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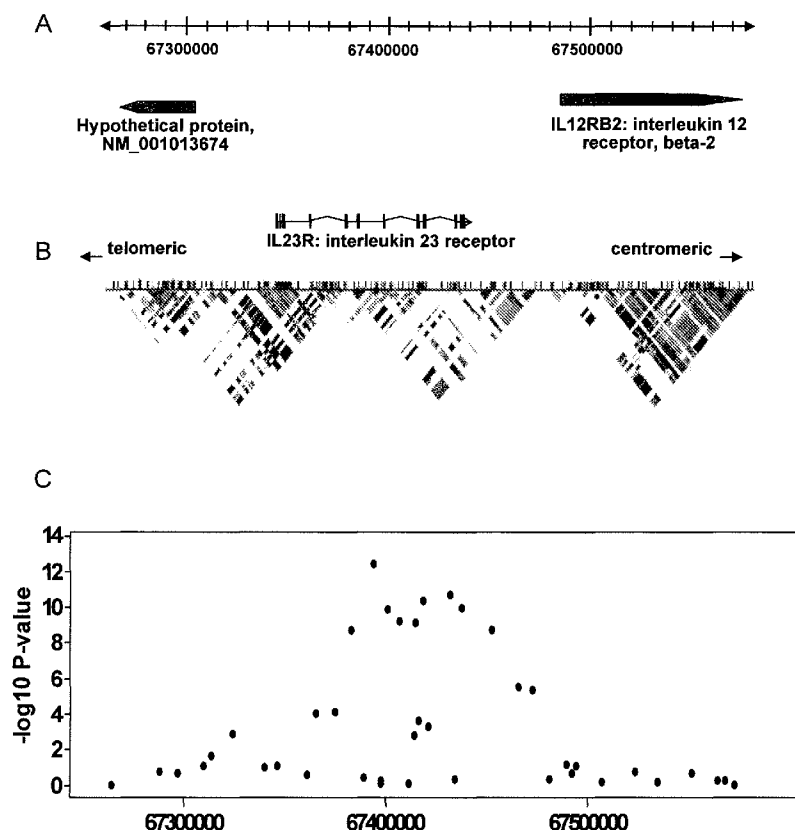
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(54) Title: METHODS OF USING SINGLE NUCLEOTIDE POLYMORPHISMS IN THE IL23R GENE TO PREDICT OR DI-
AGNOSE INFLAMMATORY BOWEL DISEASE



(57) Abstract: The inventors performed a genome-wide association study and identified interleukin-23 receptor (IL-23R) as an inflammatory bowel disease gene. Additionally, the inventors found both protective and risk allelic variants and haplotypes for Crohn's Disease. The inventors have also found that in non-Jewish individuals, risk haplotypes are associated with a higher median anti-IL2 antibody level. The invention provides methods of identifying at-risk individuals and predicting disease course by determining the presence or absence in the individual of protective and risk variants in IL-23R.



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METHODS OF USING SINGLE NUCLEOTIDE POLYMORPHISMS IN THE IL23R GENE TO PREDICT OR DIAGNOSE INFLAMMATORY BOWEL DISEASE

FIELD OF THE INVENTION

5 The invention relates generally to the fields of inflammation and autoimmunity and autoimmune disease and, more specifically, to genetic methods for diagnosing inflammatory bowel disease, Crohn's disease, and other autoimmune diseases.

BACKGROUND

10 All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the
15 presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

 Crohn's disease (CD) and ulcerative colitis (UC), the two common forms of idiopathic inflammatory bowel disease (IBD), are chronic, relapsing inflammatory disorders of the gastrointestinal tract. Each has a peak age of onset in the second to
20 fourth decades of life and prevalences in European ancestry populations that average approximately 100-150 per 100,000 (D. K. Podolsky, N Engl J Med 347, 417 (2002); E. V. Loftus, Jr., Gastroenterology 126, 1504 (2004)). Although the precise etiology of IBD remains to be elucidated, a widely accepted hypothesis is that ubiquitous, commensal intestinal bacteria trigger an inappropriate, overactive, and ongoing mucosal immune
25 response that mediates intestinal tissue damage in genetically susceptible individuals (D. K. Podolsky, N Engl J Med 347, 417 (2002)). Genetic factors play an important role in IBD pathogenesis, as evidenced by the increased rates of IBD in Ashkenazi Jews, familial aggregation of IBD, and increased concordance for IBD in monozygotic
30 compared to dizygotic twin pairs (S. Vermeire, P. Rutgeerts, Genes Immun 6, 637 (2005)). Moreover, genetic analyses have linked IBD to specific genetic variants, especially CARD15 variants on chromosome 16q12 and the IBD5 haplotype (spanning

the organic cation transporters, SLC22A4 and SLC22A5, and other genes) on chromosome 5q31 (S. Vermeire, P. Rutgeerts, *Genes Immun* 6, 637 (2005); J.P. Hugot et al., *Nature* 411, 599 (2001); Y. Ogura et al., *Nature* 411, 603 (2001); J. D. Rioux et al., *Nat Genet* 29, 223 (2001); V. D. Peltekova et al., *Nat Genet* 36, 471 (2004)). CD and UC are thought to be related disorders that share some genetic susceptibility loci but differ at others.

The interleukin 23/interleukin 17 pathway, in general, has been the focus of published research in inflammatory bowel disease and other chronic, immunologically-mediated disorders. Antibodies directed against the subunit of IL-23 that is shared with IL-12 (p40) have shown promise as a treatment for inflammatory bowel disease and other chronic, immune-mediated disorders. However, although the IL23/IL17 pathway has been generally linked with inflammation, there has been little if any evidence of a specific mechanism. Furthermore, much of the attention regarding the involvement of IL-23 has been focused upon the interaction between the p40 subunit and the IL12Rbeta1 receptor subunit, due to a perceived higher affinity as compared to the interaction between the p35 subunit and the IL23R receptor subunit. Thus, although the IL-23 signaling pathway has been generally hypothesized to have involvement with various inflammatory disorders, a specific involvement of the IL23R receptor subunit with IBD has not been described with any kind of detail.

The replicated associations between CD and variants in CARD15 and the IBD5 haplotype do not fully explain the genetic risk for CD. Thus, there is need in the art to determine other genes, allelic variants and/or haplotypes that may assist in explaining the genetic risk, diagnosing, and/or predicting susceptibility for or protection against inflammatory bowel disease including but not limited to CD and/or UC.

SUMMARY OF THE INVENTION

Various embodiments provide methods of diagnosing susceptibility to Crohn's Disease in an individual, comprising determining the presence or absence of one or more risk haplotypes at the IL23R locus, where the presence of one or more risk haplotypes is diagnostic of susceptibility to Crohn's Disease. The risk haplotypes can be selected from the group consisting of Block 2 H3 haplotype and Block 3 H8

haplotype, or any combination thereof, with the presence of two risk haplotypes presenting a greater susceptibility than the presence of one or none, and the presence of one risk haplotype can present a greater susceptibility than the presence of none, but less than the presence of two. Risk haplotypes can also include one or more variant alleles selected from rs1569922, rs1004819, rs2201841, rs10889677, rs11209032 and rs1495965. The presence of one or more risk haplotypes can also be diagnostic of susceptibility to Crohn's Disease in a non-Jewish individual, and can be indicative of a higher median anti-I2 antibody level.

Further embodiments provide methods of determining a lower probability of developing Crohn's Disease in an individual, comprising determining the presence or absence of one or more protective haplotypes at the IL23R locus, where the presence of one or more of protective haplotypes is diagnostic of protection against Crohn's Disease. The protective haplotypes can be selected from the group consisting of Block 2 H2 haplotype and Block 3 H1 haplotype, or any combination thereof, with the presence of two protective haplotypes presenting a greater protection than the presence of one or none, and the presence of one protective haplotypes can present a greater protection than the presence of none, but less than the presence of two. Protective haplotypes can also include the presence of an rs1569922 variant allele, one or more variant alleles selected from the group consisting of rs11209026, rs7517847, rs10489629, rs11465804 and rs1343151, and an Arg381Gln variant. Finally, the presence of one or more protective haplotypes can be diagnostic of protection against Crohn's Disease in a non-Jewish individual.

Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various embodiments of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

Figure 1 depicts association signals in the IL23R gene region on chromosome 1p31 in accordance with various embodiments of the present invention. (A) Genomic locations of genes on chromosome 1p31 between 67,260,000-67,580,000 base pairs (Build 35). (B) Pair-wise r^2 plot for HapMap SNPs. The IL23R gene is contained within two linkage disequilibrium blocks, and the association signals are strongest in the centromeric block which contains exons 5-11 and extends into the intergenic region between IL23R and IL12RB2. (C) The negative $\log_{10}$ association p-values (Cochran-Mantel-Haenszel chi-square test) from the combined Jewish and non-Jewish case-control cohorts are plotted for genotyped markers in the region. The association signal is strongest in the centromeric part of the IL23R gene and extends into to intergenic region between IL23R and IL12RB2. Markers in the block encompassing the IL12RB2 gene do not demonstrate significant association.

Figure 2 depicts three haplotype blocks in accordance with various embodiments of the present invention. Block 2 and Block 3 were observed to have associations with CD.

Figure 3 depicts IL23R Block 2 Haplotypes associated with CD in accordance with various embodiments of the present invention.

Figure 4 depicts IL23R Block 2 haplotypes association with CD risk in accordance with various embodiments of the present invention.

Figure 5 depicts IL23R Block 2 haplotypes associated with protection against CD in Non-Jewish individuals in accordance with an embodiment of the present invention.

Figure 6 depicts IL23R Block 3 haplotypes associated with CD in accordance with various embodiments of the present invention.

Figure 7 depicts IL23R Block 3 haplotypes associations with CD risk in accordance with various embodiments of the present invention.

Figure 8 depicts IL23R Block 3 haplotype associated with protection against CD in non-Jewish individuals in accordance with an embodiment of the present invention.

Figure 9 depicts IL23R haplotype combinations that are associated with CD in accordance with various embodiments of the present invention.

Figure 10 depicts IL23R haplotype combinations that are associated with CD in accordance with various embodiments of the present invention.

Figure 11 depicts IL23R and anti-I2 antibodies association with Block 2 haplotypes in non-Jewish individuals in accordance with an embodiment of the present invention. Higher anti-I2 levels are associated with Block 2 risk haplotypes in non-Jewish individuals.

5 Figure 12 depicts IL23R and anti-I2 antibodies association with Block 3 haplotypes in Jewish individuals in accordance with an embodiment of the present invention.

Figure 13 depicts IL23R and anti-I2 antibodies association with Block 3 haplotypes in non-Jewish individuals in accordance with various embodiments of the present invention. There are higher median anti-I2 levels with Block 3 risk haplotype.

DESCRIPTION OF THE INVENTION

All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, *Dictionary of Microbiology and Molecular Biology 3rd ed.*, J. Wiley & Sons (New York, NY 2001); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed.*, J. Wiley & Sons (New York, NY 2001); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual 3rd ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

The inventors performed a genome-wide association study testing 308,332 autosomal single nucleotide polymorphisms (SNPs) on the Illumina HumanHap300 Genotyping BeadChip. Based on these studies, the inventors found single nucleotide polymorphisms (SNPs) and haplotypes that are associated with increased or decreased risk for inflammatory bowel disease, including but not limited to CD and UC. These SNPs and haplotypes are suitable for genetic testing to identify at risk individuals and those associated with such markers as the serum expression of anti-I2 antibodies. Identification of genes that cause inflammatory bowel disease may support a new

generation of therapies and genetic testing to identify at risk individuals, predict disease course and suggest the right therapy for individual patients. The inventors have identified IL23R as an inflammatory bowel disease gene. Additionally, the inventors have found both protective and risk allelic variants (hereinafter also referred to as a “SNP”) and haplotypes for CD. The inventors have also found that in non-Jewish individuals, risk haplotypes were associated with a higher median anti-I2 antibody levels. The detection of SNPs and/or haplotypes in IL23R may be used to identify at risk individuals, predict disease course and suggest the right therapy for individual patients.

“Haplotype” as used herein refers to a set of single nucleotide polymorphisms (SNPs) on a gene or chromatid that are statistically associated.

“Protective” and “protection” as used herein refer to a decrease in susceptibility to IBD, including but not limited to CD and UC.

“Jewish” as used herein refers to an individual of Jewish descent.

“Higher median anti-I2 antibody levels” as used herein refers to levels determined relative to a standard consisting of pooled sera obtained from normal individuals. Using results expressed as ELISA units, sera with circulating anti-I2 antibody levels exceeding the reference range value are termed higher median anti-antibody levels.

As disclosed herein, in a population consisting of non-Jewish, European ancestry patients with ileal CD, three SNPs had nearly two orders of magnitude greater significance compared to the next most significant markers, and they are the only markers that remain significant at the 0.05 level after Bonferroni correction. Two of the three markers, rs2066843 ($p = 2.86 \times 10^{-09}$, corrected $p = 8.82 \times 10^{-4}$) and rs2076756 ($p = 5.12 \times 10^{-10}$, corrected $p = 1.58 \times 10^{-4}$), are in the known CD susceptibility gene, CARD15 (4, 5). The third marker, rs11209026 ($p = 5.05 \times 10^{-9}$, corrected $p = 1.56 \times 10^{-3}$), is a non-synonymous SNP (c.1142G>A, p.Arg381Gln) in the IL23R gene (GenBank Accession: NM_144701, GeneID: 149233) on chromosome 1p31. This gene encodes a subunit of the receptor for the pro-inflammatory cytokine, interleukin-23 (IL23), and was therefore an intriguing functional candidate. In addition to Arg381Gln, nine other markers in IL23R and in the intergenic region between IL23R and the adjacent

interleukin 12 receptor, beta-2 gene (IL12RB2) had association p-values < 0.0001 in the non-Jewish, ileal CD case-control cohort (Tables 1 and 3A).

As further disclosed herein, the inventors tested for association of IL23R markers in Jewish patients with ileal CD. Significant associations were observed for several of the same markers that were associated in the non-Jewish cohort (Tables 1 and 3B). In a combined analysis of the data from the two ileal CD case-control cohorts, nine markers had highly significant association p-values ranging from 3.36×10^{-13} to 1.60×10^{-9} (Tables 1 and 3B).

As disclosed herein, the inventors also performed family-based association testing (FBAT) (S. L. Lake, D. Blacker, N. M. Laird, Am J Hum Genet 67, 1515 (2000); S. Horvath, X. Xu, N. M. Laird, Eur J Hum Genet 9, 301 (2001)) of IL23R region markers in independent cohorts of nuclear families in which both parents and their CD- or UC-affected offspring were available for genotyping (Tables 2 and 4). For Arg381Gln and other IL23R markers, the inventors observed significant departure from random allele transmission to CD-affected offspring in both non-Jewish and Jewish families, providing further evidence for association between CD and IL23R. The inventors also observed distortion of allele transmission to non-Jewish, UC-affected offspring, providing evidence for association of IL23R with non-Jewish UC. There was no evidence for association of Arg381Gln or other IL23R region markers in the Jewish UC families. In a combined analysis of the data from all 883 nuclear families and both case-control cohorts, all ten IL23R markers in Table 2 showed significant association with IBD, even after Bonferroni correction for analyzing 308,332 SNPs in the original genome-wide association study (p-values ranged from 7×10^{-19} to 3.55×10^{-9} ; corrected p-values ranged from 2.16×10^{-13} to 1.09×10^{-3}).

The IL23R gene is contained within two large linkage disequilibrium blocks, and markers in the centromeric block containing exons 5-11 and part of the intergenic region between IL23R and IL12RB2 have the strongest association signals (Fig. 1). There is no significant association within IL12RB2 (Fig. 1).

The IL23R protein contains an extracellular domain (comprised of a signal sequence, an N-terminal immunoglobulin-like domain and two cytokine receptor domains), a single transmembrane domain, and a 252 amino acid cytoplasmic domain

(C. Parham et al., J Immunol 168, 5699 (2002)). Arg381, in the cytoplasmic domain, is the fifth amino acid internal to the transmembrane domain and is highly conserved between species. In contrast, two other non-synonymous IL23R SNPs, rs1884444 (His3Gln) and rs7530511 (Pro310Leu), which are located within the extracellular domain, show no evidence for disease association (Tables 3A and 3B).

Based on these findings, the embodiments of the present invention provide for methods of diagnosing and/or predicting susceptibility for or protection against inflammatory bowel disease including but not limited to CD and/or UC. In one embodiment, the present invention provides for methods of diagnosing and/or predicting susceptibility for or protection against inflammatory bowel disease in non-Jewish individuals by determining the presence or absence of a risk variant. In another embodiment, the present invention provides methods of diagnosing and/or predicting susceptibility for or protection against inflammatory bowel disease in Jewish individuals by determining the presence or absence of a risk and/or protective variant. In another embodiment, the presence or absence of a risk and/or protective variant in IL-23R suggests an appropriate therapy for patients.

Based on these discoveries, the present invention provides methods of diagnosing and/or predicting susceptibility to CD in an individual by determining the presence or absence in the individual of a variant in the IL23R gene. In one embodiment, the present invention provides methods of diagnosing and/or determining susceptibility to CD in a non-Jewish individual by determining the presence or absence in the individual of a variant in the IL23R gene. In another embodiment, the present invention provides methods of diagnosing and/or determining protection against CD in a non-Jewish individual by determining the presence or absence in the individual of a variant in the IL23R gene. In another embodiment, the present invention provides methods of diagnosing and/or determining susceptibility to CD in a Jewish individual by determining the presence or absence in the individual of a variant in the IL23R gene.

The methods may include the steps of obtaining a biological sample containing nucleic acid including the IL23R gene from the individual and determining the presence or absence of a SNP and/or a haplotype in the biological sample. The methods may further include correlating the presence or absence of the SNP and/or the haplotype to

a genetic risk, a susceptibility for or protection against inflammatory bowel disease including but not limited to CD and/or UC, as described herein. The methods may also further include recording whether a genetic risk, susceptibility for or protection against inflammatory bowel disease including but not limited to CD and/or UC exists in the
5 individual.

As used herein, the term "biological sample" means any biological matter from which nucleic acid molecules can be prepared. As non-limiting examples, the term material encompasses whole blood, plasma, saliva, cheek swab, or other bodily fluid or tissue that contains nucleic acid. In one embodiment, a method of the invention is
10 practiced with whole blood, which can be obtained readily by non-invasive means and used to prepare genomic DNA, for example, for enzymatic amplification or automated sequencing. In another embodiment, a method of the invention is practiced with tissue obtained from an individual such as tissue obtained during surgery or biopsy procedures.

15 One or more SNPs at the following locations may be used to diagnose and/or predict a risk of susceptibility to or protection against CD in a Jewish or non-Jewish individual: rs1007819, rs7517847, rs10489629, rs2201841, rs11465804, rs11209026, rs1343151, rs10889677, rs11209032, rs1495965.

In one embodiment the presence of an rs11209026 variant (c1142G>A, p.Arg381Gln) is diagnostic or predictive of protection against CD in an individual.
20

In another embodiment, the presence of an rs1004819 variant is diagnostic or predictive of susceptibility to CD. In another embodiment, the presence of an rs7517847 variant is diagnostic or predictive of a protection against CD. In another embodiment, the presence of an rs10489629 variant is diagnostic or predictive of a
25 protection against CD. In another embodiment, the presence of an rs2201841 variant is diagnostic or predictive of susceptibility to CD. In another embodiment, the presence of an rs11465804 variant is diagnostic or predictive of a protection against CD. In another embodiment, the presence of an rs1343151 variant is diagnostic or predictive of a protection against CD. In another embodiment, the presence of an rs10889677 variant
30 is diagnostic or predictive of susceptibility to CD. In another embodiment, the presence of an rs11209032 variant is diagnostic or predictive of susceptibility to CD. In another

embodiment, the presence of an rs1495965 variant is diagnostic or predictive of susceptibility to CD.

The identities of the markers, their location on the gene and their nucleotide substitutions may be found in tables 3A and 3B.

5

The inventors also observed three haplotype blocks in the IL23R gene. Blocks 2 and 3 were found to have associations with CD. Both protective and risk haplotypes for CD were identified in IL23R. In non-Jewish individuals, risk haplotypes were associated with higher median anti-I2 levels. The results of the inventors' study implicate IL23R variation in the pathogenesis of CD.

10

Block 1 includes SNPs identified as rs11209008, rs12041056, rs1884444, and rs6671221. Block 2 includes SNPs identified as rs1004819, rs790631, and rs2863212. Block 3 includes SNPs identified as rs7530511, rs7528924, rs2201841, rs11804284, rs11465804, rs10489628, and rs1343151. (See figure 2.)

15

IL23R Block 2 haplotypes are associated with CD. The association of Block 2 H2 was only found to be significant in non-Jewish individuals. The association of Block 2 H3 was found in both Jewish and non-Jewish individuals, but only found to be significant in non-Jewish individuals. (See figure 3.) Figure 4 depicts IL23R Block 2 haplotypes and the associated CD risk. Block 2 H3 is associated with a risk for CD and Block 2 H2 is associated with a protection against CD. IL23R Block 2 protection is associated with CD in non-Jewish individuals. The association of Block 2 H2 was only found to be significant in non-Jewish individuals. The association of Block 2 H3 is in both Jewish and non-Jewish individuals, but only found to be significant in non-Jewish individuals. (See figure 5.)

20

IL23R Block 3 haplotypes are associated with CD. Block 3 H1 is significant only in non-Jewish individuals. Block 3 H8 is present in both Jewish and non-Jewish individuals, but only found to be significant in non-Jewish individuals. (See figure 6.) Figure 7 depicts IL23R Block 3 haplotypes and the associated CD risk. Block 3 H8 is associated with a risk for CD and Block 3 H1 is associated with a protection against CD. Block 3 protection is associated with CD in non-Jewish individuals. (See figure 8.)

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Certain IL23R Haplotype combinations are associated with CD, as depicted in figures 9 and 10. Block 2 H3 and Block 3 H8 are associated with a risk for CD. Block 2 H2 and Block 3 H1 are associated with a protection against CD. Rs1569922, Block 2 H3, Block 3 H8 are associated with a risk for CD. Rs1569922, Block 2 H2, Block 3 H1 are associated with protection against CD.

As such, additional embodiments of the present invention provide for methods for diagnosing or predicting susceptibility to CD in an individual by determining the presence or absence of a haplotype in the individual.

In one embodiment, the presence of Block 3 H1 haplotype may indicate a protection against CD. In one embodiment, the presence of Block 3 H1 haplotype may indicate a protection against CD in non-Jewish individuals.

In another embodiment, the presence of Block 2 H2 haplotype may indicate a protection against CD. In a particular embodiment, the presence of Block 2 haplotype H2 may indicate protection against CD in non-Jewish individuals.

In another embodiment, the presence of Block 2 H3 haplotype may indicate a susceptibility to CD. In another embodiment, the presence of Block 3 H8 haplotype may indicate a susceptibility to CD.

In other embodiments, haplotype combinations may be associated with CD in a cumulative manner.

In one embodiment, the presence of one or two haplotypes selected from the group consisting of Block 2 H3 and Block 3 H8 may confer an increased risk in susceptibility to CD. In one embodiment, the presence of two haplotypes selected from the group consisting Block 2 H3 and Block 3 H8 may confer a higher risk of susceptibility to CD as compared to the presence of one or none of these haplotypes.

(See e.g., figure 9.)

In one embodiment, the presence of one or two haplotypes selected from the group consisting of Block 2 H3 and Block 3 H8 may confer an increased risk of susceptibility to CD. In one embodiment, the presence of two haplotypes selected from the group consisting Block 2 H3 and Block 3 H8 may confer a higher risk of susceptibility to CD as compared to the presence of one or none of these haplotypes.

(See e.g., figure 10.)

In another embodiment, the presence of one of the following SNP rs1569922, haplotype Block 2 H3 or haplotype Block 3 H8, may indicate a risk of susceptibility to CD. In one embodiment, the presence of two of the following, in any combination, SNP rs1569922, haplotype Block 2 H3 and haplotype Block 3 H8 may indicate a higher risk of susceptibility to CD as compared to the presence of only one or none. In another embodiment, the presence of SNP rs1569922 and two haplotypes selected from the group consisting of Block 2 H3 and Block 3 H8, may indicate an even higher risk of susceptibility to CD as compared to the presence of only two, one or none.

The identities of the haplotypes and their nucleotide substitutions may be found in table 6. The location of the SNPs may be found in table 5.

Additional embodiments of the present invention may also be used to diagnose or predict susceptibility to a particular subtype of Crohn's disease in a patient. Such a subtype can be, for example, a clinical subtype of Crohn's disease with features of ulcerative colitis (U.S. Pat. No. 5,932,429) or clinical subtype of Crohn's disease having fibrostenosis. One skilled in the art will understand that these and other clinical subtypes of Crohn's disease also can be diagnosed by detecting the presence or absence of a SNP and/or a haplotype as described herein.

Figure 11 depicts IL23R and anti-I2 antibodies association with Block 2 haplotypes in non-Jewish individuals. The effect of Block 2 H3 is only found in non-Jewish individuals ($p=0.005$). Higher I2 levels were associated with Block 2 risk haplotype in non-Jewish individuals.

Figure 12 depicts IL23R and anti-I2 antibodies association with Block 3 haplotypes in Jewish individuals. This association was only observed in Jewish individuals.

Figure 13 depicts IL23R and anti-I2 antibodies association with Block 3 haplotypes in non-Jewish individuals. Higher median I2 levels with Block 3 risk haplotype were observed.

In one embodiment, the presence of a haplotype in Block 2 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies. In a particular embodiment, the presence of a haplotype in Block 2 may indicate the

presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies in non-Jewish individuals. In one embodiment, the haplotype may be Block 2 H3. In another embodiment, the presence of SNP rs1004819 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies. In a particular embodiment, the presence of SNP rs1004819 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies in non-Jewish individuals. See figure 11.

In another embodiment, the presence of a haplotype in Block 3 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies. In a particular embodiment, the presence of a haplotype in Block 3 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies in Jewish individuals. In one embodiment, the haplotype may be Block 3 H4. In another embodiment, the presence of SNP rs11465804 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies. In a particular embodiment, the presence of SNP rs11465804 may indicate the presence of anti-I2 antibodies in Jewish individuals. See figure 12. In a particular embodiment, the presence of a haplotype in Block 3 may indicate the presence of anti-I2 antibodies and/or higher serum levels of anti-I2 antibodies in non-Jewish individuals. In one embodiment, the haplotype may be Block 3 H8. See figure 13.

The presence of anti-I2 antibodies may indicate that the individual has a fibrostenotic subtype of CD; for example, as described in U.S. Patent Publication No. 2004/0203076, herein incorporated by reference as though fully set forth in its entirety. The presence of anti-I2 antibodies may also indicate that the individual does not have ulcerative colitis-like CD; for example, also as described in U.S. Patent Publication No. 2004/0203076. Thus, the presence of Block 2 and/or Block 3 risk haplotype(s) may indicate that the individual has a fibrostenotic subtype of CD and/or does not have ulcerative colitis-like CD. In particular embodiments, the presence of Block 2 H3, Block 3 H4, Block 3 H8 and/or Block 3 H10 haplotype(s) may indicate that the individual has a fibrostenotic subtype of CD and/or does not have ulcerative colitis-like CD.

The strength of the association between a haplotype or allele and CD may be characterized by a particular odds ratio. See Tables 1, 3A, and 3B. Methods for determining an odds ratio are well known in the art (see, for example, Schlesselman et

al., Case Control Studies: Design, Conduct and Analysis Oxford University Press, New York (1982)).

A variety of methods can be used to determine the presence or absence of an IL23R variant allele or haplotype. As an example, enzymatic amplification of nucleic acid from an individual may be used to obtain nucleic acid for subsequent analysis. The presence or absence of an IL23R variant allele or haplotype may also be determined directly from the individual's nucleic acid without enzymatic amplification.

Analysis of the nucleic acid from an individual, whether amplified or not, may be performed using any of various techniques. Useful techniques include, without limitation, polymerase chain reaction based analysis, sequence analysis and electrophoretic analysis. As used herein, the term "nucleic acid" means a polynucleotide such as a single or double-stranded DNA or RNA molecule including, for example, genomic DNA, cDNA and mRNA. The term nucleic acid encompasses nucleic acid molecules of both natural and synthetic origin as well as molecules of linear, circular or branched configuration representing either the sense or antisense strand, or both, of a native nucleic acid molecule.

The presence or absence of an IL23R variant allele or haplotype may involve amplification of an individual's nucleic acid by the polymerase chain reaction. Use of the polymerase chain reaction for the amplification of nucleic acids is well known in the art (see, for example, Mullis et al. (Eds.), The Polymerase Chain Reaction, Birkhauser, Boston, (1994)).

A TaqmanB allelic discrimination assay available from Applied Biosystems may be useful for determining the presence or absence of an IL23R variant allele. In a TaqmanB allelic discrimination assay, a specific, fluorescent, dye-labeled probe for each allele is constructed. The probes contain different fluorescent reporter dyes such as FAM and VICTM to differentiate the amplification of each allele. In addition, each probe has a quencher dye at one end which quenches fluorescence by fluorescence resonant energy transfer (FRET). During PCR, each probe anneals specifically to complementary sequences in the nucleic acid from the individual. The 5' nuclease activity of Taq polymerase is used to cleave only probe that hybridize to the allele. Cleavage separates the reporter dye from the quencher dye, resulting in increased

fluorescence by the reporter dye. Thus, the fluorescence signal generated by PCR amplification indicates which alleles are present in the sample. Mismatches between a probe and allele reduce the efficiency of both probe hybridization and cleavage by Taq polymerase, resulting in little to no fluorescent signal. Improved specificity in allelic discrimination assays can be achieved by conjugating a DNA minor groove binder (MGB) group to a DNA probe as described, for example, in Kutyavin et al., "3'-minor groove binder-DNA probes increase sequence specificity at PCR extension temperature," *Nucleic Acids Research* 28:655-661 (2000)). Minor groove binders include, but are not limited to, compounds such as dihydrocyclopyrroloindole tripeptide (DPI.).

Sequence analysis also may also be useful for determining the presence or absence of an IL23R variant allele or haplotype.

Restriction fragment length polymorphism (RFLP) analysis may also be useful for determining the presence or absence of a particular allele (Jarcho et al. in Dracopoli et al., *Current Protocols in Human Genetics* pages 2.7.1-2.7.5, John Wiley & Sons, New York; Innis et al., (Ed.), *PCR Protocols*, San Diego: Academic Press, Inc. (1990)). As used herein, restriction fragment length polymorphism analysis is any method for distinguishing genetic polymorphisms using a restriction enzyme, which is an endonuclease that catalyzes the degradation of nucleic acid and recognizes a specific base sequence, generally a palindrome or inverted repeat. One skilled in the art understands that the use of RFLP analysis depends upon an enzyme that can differentiate two alleles at a polymorphic site.

Allele-specific oligonucleotide hybridization may also be used to detect a disease-predisposing allele. Allele-specific oligonucleotide hybridization is based on the use of a labeled oligonucleotide probe having a sequence perfectly complementary, for example, to the sequence encompassing a disease-predisposing allele. Under appropriate conditions, the allele-specific probe hybridizes to a nucleic acid containing the disease-predisposing allele but does not hybridize to the one or more other alleles, which have one or more nucleotide mismatches as compared to the probe. If desired, a second allele-specific oligonucleotide probe that matches an alternate allele also can be used. Similarly, the technique of allele-specific oligonucleotide amplification can be used to selectively amplify, for example, a disease-predisposing allele by using an allele-

specific oligonucleotide primer that is perfectly complementary to the nucleotide sequence of the disease-predisposing allele but which has one or more mismatches as compared to other alleles (Mullis et al., supra, (1994)). One skilled in the art understands that the one or more nucleotide mismatches that distinguish between the disease-predisposing allele and one or more other alleles are preferably located in the center of an allele-specific oligonucleotide primer to be used in allele-specific oligonucleotide hybridization. In contrast, an allele-specific oligonucleotide primer to be used in PCR amplification preferably contains the one or more nucleotide mismatches that distinguish between the disease-associated and other alleles at the 3' end of the primer.

A heteroduplex mobility assay (HMA) is another well known assay that may be used to detect a SNP or a haplotype. HMA is useful for detecting the presence of a polymorphic sequence since a DNA duplex carrying a mismatch has reduced mobility in a polyacrylamide gel compared to the mobility of a perfectly base-paired duplex (Delwart et al., Science 262:1257-1261 (1993); White et al., Genomics 12:301-306 (1992)).

The technique of single strand conformational, polymorphism (SSCP) also may be used to detect the presence or absence of a SNP and/or a haplotype (see Hayashi, K., Methods Applic. 1:34-38 (1991)). This technique can be used to detect mutations based on differences in the secondary structure of single-strand DNA that produce an altered electrophoretic mobility upon non-denaturing gel electrophoresis. Polymorphic fragments are detected by comparison of the electrophoretic pattern of the test fragment to corresponding standard fragments containing known alleles.

Denaturing gradient gel electrophoresis (DGGE) also may be used to detect a SNP and/or a haplotype. In DGGE, double-stranded DNA is electrophoresed in a gel containing an increasing concentration of denaturant; double-stranded fragments made up of mismatched alleles have segments that melt more rapidly, causing such fragments to migrate differently as compared to perfectly complementary sequences (Sheffield et al., "Identifying DNA Polymorphisms by Denaturing Gradient Gel Electrophoresis" in Innis et al., supra, 1990).

Other molecular methods useful for determining the presence or absence of a SNP and/or a haplotype are known in the art and useful in the methods of the invention. Other well-known approaches for determining the presence or absence of a SNP and/or a haplotype include automated sequencing and RNAase mismatch techniques (Winter et al., Proc. Natl. Acad. Sci. 82:7575-7579 (1985)). Furthermore, one skilled in the art understands that, where the presence or absence of multiple alleles or haplotype(s) is to be determined, individual alleles can be detected by any combination of molecular methods. See, in general, Birren et al. (Eds.) Genome Analysis: A Laboratory Manual Volume 1 (Analyzing DNA) New York, Cold Spring Harbor Laboratory Press (1997). In addition, one skilled in the art understands that multiple alleles can be detected in individual reactions or in a single reaction (a "multiplex" assay). In view of the above, one skilled in the art realizes that the methods of the present invention for diagnosing or predicting susceptibility to or protection against CD in an individual may be practiced using one or any combination of the well known assays described above or another art-recognized genetic assay.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

EXAMPLES

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

One of the study populations consisted of 567 non-Jewish, European ancestry patients with ileal CD and 571 non-Jewish controls. The inventors initially focused on ileal CD, the most common location of CD, to minimize pathogenic heterogeneity. After exclusion of study subjects with genotype completion rates less than 94%, the inventors included 547 cases and 548 controls in subsequent analyses. Single-marker allelic tests were performed using χ^2 statistics for all autosomal markers. Three SNPs had nearly two orders of magnitude greater significance compared to the next most significant markers, and they are the only markers that remain significant at the 0.05 level after Bonferroni correction. Two of the three markers, rs2066843 ($p = 2.86 \times 10^{-9}$, corrected $p = 8.82 \times 10^{-4}$) and rs2076756 ($p = 5.12 \times 10^{-10}$, corrected $p = 1.58 \times 10^{-4}$), are in the known CD susceptibility gene, CARD15 (4, 5). The third marker, rs11209026 ($p = 5.05 \times 10^{-9}$, corrected $p = 1.56 \times 10^{-3}$), is a non-synonymous SNP (c.1142G>A, p.Arg381Gln) in the IL23R gene (GenBank Accession: NM_144701, GeneID: 149233) on chromosome 1p31. This gene encodes a subunit of the receptor for the pro-inflammatory cytokine, interleukin-23 (IL23), and was therefore an intriguing functional candidate. In addition to Arg381Gln, nine other markers in IL23R and in the intergenic region between IL23R and the adjacent interleukin 12 receptor, beta-2 gene (IL12RB2) had association p-values < 0.0001 in the non-Jewish, ileal CD case-control cohort (Tables 1 and 3A).

Table 1. Non-Jewish and Jewish ileal Crohn's disease (CD) case-control association study results for IL23R region markers with p-values < 0.0001 in the non-Jewish cohort. Minor allele frequencies (MAF), allelic test p-values, and odds ratios (OR) with 95% confidence intervals (CI) are shown for each case-control cohort. The ORs shown are for the minor allele. Combined Cochran-Mantel-Haenszel p-values are also shown.

Table 1

Marker	Location	Non-Jewish case-control cohort				Jewish case-control cohort				Combined p-value
		CD (n=547) MAF	Control (n=548) MAF	p-value	OR [95%CI]	CD (n=401) MAF	Control (n=433) MAF	p-value	OR [95%CI]	
rs1007819	intron	0.374	0.280	3.79E-06	1.53 [1.27, 1.84]	0.426	0.334	1.00E-04	1.48 [1.21, 1.82]	1.54E-09

rs7517847	Intron	0.331	0.443	1.09E-07	0.62 [0.52,0.74]	0.240	0.352	5.84E-07	0.58 [0.47,0.72]	3.36E-13
rs10489629	Intron	0.378	0.475	4.27E-06	0.67 [0.56,0.80]	0.355	0.465	5.79E-06	0.63 [0.52,0.77]	1.14E-10
rs2201841	Intron	0.385	0.291	4.57E-06	1.52 [1.27,1.83]	0.414	0.315	2.92E-05	1.53 [1.25,1.89]	5.46E-10
rs11465804	Intron	0.020	0.063	7.52E-07	0.30 [0.18,0.51]	0.048	0.096	1.39E-04	0.47 [0.31,0.71]	5.97E-10
rs11209026	Arg381Gln	0.019	0.070	5.05E-09	0.26 [0.15,0.43]	0.033	0.070	7.95E-04	0.45 [0.27,0.73]	3.55E-11
rs1343151	Intron	0.275	0.370	2.26E-06	0.65 [0.54,0.78]	0.229	0.336	1.69E-06	0.59 [0.47,0.73]	1.64E-11
rs10889677	exon-3'UTR	0.385	0.288	1.82E-06	1.55 [1.29,1.86]	0.419	0.316	1.51E-05	1.56 [1.27,1.91]	9.58E-11
rs11209032	inter-genic	0.393	0.293	1.03E-06	1.56 [1.30,1.87]	0.382	0.298	3.49E-04	1.45 [1.18,1.79]	1.60E-09
rs1495965	Inter-genic	0.498	0.412	2.93E-05	1.44 [1.21,1.71]	0.469	0.412	0.0204	1.26 [1.03,1.53]	2.55E-06

Table 3A. Summary of markers for the non-Jewish case-control cohort corresponding to the genomic window shown in Figure 1. Shown are information about the markers (rs number and base pair position on chromosome 1, Build 35), genotype counts for Crohn's disease (CD) cases and controls, p-values for the Hardy-Weinberg test (HW-P) and Fisher's exact test for allelic counts (Allele-P). Minor allele frequencies (MAF) for cases and controls, odds ratios (ORs) and 95% confidence intervals (CI) for the first allele are shown.

Table 3A

Non-Jewish case-control cohort																
		CD genotypes				Control genotypes						CD	Control	CI-		CI-
marker	position	1	2	11	12	22	11	12	22	HW-P	Allele-P	MAF	MAF	OR	Lower	Upper
rs10789220	67263230	A	G	270	229	43	258	235	48	0.59	0.45	0.29	0.31	1.08	0.89	1.30
rs1830513	67287570	A	G	10	138	394	12	129	403	0.66	0.76	0.15	0.14	1.04	0.81	1.34
rs2863202	67296356	A	G	14	163	366	17	155	372	0.86	0.91	0.18	0.17	1.02	0.81	1.27
rs3762318	67309140	A	G	356	163	12	389	132	19	0.068	0.25	0.18	0.16	0.87	0.69	1.10
rs10489631	67313136	A	G	174	283	86	163	257	124	0.24	0.034	0.42	0.46	1.20	1.01	1.43
rs4655683	67323634	A	G	35	227	281	72	232	240	0.18	2.95E-04	0.27	0.35	0.71	0.59	0.86
rs12041056	67339281	A	G	102	286	155	88	269	185	0.55	0.057	0.45	0.41	1.18	0.99	1.40
rs1884444	67345833	A	C	167	284	92	156	263	125	0.49	0.058	0.43	0.47	1.18	0.99	1.40
rs6687620	67360481	A	G	9	143	390	11	109	424	0.21	0.059	0.15	0.12	1.27	0.99	1.65
rs2064689	67365031	A	G	28	204	311	58	221	265	0.24	2.58E-04	0.24	0.31	0.70	0.58	0.85
rs10489630	67374643	A	C	226	263	52	188	260	96	0.71	2.80E-04	0.34	0.42	1.38	1.16	1.65
rs1004819	67382234	A	G	66	274	203	36	233	275	0.15	3.79E-06	0.37	0.28	1.53	1.27	1.84
rs790631	67388943	A	G	262	247	32	288	217	38	0.74	0.36	0.29	0.27	0.92	0.76	1.11
rs7517847	67393690	A	C	241	238	59	164	274	102	0.51	1.09E-07	0.33	0.44	1.61	1.34	1.92
rs2863212	67397137	A	G	435	101	7	432	102	10	0.17	0.68	0.11	0.11	1.07	0.81	1.41
rs7530511	67397408	A	G	9	114	420	10	115	419	0.52	0.90	0.12	0.12	0.98	0.75	1.27
rs10489629	67400370	A	G	207	262	74	145	281	118	0.41	4.27E-06	0.38	0.48	1.49	1.25	1.78
rs2201841	67406223	A	G	194	280	69	274	223	47	0.86	4.57E-06	0.38	0.29	0.66	0.55	0.79
rs11804284	67411275	A	G	9	114	420	10	115	419	0.52	0.90	0.12	0.12	0.98	0.75	1.27
rs12030948	67413786	A	C	78	282	178	76	231	232	0.13	0.015	0.41	0.36	1.25	1.04	1.49
rs11465804	67414547	A	C	519	22	0	475	64	2	0.92	7.52E-07	0.02	0.063	3.23	1.95	5.53
rs10489628	67416128	A	G	65	255	223	93	263	188	0.95	0.0055	0.35	0.41	0.78	0.65	0.93
rs11209026	67417979	A	G	0	21	521	3	70	468	0.83	5.05E-09	0.019	0.070	0.26	0.15	0.43
rs6682033	67420691	A	G	310	191	42	260	243	41	0.12	0.019	0.25	0.30	1.26	1.04	1.52
rs1343151	67431150	A	G	47	205	291	63	277	204	0.032	2.26E-06	0.28	0.37	0.65	0.54	0.78
rs10889675	67434237	A	C	3	99	434	10	103	430	0.19	0.26	0.10	0.11	0.85	0.64	1.13
rs10889677	67437141	A	C	69	280	194	44	225	275	0.83	1.82E-06	0.38	0.29	1.55	1.29	1.86
rs7539328	67444624	A	G	39	184	316	69	203	266	0.0029	1.48E-04	0.24	0.32	0.69	0.57	0.84
rs11209032	67452113	A	G	73	280	189	36	247	261	0.026	1.03E-06	0.39	0.29	1.56	1.30	1.87
rs1495965	67465529	A	G	128	285	130	179	282	83	0.10	2.93E-05	0.50	0.41	0.69	0.58	0.83
rs924080	67472161	A	G	180	259	97	125	283	131	0.24	1.19E-04	0.42	0.49	1.40	1.17	1.66
rs12131065	67481027	A	G	25	200	318	30	218	296	0.21	0.18	0.23	0.26	0.87	0.71	1.07
rs3790558	67489042	A	C	168	275	100	148	275	121	0.75	0.078	0.44	0.48	1.16	0.98	1.38
rs10489627	67491697	A	G	252	230	61	232	233	79	0.10	0.086	0.32	0.36	1.17	0.98	1.40
rs2066445	67493996	A	G	19	142	382	18	178	348	0.41	0.066	0.17	0.20	0.81	0.65	1.02
rs1495964	67506839	A	G	201	250	92	179	272	93	0.55	0.32	0.40	0.42	1.09	0.92	1.30
rs3790565	67523377	A	G	361	164	18	360	169	15	0.36	0.96	0.18	0.18	0.99	0.79	1.24
rs3790567	67534398	A	G	35	195	312	28	195	315	0.76	0.55	0.24	0.23	1.06	0.87	1.30
rs3828069	67551594	A	G	379	154	10	359	161	24	0.28	0.056	0.16	0.19	1.25	0.99	1.57
rs4297265	67564356	A	G	198	250	95	174	271	98	0.67	0.26	0.41	0.43	1.11	0.93	1.32
rs2270614	67568042	A	G	96	249	198	98	271	175	0.70	0.28	0.41	0.43	0.91	0.76	1.08
rs7555183	67572648	A	G	48	226	269	62	239	243	0.78	0.065	0.30	0.33	0.84	0.70	1.01

Example 2

The inventors next tested for association of IL23R markers in an independent, Jewish case-control cohort containing 401 patients with ileal CD and 433 controls. Significant associations were observed for several of the same markers that were associated in the non-Jewish cohort (Tables 1 and 3B). In a combined analysis of the data from the two ileal CD case-control cohorts, nine markers had highly significant association p-values ranging from 3.36×10^{-13} to 1.60×10^{-9} (Tables 1 and 3B).

Table 3B. Summary of markers, data and results for the Jewish case-control cohort corresponding to the genomic window shown in Figure 1. The final column lists the combined p-value (non-Jewish and Jewish cohorts) obtained using the Cochran-Mantel-Haenszel test graphed in Figure 1.

Table 3B

Jewish case-control cohort																	Combined
		CD			Control												
		genotypes			genotypes												
marker	position	1	2	11	12	22	11	12	22	HW-P	Allele-P	CD	Control	OR	CI-	CI-	Combined
												MAF	MAF		Lower	Upper	Mantel
rs10789220	67263230	A	G	199	163	37	230	169	33	0.80	0.28	0.30	0.27	0.88	0.71	1.10	0.89
rs1830513	67287570	A	G	10	94	297	6	86	340	0.83	0.090	0.14	0.11	1.29	0.96	1.75	0.17
rs2863202	67296356	A	G	20	123	258	12	123	298	0.87	0.089	0.20	0.17	1.25	0.97	1.61	0.21
rs3762318	67309140	A	G	218	145	33	251	156	25	0.91	0.19	0.27	0.24	0.86	0.69	1.08	0.082
rs10489631	67313136	A	G	148	203	49	146	225	62	0.10	0.27	0.38	0.40	1.12	0.91	1.37	0.020
rs4655683	67323634	A	G	18	153	230	21	175	237	0.11	0.49	0.24	0.25	0.92	0.73	1.16	1.19E-03
rs12041056	67339281	A	G	89	202	109	82	239	112	0.02	0.69	0.48	0.47	1.04	0.85	1.27	0.091
rs1884444	67345833	A	C	142	205	54	147	222	64	0.18	0.58	0.39	0.40	1.06	0.87	1.30	0.072
rs6687620	67360481	A	G	7	90	303	7	104	322	0.67	0.72	0.13	0.14	0.95	0.71	1.27	0.24
rs2064689	67365031	A	G	6	107	288	12	131	290	0.54	0.098	0.15	0.18	0.80	0.61	1.05	8.52E-05
rs10489630	67374643	A	C	212	163	26	201	197	35	0.17	0.074	0.27	0.31	1.22	0.98	1.51	7.07E-05
rs1004819	67382234	A	G	68	206	127	45	199	189	0.49	1.00E-04	0.43	0.33	1.48	1.21	1.82	1.54E-09
rs790631	67388943	A	G	181	183	36	199	199	35	0.13	0.75	0.32	0.31	0.96	0.78	1.19	0.38
rs7517847	67393690	A	C	229	147	22	185	191	57	0.49	5.84E-07	0.24	0.35	1.72	1.38	2.15	3.36E-13
rs2863212	67397137	A	G	343	57	1	366	64	3	0.91	0.58	0.07	0.081	1.11	0.76	1.62	0.51
rs7530511	67397408	A	G	3	77	321	5	83	345	1.00	0.81	0.10	0.11	0.96	0.69	1.33	0.80
rs10489629	67400370	A	G	164	189	48	119	225	89	0.36	5.79E-06	0.36	0.47	1.58	1.29	1.93	1.14E-10
rs2201841	67406223	A	G	129	212	60	203	187	43	0.99	2.92E-05	0.41	0.32	0.65	0.53	0.80	5.46E-10
rs11804284	67411275	A	G	3	72	325	3	81	349	0.47	0.87	0.10	0.10	0.97	0.69	1.35	0.80
rs12030948	67413786	A	C	78	213	104	75	209	147	0.96	0.042	0.47	0.42	1.23	1.01	1.50	1.34E-03
rs11465804	67414547	A	C	362	36	1	347	78	2	0.28	1.39E-04	0.048	0.10	2.12	1.41	3.25	5.97E-10
rs10489628	67416128	A	G	37	176	188	53	214	166	0.21	0.013	0.31	0.37	0.77	0.63	0.95	1.96E-04
rs11209026	67417979	A	G	0	26	374	1	58	372	0.42	7.95E-04	0.033	0.070	0.45	0.27	0.73	3.55E-11
rs6682033	67420691	A	G	270	118	13	250	162	20	0.33	6.55E-03	0.18	0.23	1.39	1.09	1.79	4.10E-04
rs1343151	67431150	A	G	21	142	238	41	209	183	0.09	1.69E-06	0.23	0.34	0.59	0.47	0.73	1.64E-11
rs10889675	67434237	A	C	8	92	300	3	110	316	0.046	1	0.14	0.14	1.00	0.75	1.34	0.42
rs10889677	67437141	A	C	63	210	128	44	186	203	0.88	1.51E-05	0.42	0.32	1.56	1.27	1.91	9.58E-11
rs7539328	67444624	A	G	37	115	243	53	160	219	0.01	2.01E-03	0.24	0.31	0.71	0.56	0.88	8.44E-07
rs11209032	67452113	A	G	63	180	158	41	176	216	0.56	3.49E-04	0.38	0.30	1.45	1.18	1.79	1.60E-09
rs1495965	67465529	A	G	112	202	87	142	225	66	0.13	0.020	0.47	0.41	0.79	0.65	0.97	2.55E-06
rs924080	67472161	A	G	132	185	80	101	226	100	0.23	0.010	0.43	0.50	1.30	1.06	1.58	3.83E-06
rs12131065	67481027	A	G	13	126	262	12	135	286	0.41	0.80	0.19	0.18	1.04	0.81	1.34	0.39
rs3790558	67489042	A	C	120	189	92	117	212	104	0.68	0.43	0.47	0.48	1.08	0.89	1.32	0.065
rs10489627	67491697	A	G	168	183	50	182	196	55	0.84	1.00	0.35	0.35	1.00	0.82	1.23	0.20
rs2066445	67493996	A	G	12	103	286	13	119	301	0.77	0.64	0.16	0.17	0.94	0.71	1.22	0.081
rs1495964	67506839	A	G	88	215	98	99	234	100	0.09	0.66	0.49	0.50	0.96	0.79	1.16	0.67
rs3790565	67523377	A	G	192	176	33	235	172	26	0.46	0.056	0.30	0.26	0.81	0.65	1.01	0.15
rs3790567	67534398	A	G	50	199	151	51	218	162	0.083	0.92	0.37	0.37	1.01	0.82	1.24	0.62
rs3828069	67551594	A	G	298	97	6	324	106	3	0.070	0.72	0.14	0.13	0.94	0.70	1.27	0.20
rs4297265	67564356	A	G	89	216	95	100	232	100	0.12	0.77	0.49	0.50	0.97	0.80	1.18	0.52
rs2270614	67568042	A	G	95	217	89	101	233	99	0.11	0.84	0.49	0.50	1.02	0.84	1.24	0.52
rs7555183	67572648	A	G	39	201	161	37	190	206	0.46	0.067	0.35	0.30	1.22	0.99	1.50	0.89

Example 3

The inventors also performed family-based association testing (FBAT) (S. L. Lake, D. Blacker, N. M. Laird, Am J Hum Genet 67, 1515 (2000); S. Horvath, X. Xu, N. M. Laird, Eur J Hum Genet 9, 301 (2001)) of IL23R region markers in independent cohorts of nuclear families in which both parents and their CD- or UC-affected offspring were available for genotyping (Tables 2 and 4). For Arg381Gln and other IL23R markers, the inventors observed significant departure from random allele transmission to CD-affected offspring in both non-Jewish and Jewish families, providing further evidence for association between CD and IL23R. The inventors also observed distortion of allele transmission to non-Jewish, UC-affected offspring, providing evidence for association of IL23R with non-Jewish UC. There was no evidence for association of Arg381Gln or other IL23R region markers in the Jewish UC families. In a combined analysis of the data from all 883 nuclear families and both case-control cohorts, all ten IL23R markers in Table 2 showed significant association with IBD, even after Bonferroni correction for analyzing 308,332 SNPs in the original genome-wide association study (p-values ranged from 7×10^{-19} to 3.55×10^{-9} ; corrected p-values ranged from 2.16×10^{-13} to 1.09×10^{-3}).

Table 2. Family-based and combined (case-control and family-based) association results. Family-based association p-values were computed using the empirical variance estimator implemented in the FBAT software package (S. L. Lake, D. Blacker, N. M. Laird, Am J Hum Genet 67, 1515 (2000); S. Horvath, X. Xu, N. M. Laird, Eur J Hum Genet 9, 301 (2001)). Combined Fisher p-values for all case-control (Table 1) and nuclear family cohorts are also shown.

Table 2

	Non-Jewish CD (518 families, 651 affected offspring)	Non-Jewish UC (215 families, 251 affected offspring)	Jewish CD (77 families, 99 affected offspring)	Jewish UC (80 families, 91 affected offspring)	All IBD (883 families, 1,119 affected offspring)	Combined (family-based and case-control)
marker	p-value	p-value	p-value	p-value	p-value	p-value
rs1004819	3.60E-05	1.20E-03	1.24E-02	5.47E-01	6.06E-08	1.78E-14
rs7517847	2.30E-05	2.71E-01	3.50E-02	5.00E-01	1.80E-05	9.99E-16
rs10489629	1.87E-03	2.70E-01	4.33E-01	8.21E-01	1.27E-03	1.62E-11
rs2201841	5.80E-04	3.21E-04	3.50E-02	5.69E-01	1.04E-07	1.10E-14
rs11465804	1.32E-04	2.70E-03	8.90E-05	3.71E-01	3.46E-09	3.33E-16
rs11209026	8.00E-06	2.97E-04	9.41E-04	4.91E-01	1.32E-10	7.00E-19
rs1343151	9.63E-02	8.51E-02	3.30E-02	1.89E-01	1.24E-03	2.74E-12
rs10889677	2.60E-03	3.35E-04	5.88E-02	7.32E-01	1.65E-06	3.40E-14
rs11209032	2.68E-03	3.57E-04	3.48E-02	7.50E-01	2.41E-06	5.50E-13
rs1495965	4.07E-04	1.74E-02	3.93E-02	9.21E-01	1.72E-05	3.55E-09

Example 6

The glutamine allele of Arg381Gln is much less common than the arginine allele, being present at an allelic frequency of 1.9% in the non-Jewish patients with ileal CD and 7.0% in non-Jewish controls. Interestingly, the glutamine allele appears to protect against development of CD in both non-Jewish [odds ratio (OR) 0.26, 95% confidence interval (CI) (0.15-0.43)] and Jewish [OR 0.45, 95% CI (0.27 to 0.73)] case-control cohorts. The glutamine allele is also significantly under-transmitted from heterozygous parents to non-Jewish and Jewish CD-affected offspring, non-Jewish UC-affected offspring, and all IBD-affected offspring (transmitted:non-transmitted 45:130, $p = 1.32 \times 10^{-10}$ for the IBD phenotype in all 883 families) (Tables 2, 4A and 4B). The observation of an uncommon protective allele and a common risk allele reflects an emerging theme in complex genetics; namely, that functional genetic variation exerts a continuum of susceptibility, neutral and protective effects, and alleles conferring protection against one disease may result in increased risk for another (J. H. Nadeau, E. J. Topol, Nat Genet 38, 1095 (2006)).

Table 4A. Summary of family-based association test results in the non-Jewish CD and non-Jewish UC cohorts. Shown is information about the markers (rs number and base pair position, pos, on chromosome 1), the over-transmitted allele, counts of transmitted (T) and un-transmitted (U) alleles, and Chi square- and p-values computed using the empirical variance estimator implemented in the FBAT software package.

Table 4A

marker	pos	Non-Jewish CD					Non-Jewish UC				
		Over-transmitted	T	U	Chi square	P value	Over-transmitted	T	U	Chi square	P value
rs3762318	67309140	C	192	162	2.344	0.125786	T	67	62	0.200	0.654721
rs7540900	67309316	C	160	134	2.074	0.149866	A	53	52	0.009	0.925052
rs4655683	67323634	G	296	260	2.021	0.155139	G	108	96	0.720	0.396144
rs11465770	67345984	C	141	101	6.504	0.010763	C	62	39	4.681	0.030491
rs11465791	67361517	A	77	73	0.110	0.740613	A	30	18	3.130	0.076843
rs2064689	67365031	G	278	237	2.875	0.089952	A	101	96	0.126	0.723009
rs6656929	67373062	A	325	265	5.943	0.014772	T	114	111	0.042	0.837137
rs10489630	67374643	T	322	265	5.521	0.018788	T	117	104	0.720	0.396144
rs1004819	67382234	T	354	252	17.087	3.60E-005	T	134	85	10.485	0.001204
rs790633	67391014	C	259	245	0.358	0.549806	C	120	91	4.206	0.040291
rs7517847	67393690	T	359	252	17.927	2.30E-005	T	126	109	1.209	0.271490
rs10489629	67400370	A	365	284	9.676	0.001867	A	135	116	1.215	0.270248
rs4655692	67403686	G	236	223	0.445	0.504501	G	102	68	6.283	0.012193
rs2201841	67406223	C	327	241	11.839	5.80E-004	C	139	83	12.944	3.21E-004
rs12070470	67409292	T	157	121	5.062	0.024449	T	67	46	3.706	0.054221
rs11465804	67414547	T	72	31	14.617	1.32E-004	T	36	15	9.000	0.002700
rs10489628	67416128	C	339	300	2.116	0.145775	T	119	115	0.059	0.807671
rs10789229	67417595	C	321	288	1.895	0.168630	T	121	97	2.361	0.124430
rs11209026	67417979	G	68	23	20.050	8.00E-006	G	34	10	13.091	2.97E-004
rs1343151	67431150	C	289	249	2.766	0.096270	C	111	85	2.965	0.085089
rs10889677	67437141	A	322	246	9.066	0.002604	A	136	82	12.866	3.35E-004
rs7539328	67444624	G	245	212	2.393	0.121917	A	77	71	0.231	0.630954
rs2863209	67445367	G	130	124	0.142	0.706565	A	59	33	6.500	0.010787
rs17303361	67451845	G	178	175	0.024	0.876885	A	77	58	2.714	0.099454
rs11209032	67452113	A	335	262	9.017	0.002675	A	148	90	12.742	3.57E-004
rs1495965	67465529	G	369	279	12.500	4.07E-004	G	152	113	5.654	0.017413
rs924080	67472161	T	323	271	4.135	0.042002	T	136	103	4.660	0.030876

Table 4B. Summary of family-based association test results in the Jewish CD and Jewish UC cohorts. Shown is information about the markers (rs number and base pair position, pos, on chromosome 1), the over-transmitted allele, counts of transmitted (T) and un-transmitted (U) alleles, and Chi square- and p-values computed using the empirical variance estimator implemented in the FBAT software package.

Table 4B

marker	Jewish CD					Jewish UC				
	Over-transmitted	T	U	Chi square	P value	Over-transmitted	T	U	Chi square	P value
rs3762318	C	36	31	0.342	0.558409	T	36	27	1.209	0.271539
rs7540900	A	28	26	0.069	0.792849	A	30	15	5.000	0.025347
rs4655683	A	34	27	0.831	0.362126	G	34	29	0.455	0.500184
rs11465770	C	20	16	0.444	0.504985	T	23	17	0.857	0.354540
rs11465791	A	22	20	0.100	0.751830	A	20	9	5.261	0.021810
rs2064689	G	24	23	0.020	0.886403	G	30	22	1.333	0.248213
rs6656929	T	43	33	1.667	0.196706	-	39	39	0.000	1.000000
rs10489630	T	38	34	0.235	0.627626	G	37	35	0.061	0.805541
rs1004819	T	54	34	6.250	0.012419	T	42	37	0.362	0.547221
rs790633	C	44	36	1.103	0.293511	C	46	39	0.516	0.472643
rs7517847	T	46	29	4.446	0.034980	G	42	37	0.455	0.500184
rs10489629	A	52	44	0.615	0.432768	G	44	42	0.051	0.820847
rs4655692	G	38	30	1.000	0.317311	G	39	32	0.671	0.412622
rs2201841	C	52	35	4.446	0.034980	C	43	38	0.325	0.568811
rs12070470	T	25	18	1.089	0.296718	C	28	24	0.333	0.563703
rs11465804	T	28	2	15.364	8.90E-005	G	12	8	0.800	0.371093
rs10489628	T	50	35	2.419	0.119844	C	43	42	0.014	0.905530
rs10789229	C	44	38	0.375	0.540291	T	45	23	6.541	0.010544
rs11209026	G	20	1	10.939	9.41E-004	A	9	6	0.474	0.491297
rs1343151	C	48	28	4.545	0.033006	C	34	24	1.724	0.189161
rs10889677	A	51	36	3.571	0.058782	A	42	39	0.117	0.732440
rs7539328	G	34	29	0.352	0.552920	G	36	23	2.864	0.090559
rs2863209	G	13	12	0.043	0.834827	A	16	13	0.391	0.531615
rs17303361	A	31	23	0.941	0.331976	G	36	29	0.860	0.353837
rs11209032	A	53	34	4.457	0.034763	A	41	38	0.101	0.750485
rs1495965	G	54	35	4.247	0.039318	A	47	46	0.010	0.920738
rs924080	T	62	30	9.660	0.001883	T	48	41	0.710	0.399396

Example 7

- 5 The inventors found that several IL23R markers other than Arg381Gln are also associated with IBD (Tables 1, 2, 3A, 3B, 4A and 4B). Marker rs11465804 is an intronic variant in a non-conserved region and is in significant linkage disequilibrium with Arg381Gln ($r^2 = 0.84$ in the case-control data) and therefore is unlikely to confer disease risk independent of the latter. However, other markers show evidence for
- 10 association that appears to be independent of Arg381Gln. For example, rs7517847, which has the most significant association p-value (3.36×10^{-13}) in the combined

analysis of both ileal CD case-control cohorts (Table 1) is not in significant linkage disequilibrium with Arg381Gln ($r^2 = 0.03$ in the case-control data). To evaluate the association that is independent of the Arg381Gln signal, the inventors performed a Cochran-Mantel-Haenszel test using the case-control data with strata given by the Arg381Gln genotypes. The p-values for these conditional tests (Table 5) demonstrate multiple residual association signals throughout IL23R, indicating that there are multiple risk variants in the region. The IL23R gene is expressed as at least six alternatively spliced mRNAs, which generate diverse isoforms of the receptor protein (X. Y. Zhang et al., Immunogenetics 57, 934 (2006)). The most common splice variants result in the deletion of exons 7 and/or 10. While not wishing to be bound by any particular theory, the inventors speculate that the multiple genetic association signals detected in the centromeric portion of IL23R (Fig. 1) could be due to differential effects of SNPs on splicing.

Table 5. Association results from the case-control cohorts for the IL23R markers conditional on Arg381Gln. The p-values shown were obtained using the Cochran-Mantel-Haenszel test with strata defined based on Arg381Gln genotypes.

Table 5

marker	location	non-Jewish p-value	Jewish p-value
rs1884444	67345833	0.095173	0.758978
rs6687620	67360481	0.098628	0.678675
rs2064689	67365031	0.006525	0.411675
rs10489630	67374643	0.008581	0.561843
rs1004819	67382234	0.000777	0.002599
rs790631	67388943	0.227579	0.879053
rs7517847	67393690	0.000222	0.000360
rs2863212	67397137	0.589475	0.529978
rs7530511	67397408	0.797748	0.745172
rs10489629	67400370	0.002257	0.000452
rs2201841	67406223	0.000177	0.000327
rs11804284	67411275	0.797748	0.866304
rs12030948	67413786	0.000033	0.003526
rs11465804	67414547	0.485862	0.120375
rs10489628	67416128	0.000768	0.005872
rs6682033	67420691	0.000538	0.004851
rs1343151	67431150	0.000616	0.000230
rs10889675	67434237	0.085683	0.193108
rs10889677	67437141	0.000140	0.000221

Example 8

The inventors found no evidence for association with the IL12RB1 gene, which encodes the second subunit of the IL-23 receptor heterodimer (C. Parham et al., J Immunol 168, 5699 (2002)), or the IL23A and IL12B genes, which encode the functional IL-23 heterodimer (B. Oppmann et al., Immunity 13, 715 (2000)), in our non-Jewish, ileal CD, case-control cohort.

Example 9

Previous work with mouse models has documented a requirement for IL-23 in murine colitis (D. Yen et al., J Clin Invest 116, 1310 (2006)), experimental autoimmune encephalitis (D. J. Cua et al., Nature 421, 744 (2003)) and collagen-induced arthritis (C. A. Murphy et al., J Exp Med 198, 1951 (2003)). IL-23 activity is present in the terminal ileum (C. Becker et al., J Clin Invest 112, 693 (2003)) and colon (I. J. Fuss et al., Inflamm Bowel Dis 12, 9 (2006)), and the present study demonstrates that IL23R variants are associated with both small and large intestinal inflammation. Furthermore, transgenic expression of IL-23 results in severe systemic inflammation, including in the small and large intestine (M. T. Wiekowski et al., J Immunol 166, 7563 (2001)), highlighting this pathway's particular role in promoting strong activation of effector T cells and perpetuation of organ-specific inflammatory responses. At least part of this effect is likely mediated via inflammatory, IL-17-producing T cells (S. Aggarwal, N. Ghilardi, M. H. Xie, F. J. de Sauvage, A. L. Gurney, J Biol Chem 278, 1910 (2003); C. L. Langrish et al., J Exp Med 201, 233 (2005); E. Bettelli et al., Nature 441, 235 (2006); P. R. Mangan et al., Nature 441, 231 (2006); M. Veldhoen, R. J. Hocking, C. J. Atkins, R. M. Locksley, B. Stockinger, Immunity 24, 179 (2006)), and elevated IL-17 levels have been observed in the colonic mucosa of both CD and UC patients (S. Fujino et al., Gut 52, 65 (2003)).

Taken together, this would suggest that blocking IL-23 function would be efficacious in treating IBD. In support of this, anti-p40 administration, which would block both IL-23 and IL-12 pro-inflammatory activities, has shown promising results in IBD (P. J. Mannon et al., N Engl J Med 351, 2069 (2004)). It has been postulated that specific targeting of the IL23-p19/IL23R pathway may be particularly effective in blocking organ-specific inflammation, with less compromise of protective responses (B. S. McKenzie,

R. A. Kastelein, D. J. Cua, Trends Immunol 27, 17 (2006)). However, at least one model of murine colitis is worsened in the absence of IL-23, implicating a role for IL-23 in the down-regulation of IL-12 (C. Becker et al., J Immunol 177, 2760 (2006)). In addition, IL-23 function may be important for proper responses to mycobacterial (F. A. Verreck et al., Proc Natl Acad Sci U S A 101, 4560 (2004); A. M. Cooper et al., J Immunol 168, 1322 (2002)) and intestinal infections (P. R. Mangan et al., Nature 441, 231 (2006)). In assessing therapeutic approaches, the strong protective effect of the Arg381Gln allele could potentially be exploited to define desired functional outcomes (J. H. Nadeau, E. J. Topol, Nat Genet 38, 1095 (2006)). The contribution of the IL23R pathway to IBD will likely involve more than simple gain or loss of function IL23R variants.

Example 10

Table 6. IL23R Haplotype Identification

Block 2		rs1004819	rs790631					
	H1	1	2					
	H2	1	1					
	H3	2	1					
	1 is	G	A					
	2 is	A	G					
Block 3		rs7530511	rs7528924	rs2201841	rs11804284	rs11465804	rs10489628	rs1343151
	H1	1	1	1	1	1	2	2
	H2	1	1	1	1	1	2	1
	H4	1	1	1	1	2	1	2
	H8	1	1	2	1	1	1	1
	H10	1	2	1	1	1	1	1
	H13	2	2	1	2	1	1	1
	1 is	G	A	A	G	A	G	G
	2 is	A	G	G	A	C	A	A
rs1569922	1 is C	2 is T						

Example 11

Subject ascertainment and diagnostic classification

In all cases, informed consent was obtained using protocols approved by the local institutional review board. Cases and geographically matched controls were ascertained through Baltimore, Chicago, Montreal, Pittsburgh, Los Angeles, and Toronto Genetics Research Centers, with additional age and ethnicity-matched controls provided by the New York Health project. The diagnosis of IBD requires a) one or more symptoms of diarrhea, rectal bleeding, abdominal pain, fever, or complicated perianal disease, b) occurring on two or more occasions separated by at least 8 weeks or ongoing symptoms of at least 6 weeks duration, and c) objective evidence of inflammation from radiologic, endoscopic, and histologic evaluation. Ileal CD involvement was defined as mucosal ulceration, cobblestoning, stricturing or bowel wall thickening from endoscopy reports, barium X-rays, operative reports and/or pathology resection specimen reports.

Example 12

Genotyping methods

For the genome-wide association studies, approximately 750ng of genomic DNA was used to genotype each sample on the Illumina HumanHap300 BeadChip at the Feinstein Institute for Medical Research. Samples were processed according to the Illumina Infinium 2 assay manual. Briefly, each sample was whole-genome amplified, fragmented, precipitated and resuspended in appropriate hybridization buffer. Denatured samples were hybridized on prepared HumanHap300 beadchips for a minimum of 16 hours at 48°C. Following hybridization, the beadchips were processed for the single base extension reaction, signal amplification and imaged on an Illumina Bead Array Reader. Normalized bead intensity data obtained for each sample was loaded into the Illumina Beadstudio 2.0 software which converted fluorescent intensities into SNP genotypes. The IL23R region genotyping in replication cohorts was genotyped using primer extension chemistry and mass spectrometric analysis (iPlex assay) using Sequenom Genetics Services.

Example 13

Data processing

The data from the genome-wide association studies were used to detect possible relatedness in the case-control cohorts. The Hardy-Weinberg disequilibrium test was performed on the genotype data from controls and the inventors investigated the relationship between Hardy-Weinberg disequilibrium and genotype yield (call rate). The data (not shown) suggested a 94% genotype completion threshold for inclusion of samples in the genetic association analyses, as samples with less than 94% call rate tended to have a bias towards increased heterozygote calls.

The genotype data from the family-based cohorts were used to determine Mendelian inconsistencies and departures from Hardy-Weinberg equilibrium. The inventors eliminated from the analysis all the families with more than two Mendelian inconsistencies and families that were not informative because a parent or the sole affected offspring failed genotyping. After cleaning, there were 883 nuclear families (875 independent) with both parents and at least one affected offspring genotyped. Eight nuclear families that we analyzed were from the same extended family as another nuclear family. After zeroing genotypes that produced residual Mendelian inconsistencies, genotype completion rates for each marker in the clean family-based association data ranged from 97.2% to 99.8%.

Example 14

Statistical analysis

The single marker analyses for the genome-wide data in each ethnic group were done using chi-square tests on allele counts; for all the markers associated at the 0.01 level, Fisher's exact tests on allelic counts were also performed and yielded the p-values reported in the manuscript. The data from the Jewish and non-Jewish case-control cohorts were analyzed jointly using a Cochran-Mantel-Haenszel chi-squared test; the inventors used the test with the option that gives an exact p-value. The analyses conditional on Arg381Gln were performed using the Cochran-Mantel-Haenszel test with strata defined based on Arg381Gln genotypes. Note that the Gln/Gln and Arg/Gln genotypes were combined to obtain a single stratum because the glutamine variant is very rare.

For the family-based association analyses, the affection status for each individual study subject in all 883 nuclear families was coded four times to reflect the following four possible phenotype and non-Jewish vs. Jewish ethnicity combinations: non-Jewish and CD-affected, non-Jewish and UC-affected, Jewish and CD-affected, Jewish and UC-affected. Counts of untransmitted and transmitted alleles from heterozygous parents to affected offspring were determined using the standard transmission/disequilibrium test implemented in the Haploview software package. Chi square- and p-values were computed using an empirical variance-covariance estimator that adjusts for the correlation among sibling marker genotypes, implemented in the FBAT software.

While the description above refers to particular embodiments of the present invention, it should be readily apparent to people of ordinary skill in the art that a number of modifications may be made without departing from the spirit thereof. The presently disclosed embodiments are, therefore, to be considered in all respects as illustrative and not restrictive. Furthermore, one of skill in the art would recognize that the invention can be applied to various inflammatory conditions and disorders and autoimmune diseases besides that of inflammatory bowel disease. It will also be readily apparent to one of skill in the art that the invention can be used in conjunction with a variety of phenotypes, such as serological markers, additional genetic variants, biochemical markers, abnormally expressed biological pathways, and variable clinical manifestations.

CLAIMS

What is claimed is:

1. A method of diagnosing susceptibility to Crohn's Disease in an individual,
5 comprising:

determining the presence or absence of one or more risk haplotypes at the IL23R locus in the individual,

wherein the presence of one or more of said risk haplotypes is diagnostic of susceptibility to Crohn's Disease.

2. The method of claim 1, wherein said risk haplotypes are selected from the group consisting of Block 2 H3 haplotype and Block 3 H8 haplotype, or any combination thereof.

3. The method of claim 2, wherein the presence of two of said risk haplotypes presents a greater susceptibility than the presence of one or none of said risk haplotypes, and the presence of one of said risk haplotypes presents a greater susceptibility than the presence of none of said risk haplotypes, but less than the presence of two of said risk haplotypes.

4. The method of claim 3, further comprising determining the presence of a SEQ. ID. NO.: 5 variant allele.

5. The method of claim 1, wherein said risk haplotypes further comprise one or more variant alleles selected from the group consisting of SEQ. ID. NO.: 1, SEQ. ID. NO.: 6, SEQ. ID. NO.: 8, SEQ. ID. NO.: 9, and SEQ. ID. NO.: 10.

6. The method of claim 1, wherein the presence of one or more of said risk haplotypes is diagnostic of susceptibility to Crohn's Disease in a non-Jewish individual.

7. A method of determining a low probability relative to a healthy individual of developing Crohn's Disease in an individual, said method comprising:

determining the presence or absence of one or more protective haplotypes at the IL23R locus in the individual,

5 wherein the presence of one or more of said protective haplotypes is diagnostic of a low probability relative to a healthy individual of developing Crohn's Disease.

8. The method of claim 7, wherein said protective haplotypes are selected from the group consisting of Block 2 H2 haplotype and Block 3 H1 haplotype, or any
10 combination thereof.

9. The method of claim 8, wherein the presence of two of said protective haplotypes presents a greater protection than the presence of one or none of said protective haplotypes; and the presence of one of said protective haplotypes presents a
15 greater protection than the presence of none of said protective haplotypes, but less than the presence of two of said protective haplotypes.

10. The method of claim 9, further comprising determining the presence of a SEQ. ID. NO.: 5 variant allele.
20

11. The method of claim 7, wherein said protective haplotypes further comprise one or more variant alleles selected from the group consisting of SEQ. ID. NO.: 2, SEQ. ID. NO.: 3, SEQ. ID. NO.: 4, SEQ. ID. NO.: 7, and SEQ. ID. NO.: 11.

12. The method of claim 7, wherein said one or more protective haplotypes contain an Arg381Gln variant.
25

13. The method of claim 7, wherein the presence of one or more of said protective haplotypes is diagnostic of a low probability relative to a healthy individual of
30 developing Crohn's Disease in a non-Jewish individual.

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Figure 1

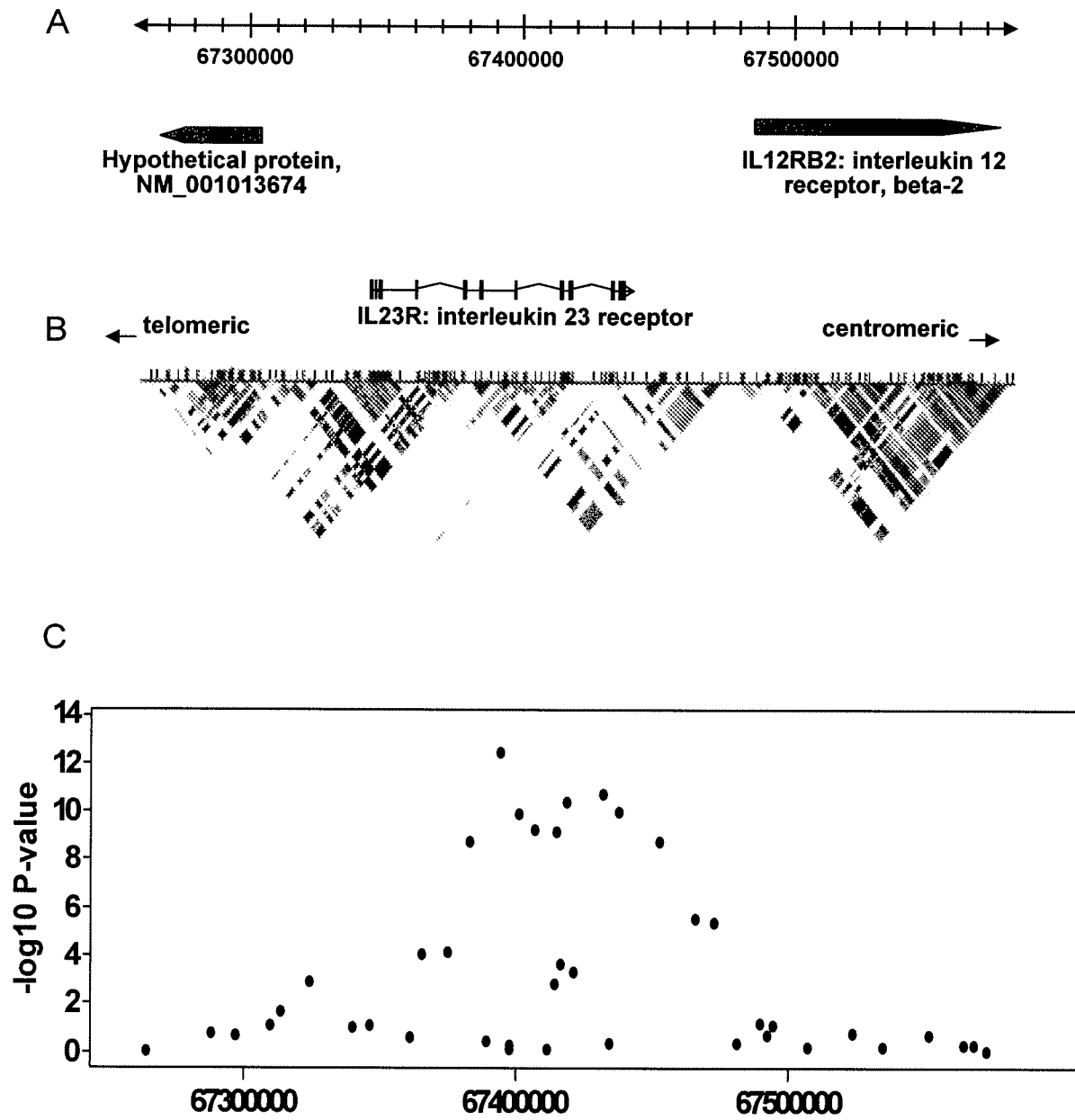
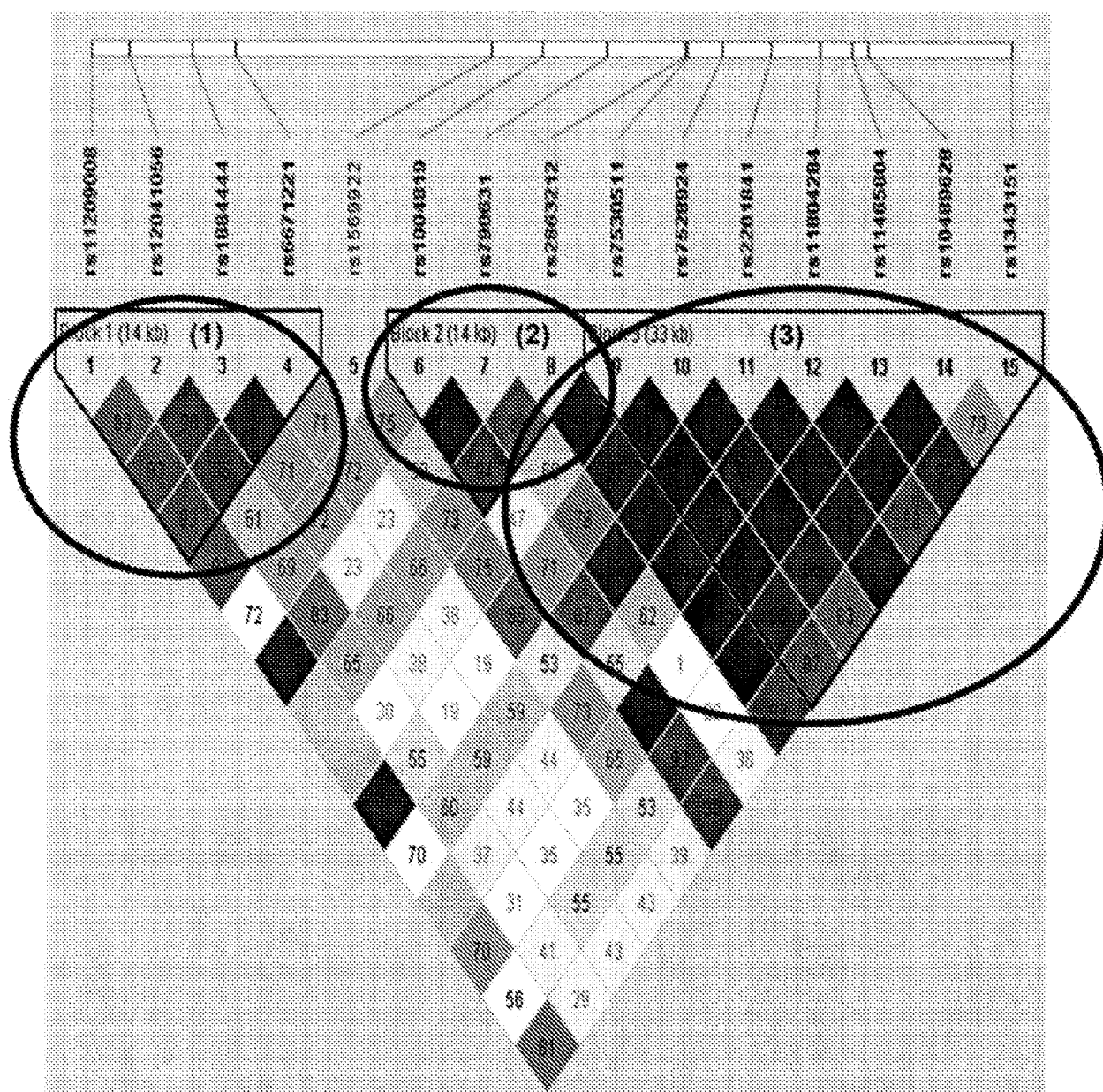


Figure 2



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Figure 3

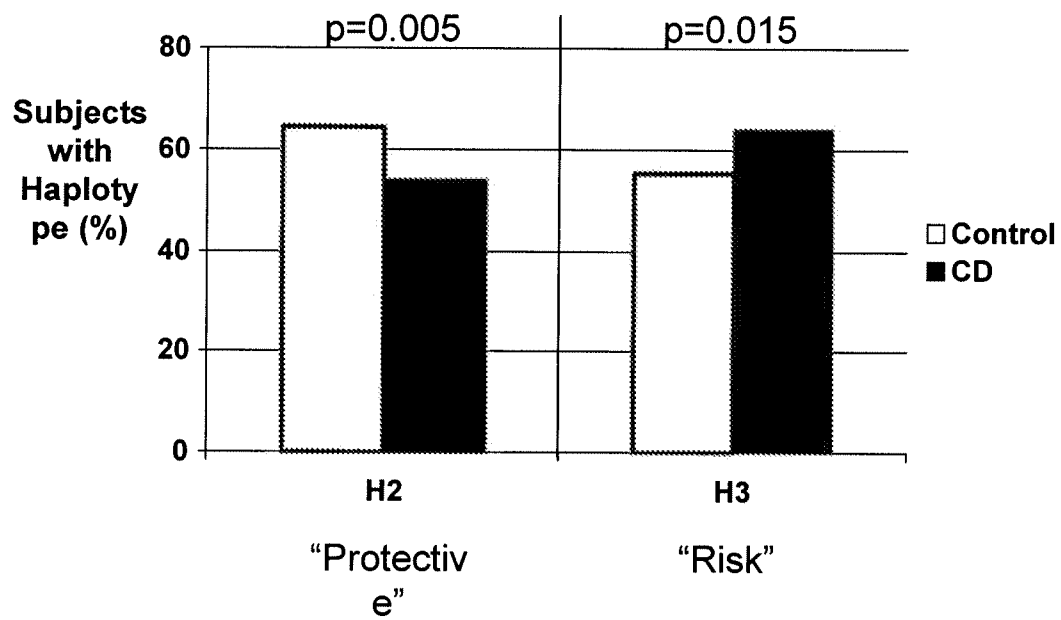


Figure 4

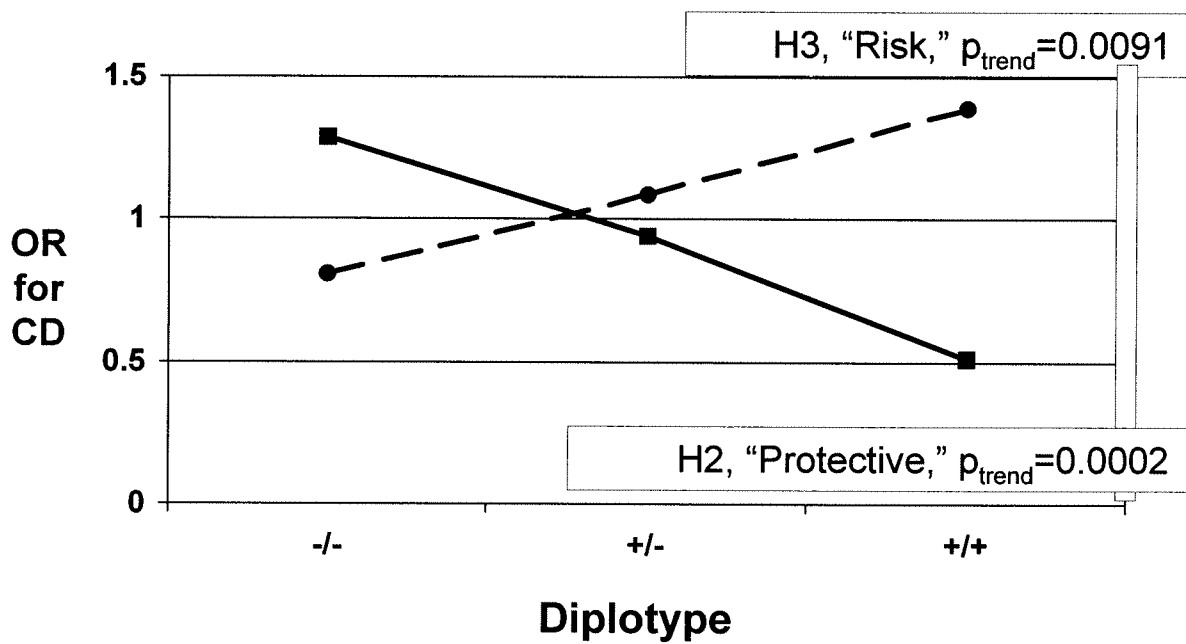


Figure 5

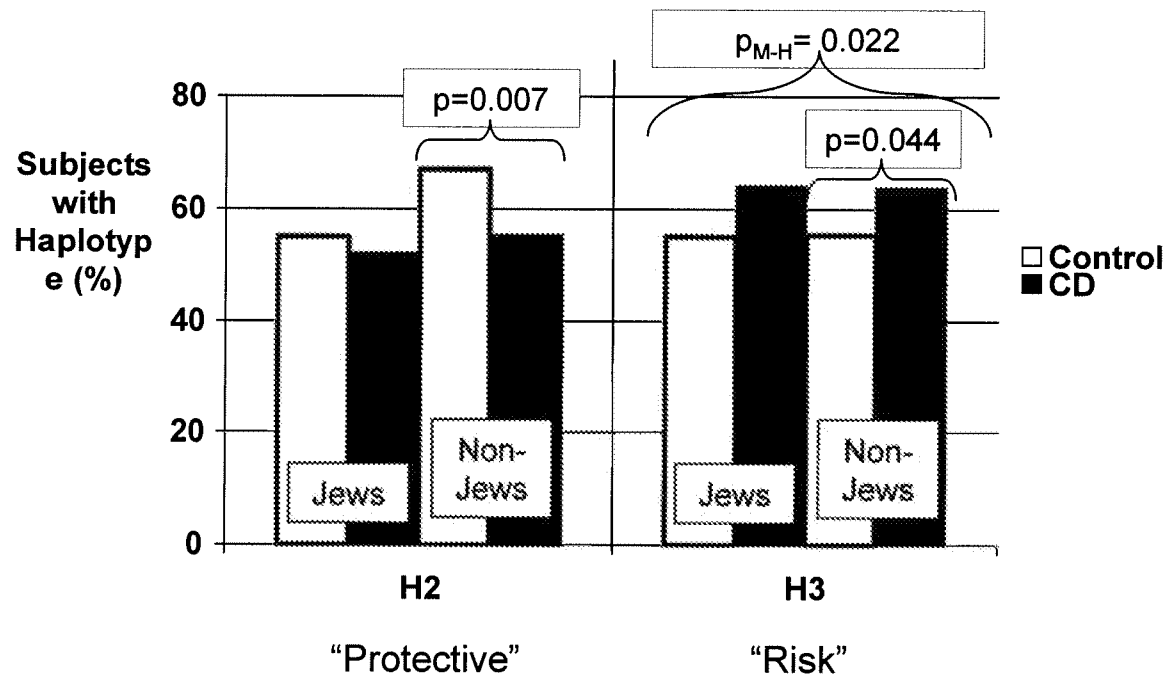
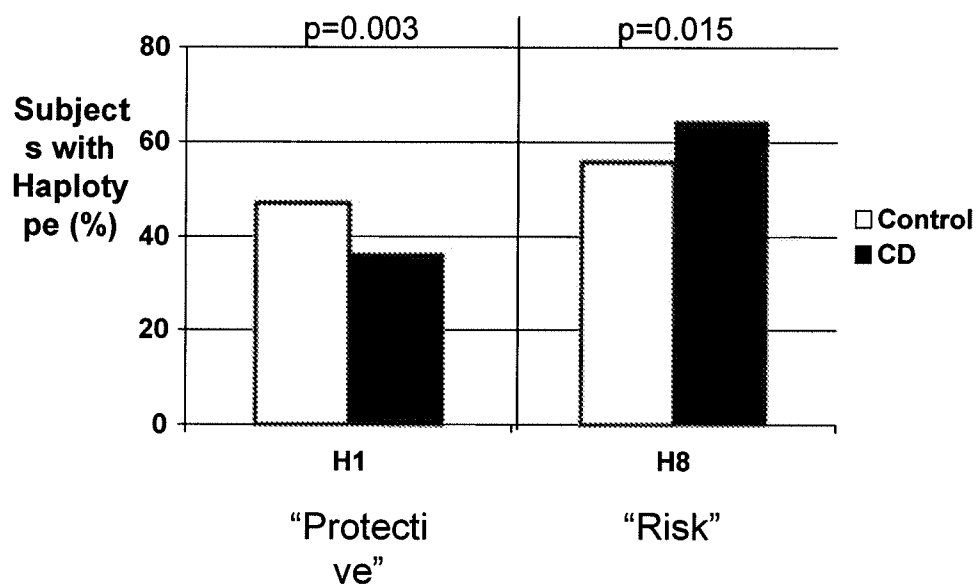


Figure 6



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Figure 7

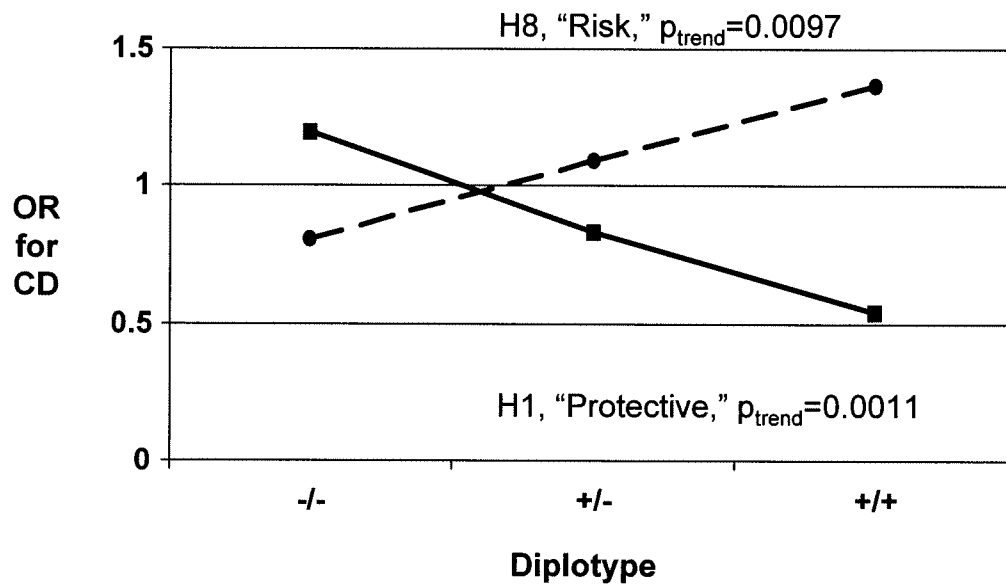
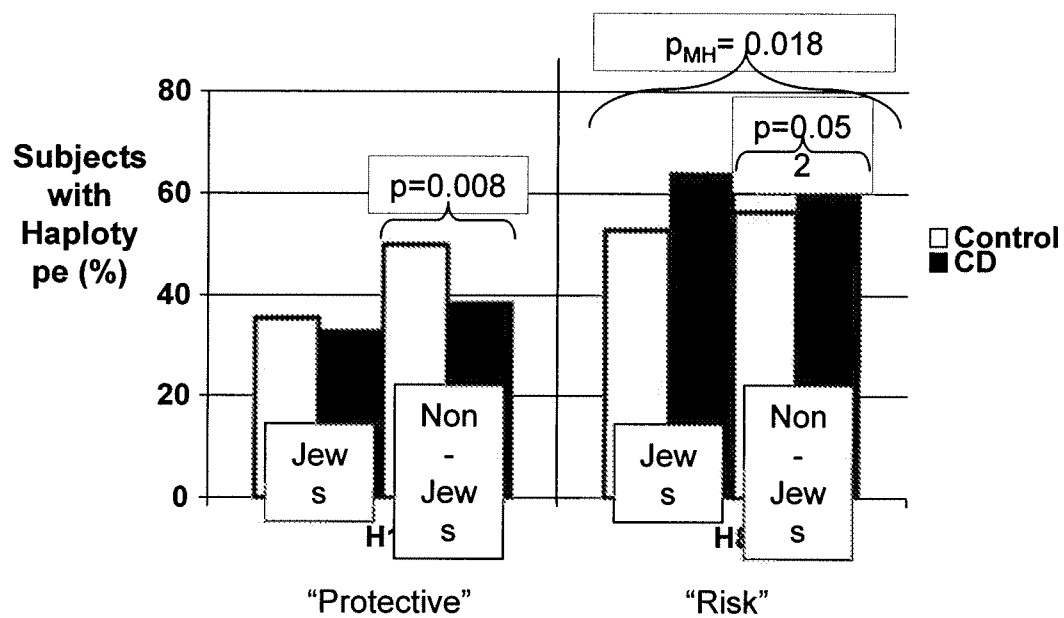


Figure 8



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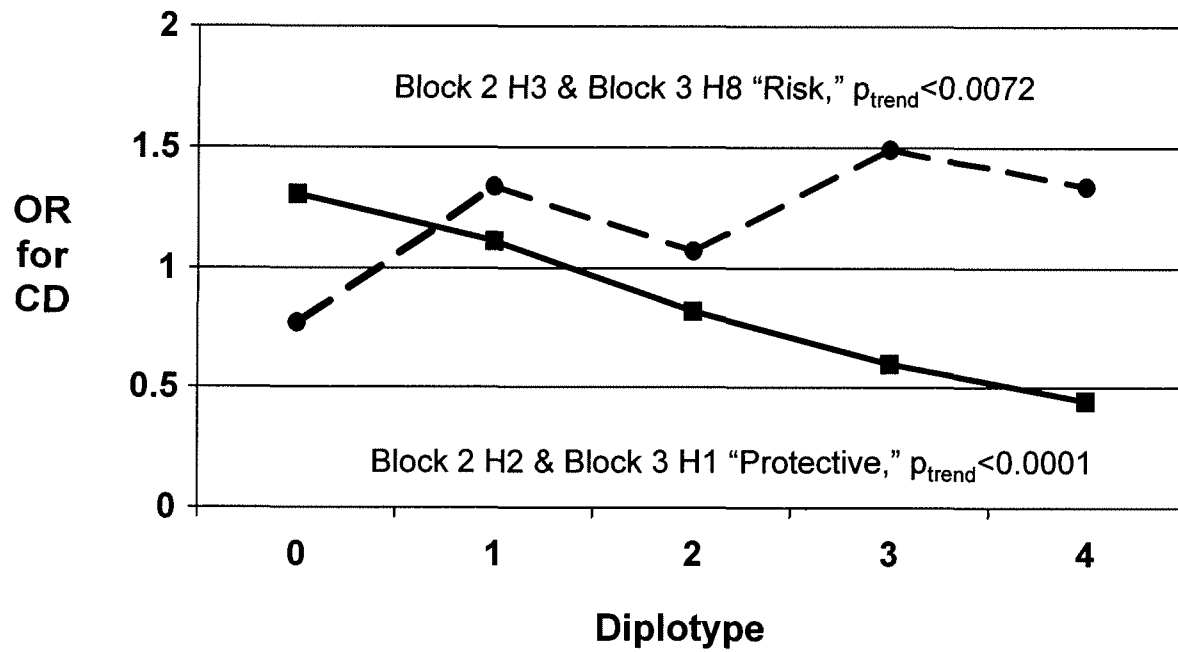


Figure 10

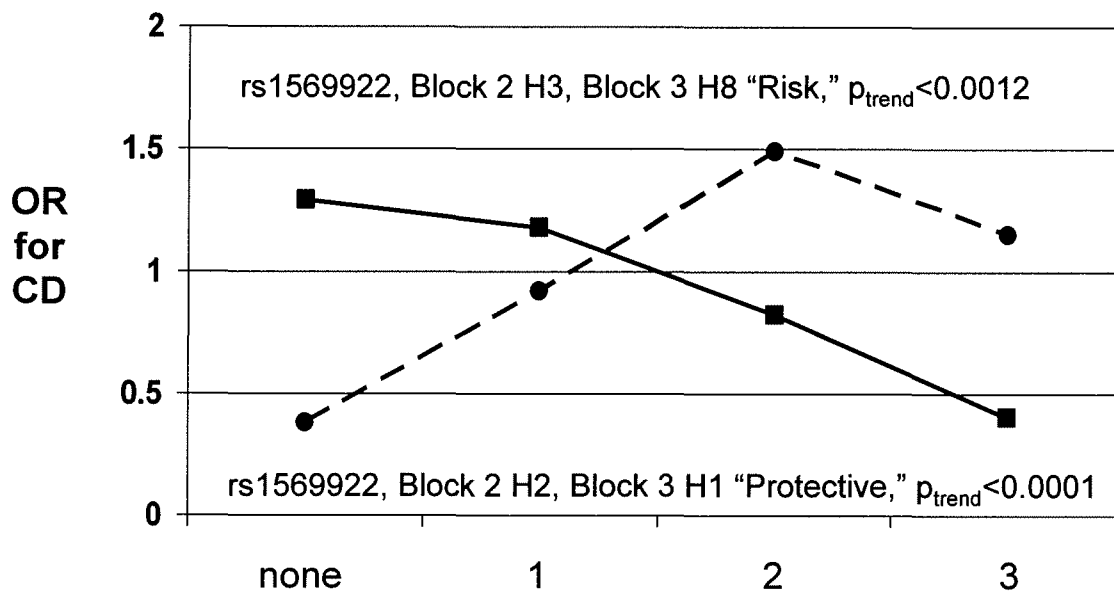


Figure 11

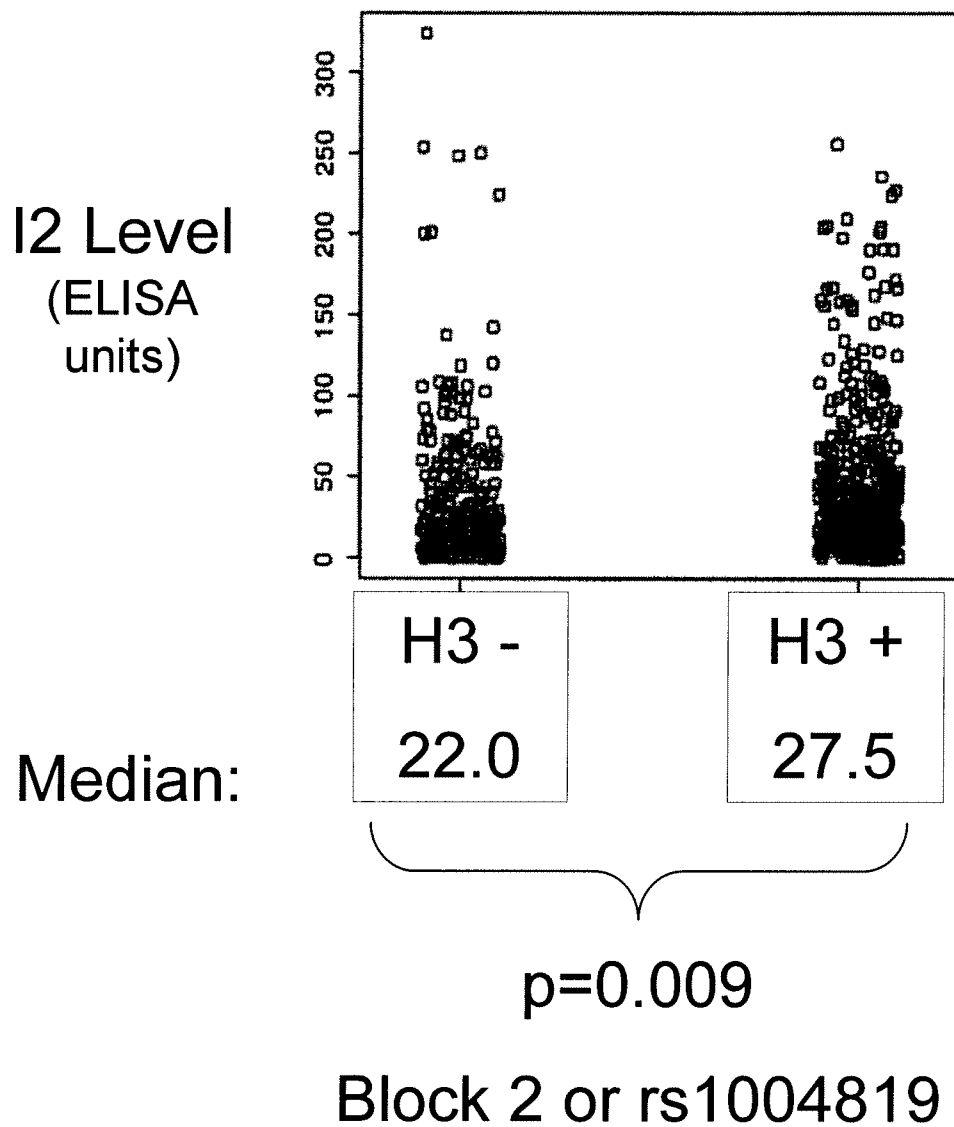
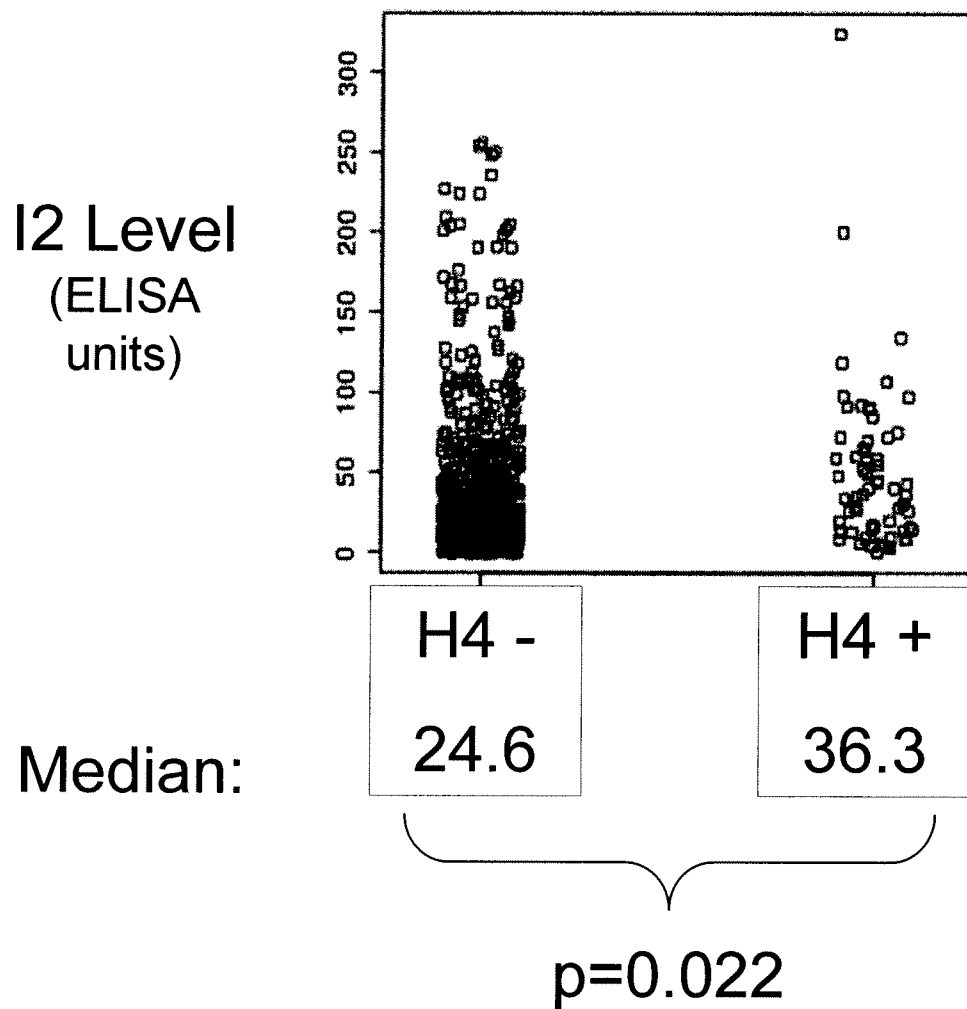


Figure 12

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Block 3 or rs11465804

Figure 13

