
rs11042572	36	11	9947929	127	SBF2	81846
rs17356792	36	11	9951097	127	SBF2	81846
rs7109648	36	11	9953641	127	SBF2	81846
rs4910090	36	11	9959866	127	SBF2	81846
rs7925889	36	11	10004895	127	SBF2	81846
rs17357710	36	11	10004943	127	SBF2	81846
rs12360569	36	11	10074011	127	SBF2	81846
rs12363292	36	11	10104544	127	SBF2	81846
rs11042643	36	11	10120941	127	SBF2	81846
rs11602057	36	11	10121032	127	SBF2	81846
rs16907561	36	11	10166479	127	SBF2	81846
rs11042655	36	11	10170202	127	SBF2	81846
rs17294511	36	11	10178648	127	SBF2	81846
rs7929332	36	11	10180933	127	SBF2	81846
rs7938543	36	11	10186427	127	SBF2	81846
rs2920151	36	11	10253243	127	SBF2	81846
rs4641466	36	11	10279602	127	SBF2	133
rs4930387	36	11	66206481	127	SPTBN2	6712
rs623022	36	11	66215556	127	SPTBN2	6712
rs639938	36	11	66217103	127	SPTBN2	6712
rs532439	36	11	66225608	127	SPTBN2	6712
rs615536	36	11	66237840	127	SPTBN2	6712
rs10791889	36	11	66250401	127	SPTBN2	6712
rs647159	36	11	75570389	127	WNT11	7481
rs11236644	36	11	75572655	127	WNT11	7481
rs581794	36	11	75572939	127	WNT11	7481
rs598143	36	11	75574220	127	WNT11	7481
rs12277860	36	11	75574295	127	WNT11	7481
rs17749202	36	11	75575022	127	WNT11	7481
rs7936750	36	11	75577055	127	WNT11	7481
rs10899175	36	11	75577129	127	WNT11	7481
rs882151	36	11	75581785	127	WNT11	7481
rs3781730	36	11	75585731	127	WNT11	7481
rs608747	36	11	75594125	127	WNT11	7481
rs1568507	36	11	75596967	127	WNT11	7481
rs663907	36	11	75600717	127	WNT11	7481
rs689419	36	11	75604615	127	WNT11	7481
rs12416814	36	11	75605089	127	WNT11	7481
rs525404	36	11	95206168	127	MTMR2	8898
rs16922615	36	11	95206706	127	MTMR2	8898
rs16922622	36	11	95207036	127	MTMR2	8898
rs611020	36	11	95207553	127	MTMR2	8898
rs17229128	36	11	95209963	127	MTMR2	8898
rs547219	36	11	95213139	127	MTMR2	8898
rs568878	36	11	95218342	127	MTMR2	8898
rs566204	36	11	95220574	127	MTMR2	8898
rs687116	36	11	95251413	127	MTMR2	8898
rs4753703	36	11	95270661	127	MTMR2	8898
rs7110786	36	11	95296296	127	MTMR2	8898
rs17301028	36	11	102485534	127	DYNC2H1	79659
rs11225553	36	11	102494416	127	DYNC2H1	79659
rs17301182	36	11	102496407	127	DYNC2H1	79659
rs11608130	36	11	102498194	127	DYNC2H1	79659
rs12577612	36	11	102502197	127	DYNC2H1	79659
rs17373533	36	11	102505175	127	DYNC2H1	79659
rs11225571	36	11	102526316	127	DYNC2H1	79659
rs17301750	36	11	102532444	127	DYNC2H1	79659
rs688906	36	11	102534726	127	DYNC2H1	79659
rs688244	36	11	102543737	127	DYNC2H1	79659
rs585692	36	11	102552217	127	DYNC2H1	79659
rs11225584	36	11	102557768	127	DYNC2H1	79659
rs17374436	36	11	102561890	127	DYNC2H1	79659
rs658804	36	11	102562258	127	DYNC2H1	79659
rs11225597	36	11	102571895	127	DYNC2H1	79659
rs685395	36	11	102572670	127	DYNC2H1	79659
rs17394217	36	11	102587768	127	DYNC2H1	79659
rs589623	36	11	102587800	127	DYNC2H1	79659
rs683608	36	11	102596197	127	DYNC2H1	79659
rs3912622	36	11	102626683	127	DYNC2H1	79659
rs11225634	36	11	102629345	127	DYNC2H1	79659
rs12574626	36	11	102658129	127	DYNC2H1	79659

## APPENDIX 1-continued

SNPs genotyped						
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rs7944311	36	11	102672402	127	DYNC2H1	79659
rs7945431	36	11	102672619	127	DYNC2H1	79659
rs11225665	36	11	102674923	127	DYNC2H1	79659
rs1430870	36	11	102678248	127	DYNC2H1	79659
rs17396421	36	11	102685655	127	DYNC2H1	79659
rs11225710	36	11	102694144	127	DYNC2H1	79659
rs313408	36	11	102696540	127	DYNC2H1	79659
rs313403	36	11	102697742	127	DYNC2H1	79659
rs313425	36	11	102715394	127	DYNC2H1	79659
rs11225731	36	11	102716667	127	DYNC2H1	79659
rs2566913	36	11	102734237	127	DYNC2H1	79659
rs1913462	36	11	102739939	127	DYNC2H1	79659
rs17308149	36	11	102803176	127	DYNC2H1	79659
rs603517	36	11	102808757	127	DYNC2H1	79659
rs590320	36	11	102815994	127	DYNC2H1	79659
rs589943	36	11	102816061	127	DYNC2H1	79659
rs642495	36	11	102819224	127	DYNC2H1	79659
rs7118365	36	11	102823025	127	DYNC2H1	79659
rs313874	36	11	102831660	127	DYNC2H1	79659
rs11611231	36	12	844587	127	HSN2	378465
rs7305099	36	12	845537	127	HSN2	378465
rs4980973	36	12	853307	127	HSN2	65125
rs1029628	36	12	1598849	127	WNT5B	81029
rs4765834	36	12	1599896	127	WNT5B	81029
rs4766399	36	12	1604821	127	WNT5B	81029
rs10848539	36	12	1613817	127	WNT5B	81029
rs2240509	36	12	1620858	127	WNT5B	81029
rs2240511	36	12	1623551	127	WNT5B	81029
rs7132752	36	12	1623995	127	WNT5B	81029
rs3803164	36	12	1625915	127	WNT5B	81029
rs3803163	36	12	1626221	127	WNT5B	81029
rs12819505	36	12	1626926	127	WNT5B	81029
rs1003939	36	12	1626939	127	WNT5B	81029
rs4766402	36	12	1627176	127	WNT5B	81029
rs2887603	36	12	1628004	127	WNT5B	81029
rs7133682	36	12	18782054	127	CAPZA3	89869
rs11831038	36	12	18786722	127	CAPZA3	93661
rs11052030	36	12	32542199	127	FGD4	121512
rs17536631	36	12	32543516	127	FGD4	121512
rs7133863	36	12	32547517	127	FGD4	121512
rs1500876	36	12	32550544	127	FGD4	121512
rs11052034	36	12	32551017	127	FGD4	121512
rs17536908	36	12	32552485	127	FGD4	121512
rs7305247	36	12	32556716	127	FGD4	121512
rs17609576	36	12	32565912	127	FGD4	121512
rs7295095	36	12	32566794	127	FGD4	121512
rs16920000	36	12	32575058	127	FGD4	121512
rs7315682	36	12	32577224	127	FGD4	121512
rs7966521	36	12	32580484	127	FGD4	121512
rs7967302	36	12	32580847	127	FGD4	121512
rs4931015	36	12	32581981	127	FGD4	121512
rs4931016	36	12	32582013	127	FGD4	121512
rs11052063	36	12	32592406	127	FGD4	121512
rs7298165	36	12	32594007	127	FGD4	121512
rs17538095	36	12	32594051	127	FGD4	121512
rs1875059	36	12	32594167	127	FGD4	121512
rs4635166	36	12	32596175	127	FGD4	121512
rs4931637	36	12	32601913	127	FGD4	121512
rs10844243	36	12	32604402	127	FGD4	121512
rs11052069	36	12	32605186	127	FGD4	121512
rs10844246	36	12	32612704	127	FGD4	121512
rs17538775	36	12	32623596	127	FGD4	121512
rs904582	36	12	32626503	127	FGD4	121512
rs9988998	36	12	32639606	127	FGD4	121512
rs12823621	36	12	32646526	127	FGD4	121512
rs10506097	36	12	32653050	127	FGD4	121512
rs999840	36	12	32653759	127	FGD4	121512
rs10844253	36	12	32655451	127	FGD4	121512
rs11052110	36	12	32668629	127	FGD4	121512
rs17539792	36	12	32669156	127	FGD4	121512
rs7962152	36	12	32670957	127	FGD4	121512
rs4018511	36	12	47641303	127	WNT10B	377
rs3741627	36	12	47645854	127	WNT10B	7480

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
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rs833839	36	12	47653157	127	WNT1; WNT10B	7480
rs590460	36	12	48736243	127	ACCN2	41
rs1108923	36	12	48744363	127	ACCN2	41
rs706793	36	12	48754036	127	ACCN2	41
rs1043011	36	12	55151307	127	GLS2	27165
rs2638315	36	12	55151323	127	GLS2	27165
rs2657879	36	12	55151605	127	GLS2	27165
rs6581096	36	12	55164387	127	GLS2	27165
rs12824907	36	12	56228373	127	DCTN2; KIF5A	10540
rs2620678	36	12	56249211	127	KIF5A	3798
rs11172254	36	12	56255005	127	KIF5A	3798
rs2888334	36	12	56262914	127	KIF5A	3798
rs775250	36	12	56263307	127	KIF5A	3798
rs1678536	36	12	56265457	127	KIF5A	3798
rs8873	36	12	56266216	127	KIF5A	3798
rs1545783	36	12	56268521	127	KIF5A	79837
rs1861810	36	12	108709305	127	TRPV4	59341
rs3742037	36	12	108710762	127	TRPV4	59341
rs10735104	36	12	108712348	127	TRPV4	59341
rs12578919	36	12	108717674	127	TRPV4	59341
rs3825396	36	12	108719081	127	TRPV4	59341
rs3825394	36	12	108725221	127	TRPV4	59341
rs10850838	36	12	108763195	127	TRPV4	59341
rs6606743	36	12	108763562	127	TRPV4	59341
rs7138273	36	12	118107127	127	HSPB8	26353
rs2278182	36	12	118108718	127	HSPB8	26353
rs11038	36	12	118116690	127	HSPB8	26353
rs1133026	36	12	118116730	127	HSPB8	26353
rs10774488	36	12	118118995	127	HSPB8	643737
rs3916065	36	12	119419007	127	DNCL1	8655
rs1169288	36	12	119901033	127	TCF1	6927
rs1169286	36	12	119903439	127	TCF1	6927
rs2245407	36	12	119908381	127	TCF1	6927
rs12427353	36	12	119911284	127	TCF1	6927
rs2071190	36	12	119915655	127	TCF1	6927
rs1169302	36	12	119916685	127	TCF1	6927
rs2464196	36	12	119919810	127	TCF1	6927
rs2464195	36	12	119919858	127	TCF1	6927
rs2259816	36	12	119919970	127	TCF1	6927
rs3999413	36	12	119922321	127	TCF1	6927
rs1169310	36	12	119923816	127	TCF1	6927
rs2313477	36	13	19656323	127	GJB2	2706
rs3751385	36	13	19660956	127	GJB2	2706
rs4769974	36	13	19663831	127	GJB2	2706
rs1932429	36	13	19669715	127	GJB2	2706
rs7984806	36	13	19670687	127	GJB2	2706
rs9552104	36	13	19673997	127	GJB2	2706
rs12889177	36	14	22561169	127	PSMB5	5693
rs10138759	36	14	22562116	127	PSMB5	5693
rs17125731	36	14	22564074	127	PSMB5	5693
rs941717	36	14	22564827	127	PSMB5	5693
rs941718	36	14	22564888	127	PSMB5	5693
rs11543947	36	14	22573861	127	PSMB5	5693
rs4981456	36	14	22581197	127	PSMB5	122706
rs1390376	36	14	51848225	127	PTGER2	5732
rs17197	36	14	51864131	127	PTGER2	5732
rs17125362	36	14	51866579	127	PTGER2	5732
rs781697	36	14	51868016	127	PTGER2	5732
rs17831718	36	14	51869786	127	PTGER2	5732
rs10483639	36	14	54376207	127	GCH1	2643
rs7142517	36	14	54376554	127	GCH1	2643
rs841	36	14	54380242	127	GCH1	2643
rs17253591	36	14	54385166	127	GCH1	2643
rs8007201	36	14	54394598	127	GCH1	2643
rs17128050	36	14	54413629	127	GCH1	2643
rs998259	36	14	54424781	127	GCH1	2643
rs3783641	36	14	54429889	127	GCH1	2643
rs3783642	36	14	54429953	127	GCH1	2643
rs8007267	36	14	54448741	127	GCH1	2643
rs3818188	36	14	101515914	127	DYNC1H1	1778
rs4906172	36	14	101524686	127	DYNC1H1	1778
rs10132469	36	14	101526144	127	DYNC1H1	1778
rs8006586	36	14	101549929	127	DYNC1H1	1778



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SNPs genotyped						
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rs1190606	36	14	101580181	127	DYNC1H1	1778
rs13749	36	14	101583980	127	DYNC1H1	1778
rs2494738	36	14	104317731	127	AKT1	207
rs2494743	36	14	104322765	127	AKT1	207
rs1130214	36	14	104330779	127	AKT1	207
rs1133154	36	15	32309849	127	SLC12A6	51234
rs4530104	36	15	32309971	127	SLC12A6	51234
rs6495639	36	15	32311528	127	SLC12A6	9990
rs4779660	36	15	32312287	127	SLC12A6	9990
rs4780233	36	15	32312327	127	SLC12A6	9990
rs16958873	36	15	32312880	127	SLC12A6	9990
rs4577050	36	15	32316240	127	SLC12A6	9990
rs17236791	36	15	32329898	127	SLC12A6	9990
rs17236798	36	15	32330164	127	SLC12A6	9990
rs2290940	36	15	32331760	127	SLC12A6	9990
rs2705343	36	15	32333213	127	SLC12A6	9990
rs2615358	36	15	32333743	127	SLC12A6	9990
rs7164902	36	15	32338374	127	SLC12A6	9990
rs7165973	36	15	32363058	127	SLC12A6	9990
rs347866	36	15	32397271	127	SLC12A6	9990
rs347867	36	15	32398256	127	SLC12A6	9990
rs8028600	36	15	32400009	127	SLC12A6	9990
rs17236840	36	15	32400051	127	SLC12A6	9990
rs17236847	36	15	32404605	127	SLC12A6	9990
rs11638692	36	15	32404636	127	SLC12A6	9990
rs652196	36	15	38163439	127	BMF	90427
rs12913170	36	15	38163500	127	BMF	90427
rs998713	36	15	38165759	127	BMF	90427
rs546220	36	15	38166552	127	BMF	90427
rs648289	36	15	38168225	127	BMF	90427
rs10518679	36	15	38169733	127	BMF	90427
rs3743129	36	15	38171071	127	BMF	90427
rs16970349	36	15	38171424	127	BMF	90427
rs588739	36	15	38172380	127	BMF	90427
rs11637681	36	15	38175263	127	BMF	90427
rs569539	36	15	38177086	127	BMF	90427
rs11630670	36	15	38198132	127	BMF	90427
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rs1197668	36	15	39927706	127	SPTBN5	51332
rs1197660	36	15	39933228	127	SPTBN5	51332
rs2305655	36	15	39934931	127	SPTBN5	51332
rs2278966	36	15	39943104	127	SPTBN5	51332
rs3816534	36	15	39946402	127	SPTBN5	51332
rs4923918	36	15	39948235	127	SPTBN5	51332
rs12593397	36	15	39953792	127	SPTBN5	51332
rs2290559	36	15	39955692	127	SPTBN5	51332
rs747779	36	15	39957870	127	SPTBN5	51332
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rs1124850	36	15	39967823	127	SPTBN5	51332
rs1618332	36	15	39972086	127	SPTBN5	51332
rs1197701	36	15	39974784	127	SPTBN5	51332
rs1672460	36	15	39975327	127	SPTBN5	51332
rs1672461	36	15	39977488	127	SPTBN5	30844
rs11636443	36	15	50106988	127	MAPK6	5597
rs8034167	36	15	50127514	127	MAPK6	5597
rs10851507	36	15	50137961	127	MAPK6	5597
rs11070879	36	15	50138955	127	MAPK6	5597
rs17612368	36	15	50149195	127	MAPK6	5597
rs1138465	36	15	87659606	127	POLG	55215
rs3087374	36	15	87660998	127	POLG	5428
rs3176208	36	15	87665767	127	POLG	5428
rs2074885	36	15	87670670	127	POLG	5428
rs2351000	36	15	87670737	127	POLG	5428
rs7495044	36	15	87685173	127	POLG	5428
rs393521	36	16	277679	127	AXIN1	8312
rs214247	36	16	289222	127	AXIN1	8312
rs214246	36	16	289294	127	AXIN1	8312
rs7200589	36	16	289332	127	AXIN1	8312
rs1204042	36	16	292737	127	AXIN1	8312
rs3842950	36	16	300318	127	AXIN1	8312
rs7359414	36	16	302639	127	AXIN1	8312

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SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
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rs11648673	36	16	317795	127	AXIN1	8312
rs12719801	36	16	321142	127	AXIN1	8312
rs12445857	36	16	326424	127	AXIN1	-99
rs370681	36	16	332462	127	AXIN1	8312
rs395901	36	16	333343	127	AXIN1	8312
rs2885415	36	16	335397	127	AXIN1	8312
rs1805105	36	16	336265	127	AXIN1	8312
rs758033	36	16	337045	127	AXIN1	8312
rs17136255	36	16	340476	127	AXIN1	8312
rs9888749	36	16	348373	127	AXIN1	8312
rs7102	36	16	11549743	127	LITAF	9516
rs9935945	36	16	11551132	127	LITAF	9516
rs11644920	36	16	11552514	127	LITAF	9516
rs8048403	36	16	11553776	127	LITAF	9516
rs4280262	36	16	11554993	127	LITAF	9516
rs11642799	36	16	11555637	127	LITAF	9516
rs7403964	36	16	11557558	127	LITAF	9516
rs3743582	36	16	11557826	127	LITAF	9516
rs9937485	36	16	11560281	127	LITAF	9516
rs8048521	36	16	11568203	127	LITAF	9516
rs6498224	36	16	11576044	127	LITAF	9516
rs12930096	36	16	11578259	127	LITAF	9516
rs12444633	36	16	11585358	127	LITAF	9516
rs1345442	36	16	11587031	127	LITAF	9516
rs1345441	36	16	11587324	127	LITAF	9516
rs11864737	36	16	30037613	127	MAPK3	5595
rs9921806	36	16	30040261	127	MAPK3	5595
rs11862377	36	16	65315471	127	DYNC1LI2	1783
rs12599882	36	16	65320348	127	DYNC1LI2	1783
rs2067040	36	16	65322310	127	DYNC1LI2	1783
rs363180	36	16	65350405	127	DYNC1LI2	283847
rs14178	36	16	66527032	127	PSMB10	5699
rs20549	36	16	66527431	127	PSMB10	5699
rs4986970	36	16	66533821	127	PSMB10	3931
rs9928594	36	16	79127742	127	DYNLRB2	83657
rs13338237	36	16	79128602	127	DYNLRB2	83657
rs10781994	36	16	79133210	127	DYNLRB2	83657
rs9937217	36	16	79140368	127	DYNLRB2	83657
rs12934612	36	16	79140777	127	DYNLRB2	-99
rs11866734	36	16	79140998	127	DYNLRB2	83657
rs3212346	36	16	88509859	127	MC1R	4157
rs3212363	36	16	88512942	127	MC1R	4157
rs4790522	36	17	3416603	127	TRPV1	7442
rs16953163	36	17	3417989	127	TRPV1	7442
rs224546	36	17	3419621	127	TRPV1	7442
rs3826503	36	17	3421410	127	TRPV1	7442
rs877610	36	17	3422240	127	TRPV1	7442
rs877611	36	17	3422315	127	TRPV1	7442
rs17706245	36	17	3423740	127	TRPV1	7442
rs161364	36	17	3424561	127	TRPV1	7442
rs8065080	36	17	3427196	127	TRPV1	7442
rs17633288	36	17	3430534	127	TRPV1	7442
rs150908	36	17	3431117	127	TRPV1	7442
rs224534	36	17	3433451	127	TRPV1	7442
rs222747	36	17	3439949	127	TRPV1	7442
rs222748	36	17	3441110	127	TRPV1	7442
rs150846	36	17	3441617	127	TRPV1	7442
rs222749	36	17	3442123	127	TRPV1	7442
rs161385	36	17	3442975	127	TRPV1	7442
rs2277675	36	17	3447259	127	TRPV1	7442
rs12944357	36	17	3453368	127	TRPV1	23729
rs222741	36	17	3455629	127	TRPV1	23729
rs17634022	36	17	3455907	127	TRPV1	23729
rs224495	36	17	3459876	127	TRPV1	23729
rs224498	36	17	3466703	127	TRPV1	23729
rs2241933	36	17	4646905	127	PSMB6	5694
rs11654690	36	17	4651636	127	PSMB6	5694
rs2074222	36	17	7070698	127	DVL2	1856
rs222837	36	17	7073280	127	DVL2	1856
rs222836	36	17	7073886	127	DVL2	1856
rs2074216	36	17	7074333	127	DVL2	1856
rs17710	36	17	7084718	127	DVL2	11337
rs222843	36	17	7086705	127	DVL2	11337

## APPENDIX 1-continued

SNPs genotyped						
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rs1993614	36	17	15072070	127	PMP22	5376
rs7538	36	17	15074382	127	PMP22	5376
rs13422	36	17	15074900	127	PMP22	5376
rs230945	36	17	15078058	127	PMP22	5376
rs17773165	36	17	15082587	127	PMP22	5376
rs3744333	36	17	15083480	127	PMP22	5376
rs17773227	36	17	15090503	127	PMP22	5376
rs230911	36	17	15093903	127	PMP22	5376
rs16951263	36	17	15101897	127	PMP22	5376
rs2072325	36	17	15102702	127	PMP22	5376
rs231020	36	17	15103114	127	PMP22	5376
rs179521	36	17	15113946	127	PMP22	5376
rs8065610	36	17	15116295	127	PMP22	5376
rs2048230	36	17	19216792	127	MAPK7	5598
rs2233072	36	17	19222421	127	MAPK7	5598
rs228271	36	17	34160006	127	PSMB3	7703
rs228273	36	17	34161649	127	PSMB3	5691
rs16968005	36	17	34161883	127	PSMB3	5691
rs228274	36	17	34162587	127	PSMB3	5691
rs228275	36	17	34164351	127	PSMB3	5691
rs65926	36	17	34169959	127	PSMB3	5691
rs764190	36	17	34170125	127	PSMB3	5691
rs1043515	36	17	34175722	127	PSMB3	8396
rs3744070	36	17	34177865	127	PSMB3	8396
rs7213337	36	17	37132954	127	HAP1	9001
rs4523977	36	17	37136876	127	HAP1	9001
rs11867808	36	17	37137198	127	HAP1	9001
rs4796691	36	17	37137315	127	HAP1	9001
rs7224601	36	17	37148507	127	HAP1	9001
rs199505	36	17	42214571	127	WNT3	7473
rs916888	36	17	42218292	127	WNT3	7473
rs199500	36	17	42218572	127	WNT3	7473
rs2074405	36	17	42221161	127	WNT3	7473
rs199497	36	17	42221762	127	WNT3	7473
rs199496	36	17	42221887	127	WNT3	7473
rs11658976	36	17	42221965	127	WNT3	7473
rs11655598	36	17	42223260	127	WNT3	7473
rs12452064	36	17	42223353	127	WNT3	7473
rs199494	36	17	42224229	127	WNT3	7473
rs10514911	36	17	42233432	127	WNT3	7473
rs7207916	36	17	42234514	127	WNT3	7473
rs11653738	36	17	42242117	127	WNT3	7473
rs3933652	36	17	42243714	127	WNT3	7473
rs3933653	36	17	42243741	127	WNT3	7473
rs3916033	36	17	42244702	127	WNT3	7473
rs3851781	36	17	42246300	127	WNT3	7473
rs7220040	36	17	42280547	127	WNT9B	7484
rs12602434	36	17	42283052	127	WNT9B	7484
rs12150651	36	17	42288568	127	WNT9B	7484
rs2165846	36	17	42296365	127	WNT9B	7484
rs12952746	36	17	42298412	127	WNT9B	7484
rs6504591	36	17	42299827	127	WNT9B	7484
rs11079740	36	17	42304099	127	WNT9B	7484
rs4968281	36	17	42305121	127	WNT9B	7484
rs1530364	36	17	42306776	127	WNT9B	7484
rs8065435	36	17	53512616	127	DYNLL2	729460
rs8069790	36	17	53513244	127	DYNLL2	729460
rs11079337	36	17	53517495	127	DYNLL2	729460
rs9900038	36	17	53524762	127	DYNLL2	140735
rs2333091	36	17	53525967	127	DYNLL2	140735
rs4293	36	17	58909398	127	ACE	1636
rs4309	36	17	58913655	127	ACE	1636
rs4311	36	17	58914495	127	ACE	1636
rs4343	36	17	58919763	127	ACE	1636
rs4362	36	17	58927493	127	ACE	1636
rs4461142	36	17	58931780	127	ACE	1636
rs4459610	36	17	58938452	127	ACE	1636
rs8066276	36	17	58942997	127	ACE	1636
rs4611524	36	17	58945384	127	ACE	1636
rs12451328	36	17	58950280	127	ACE	1636
rs6504234	36	17	59918318	127	POLG2	11232
rs1427463	36	17	59923044	127	POLG2	11232
rs9897606	36	17	59923629	127	POLG2	11232

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SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
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rs1140409	36	17	59927132	127	POLG2	1655
rs16947824	36	17	59931967	127	POLG2	1655
rs1991401	36	17	59932897	127	POLG2	1655
rs2004887	36	17	77090696	127	ACTG1	71
rs7342974	36	17	77098594	127	ACTG1	71
rs875120	36	18	27421062	127	TTR	7276
rs3764478	36	18	27424481	127	TTR	7276
rs1800458	36	18	27426863	127	TTR	7276
rs4444423	36	18	46338134	127	MAPK4	5596
rs11082830	36	18	46345270	127	MAPK4	5596
rs3853680	36	18	46350202	127	MAPK4	5596
rs8089517	36	18	46350750	127	MAPK4	5596
rs11665303	36	18	46357790	127	MAPK4	5596
rs753328	36	18	46362006	127	MAPK4	5596
rs11082832	36	18	46369429	127	MAPK4	5596
rs4939989	36	18	46369453	127	MAPK4	5596
rs11660097	36	18	46395615	127	MAPK4	5596
rs1561261	36	18	46395655	127	MAPK4	5596
rs11664092	36	18	46396472	127	MAPK4	5596
rs3867257	36	18	46400046	127	MAPK4	5596
rs4939992	36	18	46406082	127	MAPK4	5596
rs7227542	36	18	46406920	127	MAPK4	5596
rs9960447	36	18	46408176	127	MAPK4	5596
rs11875289	36	18	46414032	127	MAPK4	5596
rs2118370	36	18	46415542	127	MAPK4	5596
rs8091136	36	18	46417885	127	MAPK4	5596
rs17804574	36	18	46419749	127	MAPK4	5596
rs3894010	36	18	46421235	127	MAPK4	5596
rs3867260	36	18	46422257	127	MAPK4	5596
rs893320	36	18	46424976	127	MAPK4	5596
rs4939998	36	18	46425665	127	MAPK4	5596
rs4939999	36	18	46427395	127	MAPK4	5596
rs9953685	36	18	46435944	127	MAPK4	5596
rs3752085	36	18	46444269	127	MAPK4	5596
rs3752087	36	18	46444438	127	MAPK4	5596
rs12607365	36	18	46447672	127	MAPK4	5596
rs9956244	36	18	46449556	127	MAPK4	5596
rs1893489	36	18	46449659	127	MAPK4	5596
rs1893490	36	18	46449799	127	MAPK4	5596
rs12961853	36	18	46466397	127	MAPK4	5596
rs1545129	36	18	46474330	127	MAPK4	5596
rs17742551	36	18	46474454	127	MAPK4	5596
rs17662824	36	18	46475799	127	MAPK4	-99
rs8096108	36	18	46476874	127	MAPK4	5596
rs894768	36	18	46477656	127	MAPK4	5596
rs4260159	36	18	46483873	127	MAPK4	5596
rs6508027	36	18	46484275	127	MAPK4	5596
rs7227230	36	18	46484894	127	MAPK4	5596
rs9948424	36	18	46487076	127	MAPK4	5596
rs4939642	36	18	46488427	127	MAPK4	5596
rs11665501	36	18	46489084	127	MAPK4	5596
rs11665570	36	18	46489323	127	MAPK4	5596
rs12959952	36	18	46494835	127	MAPK4	5596
rs7240429	36	18	46497316	127	MAPK4	5596
rs4940005	36	18	46497589	127	MAPK4	5596
rs17662967	36	18	46500216	127	MAPK4	5596
rs3794900	36	18	46500325	127	MAPK4	5596
rs1807382	36	18	46508173	127	MAPK4	5596
rs7242442	36	18	46515455	127	MAPK4	5596
rs9635955	36	18	46517113	127	MAPK4	5596
rs1261084	36	18	51041158	127	TCF4	6925
rs1261070	36	18	51054083	127	TCF4	6925
rs10515969	36	18	51054812	127	TCF4	6925
rs1942265	36	18	51066565	127	TCF4	6925
rs1261134	36	18	51082761	127	TCF4	6925
rs1261115	36	18	51091526	127	TCF4	6925
rs3794894	36	18	51119198	127	TCF4	6925
rs1440475	36	18	51130347	127	TCF4	6925
rs10515970	36	18	51131633	127	TCF4	6925
rs11659559	36	18	51156932	127	TCF4	6925
rs1660242	36	18	51189674	127	TCF4	6925
rs1788025	36	18	51199676	127	TCF4	6925
rs9958125	36	18	51204583	127	TCF4	6925

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rs2119292	36	18	51233972	127	TCF4	6925
rs2919451	36	18	51235298	127	TCF4	6925
rs12963463	36	18	51250091	127	TCF4	6925
rs7231748	36	18	51260033	127	TCF4	6925
rs1452789	36	18	51266877	127	TCF4	6925
rs2924321	36	18	51276433	127	TCF4	6925
rs2924329	36	18	51286892	127	TCF4	6925
rs17596267	36	18	51292535	127	TCF4	6925
rs7233312	36	18	51294571	127	TCF4	6925
rs2958183	36	18	51301074	127	TCF4	6925
rs9960767	36	18	51306000	127	TCF4	6925
rs2924333	36	18	51307227	127	TCF4	6925
rs4801157	36	18	51315691	127	TCF4	6925
rs2958188	36	18	51316957	127	TCF4	6925
rs3017183	36	18	51319241	127	TCF4	6925
rs17512480	36	18	51324171	127	TCF4	6925
rs2924338	36	18	51326785	127	TCF4	6925
rs12956276	36	18	51326964	127	TCF4	6925
rs17597288	36	18	51328206	127	TCF4	6925
rs9964328	36	18	51328772	127	TCF4	6925
rs12606243	36	18	51335784	127	TCF4	6925
rs627685	36	18	51337090	127	TCF4	6925
rs4572488	36	18	51349604	127	TCF4	6925
rs9636107	36	18	51351115	127	TCF4	6925
rs1452787	36	18	51358205	127	TCF4	6925
rs17089887	36	18	51359254	127	TCF4	6925
rs613872	36	18	51361300	127	TCF4	6925
rs658977	36	18	51364885	127	TCF4	6925
rs13381608	36	18	51410144	127	TCF4	6925
rs590076	36	18	51411730	127	TCF4	6925
rs11672431	36	19	10684940	127	DNM2	81890
rs892086	36	19	10698677	127	DNM2	1785
rs11670097	36	19	10738127	127	DNM2	1785
rs2043332	36	19	10752239	127	DNM2	1785
rs4296360	36	19	10755240	127	DNM2	1785
rs11666111	36	19	10761633	127	DNM2	1785
rs7254425	36	19	10763389	127	DNM2	1785
rs1610095	36	19	10765689	127	DNM2	1785
rs2278444	36	19	10765700	127	DNM2	1785
rs2287029	36	19	10777684	127	DNM2	1785
rs2419233	36	19	13184759	127	CACNA1A	773
rs4926143	36	19	13186733	127	CACNA1A	773
rs1865033	36	19	13193467	127	CACNA1A	773
rs3816027	36	19	13196432	127	CACNA1A	773
rs3765012	36	19	13206657	127	CACNA1A	773
rs10421681	36	19	13210110	127	CACNA1A	773
rs4926240	36	19	13212594	127	CACNA1A	773
rs12462609	36	19	13213965	127	CACNA1A	773
rs12052059	36	19	13216068	127	CACNA1A	773
rs12611029	36	19	13216633	127	CACNA1A	773
rs12611099	36	19	13219672	127	CACNA1A	773
rs8112821	36	19	13222618	127	CACNA1A	773
rs8103699	36	19	13225012	127	CACNA1A	773
rs4926242	36	19	13229031	127	CACNA1A	773
rs2074880	36	19	13233631	127	CACNA1A	773
rs16031	36	19	13234477	127	CACNA1A	773
rs7249323	36	19	13238865	127	CACNA1A	773
rs11085840	36	19	13241883	127	CACNA1A	773
rs12973989	36	19	13242001	127	CACNA1A	773
rs7251409	36	19	13242991	127	CACNA1A	773
rs4926248	36	19	13244313	127	CACNA1A	773
rs4926250	36	19	13244718	127	CACNA1A	773
rs16030	36	19	13248904	127	CACNA1A	773
rs10424916	36	19	13253865	127	CACNA1A	773
rs4926261	36	19	13268095	127	CACNA1A	773
rs16018	36	19	13272482	127	CACNA1A	773
rs16016	36	19	13275594	127	CACNA1A	773
rs8182538	36	19	13277170	127	CACNA1A	773
rs11878230	36	19	13278011	127	CACNA1A	773
rs16015	36	19	13279707	127	CACNA1A	773
rs2292033	36	19	13288544	127	CACNA1A	773
rs2419248	36	19	13292486	127	CACNA1A	773
rs10421428	36	19	13294348	127	CACNA1A	773

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rs10407711	36	19	13303779	127	CACNA1A	773
rs2248069	36	19	13306208	127	CACNA1A	773
rs10424440	36	19	13317368	127	CACNA1A	773
rs4926155	36	19	13321244	127	CACNA1A	773
rs1742	36	19	13322447	127	CACNA1A	773
rs4926278	36	19	13326001	127	CACNA1A	773
rs12985786	36	19	13328036	127	CACNA1A	773
rs16007	36	19	13331316	127	CACNA1A	773
rs10419009	36	19	13335397	127	CACNA1A	773
rs4926281	36	19	13342892	127	CACNA1A	773
rs11670018	36	19	13344914	127	CACNA1A	773
rs2900918	36	19	13366333	127	CACNA1A	773
rs8109003	36	19	13379462	127	CACNA1A	773
rs8113506	36	19	13380929	127	CACNA1A	773
rs4926285	36	19	13392611	127	CACNA1A	773
rs1019472	36	19	13394483	127	CACNA1A	773
rs752079	36	19	13395127	127	CACNA1A	773
rs4926286	36	19	13395236	127	CACNA1A	773
rs4926287	36	19	13398717	127	CACNA1A	773
rs1422259	36	19	13400602	127	CACNA1A	773
rs8109635	36	19	13413673	127	CACNA1A	773
rs1363346	36	19	13416209	127	CACNA1A	773
rs12609229	36	19	13417718	127	CACNA1A	773
rs7254385	36	19	13417728	127	CACNA1A	773
rs933649	36	19	13418907	127	CACNA1A	773
rs11882861	36	19	13423225	127	CACNA1A	773
rs4926289	36	19	13431005	127	CACNA1A	773
rs10422148	36	19	13432311	127	CACNA1A	773
rs1363345	36	19	13435131	127	CACNA1A	773
rs4926290	36	19	13437174	127	CACNA1A	773
rs17777900	36	19	13443311	127	CACNA1A	773
rs12985705	36	19	13443682	127	CACNA1A	773
rs8113488	36	19	13444694	127	CACNA1A	773
rs8104676	36	19	13446915	127	CACNA1A	773
rs10411263	36	19	13448926	127	CACNA1A	773
rs12609735	36	19	13449516	127	CACNA1A	773
rs2112461	36	19	13451331	127	CACNA1A	773
rs2112460	36	19	13451412	127	CACNA1A	773
rs10412211	36	19	13452542	127	CACNA1A	773
rs1862259	36	19	13452949	127	CACNA1A	773
rs10409870	36	19	13455537	127	CACNA1A	773
rs1120559	36	19	13460576	127	CACNA1A	773
rs10409910	36	19	13463461	127	CACNA1A	773
rs7250452	36	19	13464731	127	CACNA1A	773
rs5021327	36	19	13471112	127	CACNA1A	773
rs2419724	36	19	13483767	127	CACNA1A	773
rs1961721	36	19	13484761	127	CACNA1A	773
rs10416904	36	19	14439813	127	PTGER1	5585
rs1042728	36	19	14442063	127	PTGER1	5585
rs2287699	36	19	14451612	127	PTGER1	10755
rs2241357	36	19	14451919	127	PTGER1	10755
rs3730051	36	19	45436537	127	AKT2	208
rs7247515	36	19	45447755	127	AKT2	208
rs12460555	36	19	45464304	127	AKT2	208
rs16974157	36	19	45464764	127	AKT2	208
rs1991823	36	19	45472165	127	AKT2	208
rs268674	36	19	45592705	127	PRX	57716
rs3745202	36	19	45592851	127	PRX	57716
rs268673	36	19	45593336	127	PRX	57716
rs1981958	36	19	45599248	127	PRX	57716
rs16974263	36	19	45605379	127	PRX	57716
rs268666	36	19	45610005	127	PRX	57716
rs268664	36	19	45612936	127	PRX	57716
rs4150992	36	19	45620784	127	PRX	29950
rs2613843	36	19	45661043	127	SPTBN4	645
rs4803342	36	19	45674215	127	SPTBN4	57731
rs10401458	36	19	45678404	127	SPTBN4	57731
rs1993726	36	19	45688331	127	SPTBN4	57731
rs7258710	36	19	45689952	127	SPTBN4	57731
rs814536	36	19	45695894	127	SPTBN4	57731
rs17656487	36	19	45695915	127	SPTBN4	57731
rs17656504	36	19	45698266	127	SPTBN4	57731
rs814526	36	19	45699889	127	SPTBN4	57731

## APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs814528	36	19	45706762	127	SPTBN4	57731
rs814534	36	19	45711905	127	SPTBN4	57731
rs10410907	36	19	45724949	127	SPTBN4	57731
rs814501	36	19	45730414	127	SPTBN4	57731
rs843777	36	19	45748632	127	SPTBN4	57731
rs1165838	36	19	45767830	127	SPTBN4	57731
rs2290682	36	19	45775284	127	SPTBN4	92799
rs450819	36	19	45777854	127	SPTBN4	92799
rs3745233	36	19	47425705	127	GSK3A	2931
rs2302485	36	19	47432964	127	GSK3A	2931
rs6087861	36	20	30333587	127	KIF3B	9371
rs13037236	36	20	30379122	127	KIF3B	9371
rs1029116	36	20	30382844	127	KIF3B	9371
rs2151437	36	20	30384608	127	KIF3B	9371
rs3813921	36	20	30385507	127	KIF3B	9371
rs14353	36	20	30386059	127	KIF3B	9371
rs13111	36	20	30386060	127	KIF3B	9371
rs8116198	36	20	32577862	127	DNCL2A	83658
rs13044031	36	20	32586696	127	DNCL2A	83658
rs2281695	36	20	32592825	127	DNCL2A	83658
rs6088519	36	20	32595852	127	DNCL2A	84557
rs6088520	36	20	32596025	127	DNCL2A	84557
rs2424994	36	20	32596578	127	DNCL2A	84557
rs6090041	36	20	62183120	127	OPRL1	4987
rs6090043	36	20	62188374	127	OPRL1	198437
rs2229205	36	20	62199875	127	OPRL1	4987
rs6089789	36	20	62202436	127	OPRL1	4987
rs4646310	36	22	18308806	127	COMT	10587
rs2020917	36	22	18308884	127	COMT	10587
rs933271	36	22	18311407	127	COMT	10587
rs740603	36	22	18325177	127	COMT	1312
rs4646312	36	22	18328337	127	COMT	1312
rs4680	36	22	18331271	127	COMT	1312
rs4646316	36	22	18332132	127	COMT	1312
rs165774	36	22	18332561	127	COMT	1312
rs174696	36	22	18333176	127	COMT	1312
rs9332377	36	22	18335692	127	COMT	1312
rs165815	36	22	18339473	127	COMT	421
rs2518823	36	22	18340188	127	COMT	421
rs2240713	36	22	18341101	127	COMT	421
rs2276008	36	22	20444036	127	MAPK1	5594
rs6928	36	22	20445004	127	MAPK1	5594
rs9340	36	22	20445353	127	MAPK1	5594
rs3810610	36	22	20445498	127	MAPK1	5594
rs13515	36	22	20445886	127	MAPK1	5594
rs13943	36	22	20446202	127	MAPK1	5594
rs1063311	36	22	20446467	127	MAPK1	5594
rs2298432	36	22	20453189	127	MAPK1	5594
rs3729910	36	22	20492126	127	MAPK1	5594
rs8141815	36	22	20521585	127	MAPK1	5594
rs12172554	36	22	20525075	127	MAPK1	5594
rs5755694	36	22	20530530	127	MAPK1	5594
rs9610470	36	22	20539139	127	MAPK1	5594
rs8141793	36	22	23157079	127	ADORA2A	646023
rs11704811	36	22	23163164	127	ADORA2A	135
rs4822489	36	22	23163760	127	ADORA2A	135
rs17004920	36	22	23164564	127	ADORA2A	135
rs2236624	36	22	23166024	127	ADORA2A	135
rs1555048	36	22	49030475	127	MAPK12	83933
rs1076649	36	22	49039645	127	MAPK11; MAPK12	6300
rs2272857	36	22	49041795	127	MAPK11; MAPK12	6300
rs2076139	36	22	49046788	127	MAPK11; MAPK12	5600
rs2235356	36	22	49052476	127	MAPK11	5600
rs6010226	36	22	49056743	127	MAPK11	23654
rs131815	36	22	49306474	127	ECGF1	29781
rs140524	36	22	49307548	127	ECGF1	29781
rs140523	36	22	49309648	127	ECGF1	9997
rs140522	36	22	49318132	127	ECGF1	440836
rs131794	36	22	49318618	127	ECGF1	440836
rs5770871	36	22	49325128	127	ECGF1	440836
rs6525485	36	X	70359570	127	GJB1	2705
rs7057082	36	X	70362347	127	GJB1	2705
rs752081	36	X	70366527	127	GJB1	2705
rs521895	36	X	102923068	127	PLP1	5354

APPENDIX 1-continued

SNPs genotyped						
SNP ID	Genome Build Version	Chr	Position	dbSNP Version	Gene Symbol	Gene ID
rs17003884	36	X	102923122	127	PLP1	5354
rs2233696	36	X	102927056	127	PLP1	5354
rs2294152	36	X	102930390	127	PLP1	5354
rs7055303	36	X	106750252	127	PRPS1	5631
rs13440633	36	X	106752682	127	PRPS1	5631
rs12116382	36	X	106754652	127	PRPS1	5631
rs5962867	36	X	106756861	127	PRPS1	5631
rs1924215	36	X	106757459	127	PRPS1	5631
rs1924216	36	X	106757741	127	PRPS1	5631
rs10521515	36	X	106760120	127	PRPS1	5631
rs10217967	36	X	106762523	127	PRPS1	5631
rs5962868	36	X	106765295	127	PRPS1	5631
rs7886132	36	X	106766918	127	PRPS1	5631
rs16985261	36	X	106767665	127	PRPS1	5631
rs5962873	36	X	106784625	127	PRPS1	5631

MtSNP Genotyped and Imputed

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SNP or Haplogroup	Position (rCRSa)	SNP Type	Call rate	MAF	SNP or Haplogroup	Position (rCRSa)	SNP Type	Call rate	MAF	
mt10034	10034	Genotyped	1.000	0.034	25	mt14365	14365	Imputed	1.000	0.007
mt10044	10044	Imputed	1.000	0.000		mt1438	1438	Imputed	1.000	0.020
mt10084	10084	Genotyped	1.000	0.007		mt14470	14470	Genotyped	0.997	0.020
mt10238	10238	Imputed	1.000	0.040		mt14582	14582	Imputed	1.000	0.007
mt10398	10398	Imputed	1.000	0.181		mt14687	14687	Imputed	0.997	0.007
mt10463	10463	Imputed	0.945	0.128		mt14766	14766	Imputed	0.997	0.470
mt10550	10550	Imputed	1.000	0.047	30	mt14793	14793	Genotyped	0.997	0.040
mt10876	10876	Imputed	0.984	0.007		mt14798	14798	Genotyped	1.000	0.101
mt10915	10915	Genotyped	1.000	0.027		mt14905	14905	Imputed	0.945	0.128
mt11251	11251	Imputed	0.945	0.241		mt15043	15043	Genotyped	1.000	0.060
mt11299	11299	Imputed	1.000	0.047		mt15218	15218	Genotyped	1.000	0.020
mt11377	11377	Genotyped	1.000	0.007	35	mt15257	15257	Genotyped	1.000	0.013
mt11467	11467	Imputed	0.992	0.228		mt15452	15452	Imputed	0.995	0.215
mt11470	11470	Imputed	1.000	0.013		mt15607	15607	Imputed	0.945	0.128
mt11485	11485	Genotyped	1.000	0.020		mt15746	15746	Imputed	1.000	0.000
mt11674	11674	Genotyped	1.000	0.020		mt15758	15758	Genotyped	1.000	0.013
mt11719	11719	Genotyped	0.997	0.470		mt15784	15784	Genotyped	1.000	0.000
mt11812	11812	Genotyped	0.945	0.064	40	mt15833	15833	Genotyped	1.000	0.020
mt11840	11840	Imputed	1.000	0.007		mt15884	15884	Genotyped	1.000	0.013
mt1189	1189	Genotyped	1.000	0.040		mt15904	15904	Imputed	0.997	0.060
mt11914	11914	Genotyped	0.934	0.065		mt15907	15907	Imputed	0.984	0.007
mt11947	11947	Imputed	1.000	0.020		mt15924	15924	Genotyped	0.997	0.060
mt12007	12007	Genotyped	0.937	0.043		mt15928	15928	Imputed	0.945	0.128
mt12239	12239	Imputed	1.000	0.000	45					
mt12308	12308	Imputed	0.992	0.228						
mt12372	12372	Genotyped	0.992	0.228						
mt12414	12414	Genotyped	1.000	0.020						
mt1243	1243	Imputed	1.000	0.020						
mt12501	12501	Imputed	1.000	0.054						
mt12612	12612	Imputed	1.000	0.081	50					
mt12618	12618	Imputed	1.000	0.013						
mt12633	12633	Genotyped	1.000	0.060						
mt12669	12669	Imputed	1.000	0.000						
mt12705	12705	Genotyped	1.000	0.087						
mt13020	13020	Genotyped	0.984	0.007						
mt13105	13105	Genotyped	0.989	0.014	55					
mt13368	13368	Imputed	0.945	0.128						
mt13617	13617	Imputed	1.000	0.101						
mt13708	13708	Genotyped	1.000	0.107						
mt13734	13734	Genotyped	1.000	0.007						
mt13740	13740	Imputed	1.000	0.007						
mt13780	13780	Imputed	1.000	0.040	60					
mt13879	13879	Genotyped	1.000	0.007						
mt13934	13934	Genotyped	1.000	0.020						
mt13965	13965	Genotyped	0.997	0.007						
mt13966	13966	Genotyped	1.000	0.013						
mt14022	14022	Imputed	1.000	0.000						
mt14167	14167	Imputed	1.000	0.047						
mt14182	14182	Genotyped	1.000	0.060	65					
mt14233	14233	Imputed	0.945	0.064						

The invention claimed is:

1. A method of treating a patient with cancer, the method comprising:
  - a. performing an assay on the patient's DNA to determine the presence or absence of a biomarker; wherein said biomarker is selected from the group consisting of a homozygous genotype of the minor allele, G, of rs4553808, a homozygous genotype of the minor allele, G, of rs1474642, a homozygous genotype of the minor allele, G, of rs12568757, a homozygous genotype of the minor allele, A, of rs11974610, 1 or 2 copies of the minor allele, G, of rs916758 and 1 or 2 copies of the minor allele, T, of rs1261134; and,
  - b. administering bortezomib to the patient lacking said biomarker.
2. The method of claim 1, wherein said biomarker is the homozygous genotype of the minor allele, G, of rs4553808.
3. The method of claim 1, wherein said biomarker is the homozygous genotype of the minor allele, G, of rs1474642.
4. The method of claim 1, wherein said biomarker is the homozygous genotype of the minor allele, G, of rs12568757.



5. The method of claim 1, wherein said biomarker is the homozygous genotype of the minor allele, A, of rs11974610.

6. The method of claim 1, wherein said biomarker is 1 or 2 copies of the minor allele, G, of rs916758.

7. The method of claim 1, wherein said biomarker is 1 or 2 copies of the minor allele, T, of rs1261134.

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