Health Conditions DNA Insight®

Technical Bulletin

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Age-related macular degeneration

Report Type: Health Conditions

About: Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries.[1] This progressive neurodegenerative disease is characterized by the loss of photoreceptors in the macula and presence of drusen. Risk factors for AMD include age and cigarette smoking, and research indicates that genetic factors are also associated with the disease.[2,3]

Genetics: Based on twin studies, it is estimated that 46% to 71% of the variation in the overall severity of age-related macular degeneration is genetically determined.[4]

The complement system plays a crucial role in the body's defense against harmful bacteria or pathogens, and dysfunction of the complement cascade may lead to significant damage to macular cells, resulting in atrophy and degeneration.[5] The test includes variants in three genes that encode proteins of the complement system: A307A (rs1061147) in the CFH gene, IVS10 (rs547154) in the C2 gene, and P314L (rs1047286) in the C3 gene. These variants are associated with increased risk for AMD.[1,5,6] The A69S variant of ARMS2, which is a mitochondrial protein, is also associated with increased risk for AMD.[7,8]

The CFH gene encodes complement factor H, which is a key regulator of the complement system. A defect in CFH may lead to uncontrolled activation of the complement system, resulting in more inflammation and damage to the cells in the retina.[9] Complement component C2 is a protease that is involved in the activation of the classical complement pathway.[9] Complement component C3 plays an important role in the activation of both classical and alternative complement pathways.[5,10]

Recommendations: Screening for impaired visual acuity should be performed in older adults as recommended by the U.S. Preventative Services Task Force.[11]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
C3	rs1047286	T	1.50	Caucasian	20.3%	Validated	19168221
ARMS2	rs10490924	T	2.20	Asian	44.0%	Validated	18436811
ARMS2	rs10490924	T	2.69	Caucasian	19.9%	Validated	16174643
CFH	rs1061147	A	2.34	Caucasian	37.2%	Validated	15870199
C2	rs547154	T[i]	0.44	Caucasian	6.2%	Validated	16518403

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
362.50 Macular degeneration (senile), unspecified	N/A

References

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7. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Human molecular genetics.* 2005;14:3227-36.
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Alzheimer's disease, late onset

Report Type: Health Conditions

About: Late-onset Alzheimer's disease (AD) accounts for approximately 95% of AD cases in the U.S.[1] This neurodegenerative disease is characterized histologically by the presence of amyloid beta plaques and neurofibrillary tangles in cortical white matter, and clinically by memory loss.[2] The strongest risk factor for AD is age. The risk of AD increases with every decade starting at about 60 years of age, so that more than 40% of people 85 or older are affected with AD. The second strongest risk factor is family history of the disease. Other risk factors for AD may include elevated cholesterol levels, coronary artery disease and abnormal glucose regulation. Research indicates that genetic factors, such as variants in the APOE gene, are also associated with onset of AD.[3]

Genetics: Although the genes and mutations that contribute to developing late-onset AD are not completely understood or identified, the epsilon-4 variant of the apolipoprotein E gene (APOE) has been associated with both, the lifetime risk for, and the age-of-onset of AD.[4,5] APOE has been confirmed as a risk factor in many studies comprised of individuals ranging in ages between 40 to 90 years.[6] The APOE gene encodes a protein that was originally identified as a cholesterol transport molecule, and yet its role in the development of AD is not well understood.

There are three common APOE alleles which have been studied with respect to their effects on AD risk. The APOE epsilon-2 allele is the least common, and is found in approximately 7% of unaffected individuals and in only 4% of people affected with AD, indicating that this allele may be partially protective against development the disease. APOE epsilon-3 is the most common allele and is found in nearly 80% of people not affected with AD. It is not believed to have protective or risk properties, but rather is thought to play a neutral role.[7]

APOE epsilon-4 is the risk conferring allele, found in approximately 14% of people not affected with AD, but in nearly 40% of all people affected with AD. An individual with one allele of APOE epsilon-4 has an increased likelihood of developing AD, and having two alleles increases risk further. In addition, epsilon-4 is associated with a tendency to develop AD at an earlier age than for those individuals who do not have the epsilon-4 allele.[8] However, it is important to note that many people who are homozygous for epsilon-4 do not develop AD and are free of dementia at a late age, suggesting that AD is caused by multiple factors: some genetic, some environmental and some due to the interaction between genes and environment.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested: The test includes two markers (rs429358, rs7412) that are used to determine a patient's APOE-epsilon 4 status.

rs429358[a] genotype	rs7412[a] genotype	APOE diplotype[b]	Caucasian[c]	African descent[c]	Asian[c]	Hispanic[c]	AD Risk[d]
T/T	T/T	e2/e2	0.9%	0.9%	0.1%	0%	Average risk
T/T	C/T	e2/e3	12.0%	9%	8.5%	5.6%	Average risk
T/T	C/C	e3/e3	60.6%	55.9%	73.9%	72.2%	Average risk
C/T	C/T	e2/e4	2.1%	0%	1.2%	0%	Above average risk
C/T	C/C	e3/e4	22.4%	30.6%	15.7%	20%	Above average risk
C/C	C/C	e4/e4	2.0%	3.6%	0.7%	2.2%	Increased risk

[a]The APOE alleles are defined[9] by two SNPs: rs429358 (C/T) and rs7412 (C/T). Thus, epsilon-2 is rs429358-T, rs7412-T; epsilon-3 is rs429358-T, rs7412-C; epsilon-4 is rs429358-C, rs7412-C. The genotype shows the SNP status for both chromosomes.

[b]APOE alleles: epsilon-2 (e2), epsilon-3 (e3), epsilon-4 (e4). The diplotype shows the allele status for both chromosomes.

[c]Diplotype frequency in a control (unaffected) population.[10]

[d]Risk of late-onset Alzheimer's disease.[6]

Limitations and Warnings: NA

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Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
331.0 Alzheimer's disease	N/A

References

1. Alzheimer's Association.. 2010 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2010;6:158-94.
2. Mattson MP. Pathways towards and away from Alzheimer's disease. *Nature.* 2004;430:631-9.
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Amyotrophic lateral sclerosis (sporadic)

Report Type: Health Conditions

About: The incidence of sporadic amyotrophic lateral sclerosis (ALS) is 1.89 per 100,000/year in North America and Europe. This progressive neurodegenerative disease is characterized by motor neuron degeneration in the primary motor cortex, brainstem, and spinal cord, which causes muscular paralysis and atrophy.[1] Research indicates that genetic factors are associated with the disease.[2,3]

Genetics: Most people who develop ALS do not have a family history of the disease. These cases are classified as sporadic ALS. However, about 10% of ALS patients have another affected family member and are classified as familial ALS (FALS). The clinical features of sporadic ALS and FALS are very similar. At least 11 genes associated with risk for familial ALS have been identified, but less progress has been made in uncovering the genetic causes of sporadic ALS.[4,5] More than 38 candidate genes have been examined in at least 76 studies, but the results have been inconclusive or could not be replicated.[6] Genome-wide association studies have identified three genes with possible association to sporadic ALS. Unfortunately, it has also been difficult to replicate these results.

One gene, DPP6, is included on the test because it showed an association with sporadic ALS in two studies, though it should be noted that there was an overlap of data between the studies.[2,3] The marker rs10260404 in the DPP6 gene was associated with ALS in a study with cases and controls from the Netherlands, the U.S., Sweden and Belgium.[3] This association was replicated in a second study of individuals from Ireland together with previously published data from the U. S. and the Netherlands cohorts.[2] However, one study with populations from Ireland, the U.S., the Netherlands and Poland[7] and another study with populations from the U.S., Italy and Germany[8] failed to find an association. Because of the conflicting evidence, the association of rs10260404 with ALS should remain tentative until more confirming evidence is found in independent studies with larger sets of patients.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
DPP6	rs10260404	C	1.20	Caucasian	43.8%	Preliminary	18084291

[a]Gene or locus containing the tested marker

[b]Markers tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
335.20 Amyotrophic lateral sclerosis Applies to: • Motor neuron disease (bulbar) (mixed type)	V82.71 Screening for genetic disease carrier status

References

1. Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. *Orphanet journal of rare diseases.* 2009;4:3.
2. Cronin S, Berger S, Ding J, et al. A genome-wide association study of sporadic ALS in a homogenous Irish population. *Human molecular genetics.* 2008;17:768-74.
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Asthma

Report Type: Health Conditions

About: Asthma affected 9% of children below the age of 18 in 2007. This chronic lung condition is characterized by airway hyperresponsiveness and bronchoconstriction, which causes wheezing and difficulty breathing. Risk factors for asthma include atopy and family history.[1] Research indicates that genetic factors, such as variants in the ORMDL3 gene, are also associated with the disease.[2]

Genetics: The genetics of asthma are not well understood, and only one gene, ORMDL3, has a clear association with the condition. The rs7216389 marker is located near ORMDL3, a gene of unknown function. A number of studies have shown an association between the marker and susceptibility to asthma, including a large research program looking at asthmatics from Germany and Great Britain.[2] ORMDL3 has also been linked to asthma in studies looking at African American, Chinese and Hispanic populations.[3,4,5] However, these projects were relatively small and further research is needed to confirm the link between ORMDL3 and susceptibility to asthma in these ethnic groups. The ORMDL3 gene has also been associated with exacerbated symptoms in patients with asthma; however, this observation also requires further validation.

The interleukin 1 receptor related gene 1 (IL1RL1) is a member of the interleukin receptor family of cytokine receptors and has been associated with asthma in early research reports.[6]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
ORMDL3	rs7216389	T	1.50	Caucasian	48.7%	Validated	18395550
ORMDL3	rs7216389	T	1.62	Hispanic	56.0%	Validated	19133921
IL1RL1	rs1420101	A	1.16	Caucasian	35.0%	Preliminary	19198610

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
493.0 Extrinsic asthma Applies to: • Asthma: ◦ allergic with stated cause ◦ atopic ◦ childhood ◦ hay ◦ platinum • Hay fever with asthma	N/A

References

1. Hill VL, Wood PR. Asthma epidemiology, pathophysiology, and initial evaluation. *Pediatrics in review.* 2009;30:331-5; quiz 335-6.
2. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature.* 2007;448:470-3.
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Atrial fibrillation

Report Type: Health Conditions

About: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. This heart condition is the leading cause of arrhythmia-related hospitalizations and can contribute to stroke. Risk factors for AF include age, diabetes, hypertension and heart failure. Research indicates that genetic factors are also associated with AF.[1,2]

Genetics: The rs2200733 marker is associated with an increased risk of AF in many populations.[3,4] How rs2200733 affects heart rhythm is unknown and may be mediated through genes in the surrounding area. The closest known gene is PITX2, which is important in controlling asymmetry of the developing heart.[5] The next closest gene is ENPEP, which encodes an aminopeptidase responsible for the breakdown of angiotensin II in the vascular endothelium. However, mutations in these genes have not yet been shown to cause AF.

The T allele of rs2200733 was found to be associated with increased risk for atrial fibrillation in a large genome-wide association study conducted in Iceland.[3] These results were replicated in the same study in a second and larger Icelandic population, as well as in two more groups of individuals of European ancestry from Sweden and the US. Collectively, these results showed that a T allele at rs2200733 increases the risk of AF. The association appears stronger for earlier onset AF in both U.S. and Icelandic groups; individuals younger than 60 years had the highest relative risk. Additionally, each T allele carried a risk of diagnosis 2.28 years earlier. A large follow-up study from four cohorts of individuals of European descent was conducted, and in all four populations, rs2200733 was strongly associated with AF.[4] This study also showed an interaction with age of onset for the marker; younger individuals (less than 60 years old) had higher risk in three of the four populations studied. This marker was also studied in a Han Chinese population from Hong Kong. Although results were similar, the sample size for this population was too small to achieve statistical significance.[3]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
PITX2	rs2200733	T	1.42	Asian	47.6%	Validated	17603472
PITX2	rs2200733	T	1.72	Caucasian	11.5%	Validated	17603472

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

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Limitations and Warnings: NA

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Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
427.31 Atrial fibrillation	N/A

References

1. Damani SB, Topol EJ. Molecular genetics of atrial fibrillation. *Genome medicine.* 2009;1:54.
2. Tsai CT, Lai LP, Hwang JJ, Lin JL, Chiang FT. Molecular genetics of atrial fibrillation. *Journal of the American College of Cardiology.* 2008;52:241-50.
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Coronary artery disease

Report Type: Health Conditions

About: Coronary artery disease (CAD), also known as coronary heart disease, is the leading cause of death in the U.S. This disease is a major consequence of atherosclerosis and can lead to chest pain and heart attack.[1] Risk factors for CAD are numerous, but family history is a major one. Research indicates that multiple genetic factors are associated with the CAD.[2]

Genetics: CAD is a complex genetic disorder. It is estimated that the genetic risk of atherosclerosis involves variants in hundreds of genes with a variety of functions in regulating blood pressure, lipid and cholesterol metabolism, pro-inflammatory processes and cell adhesion and migration.[2]

The test includes a variant at the 9p21 locus, a well-known genetic risk factor for CAD.[3] The association of 9p21 variants with early-onset CAD was first identified and replicated in a large genome-wide association study in the U.K. in 2007.[4] In this study, the C allele at the rs1333049 marker in the 9p21.3 region was associated with CAD in Caucasians. A later study of early-onset CAD replicated the risk for rs1333049 in Caucasians,[5] and yet another study that included patients from nine European study groups confirmed the association.[6] Genetic variants in the 9p21 region have also been associated with increased risk for many phenotypes related to CAD, including coronary atherosclerosis, CAD severity and progression, risk of intracranial or abdominal aortic aneurysms, as well as stroke.[3] Interestingly, the increased CAD risk conferred by 9p21 has been shown to be mitigated by a diet rich in fresh fruit and vegetables.[7]

It is not known what role 9p21 plays in cardiac function. The closest sites of interest to rs1333049 are a non-coding RNA of unknown function (ANRIL), which may regulate nearby genes, and CDKN2A and CDKN2B, which regulate the cell cycle.[8] Susceptibility at this site does not associate with other risk factors, so the effect is thought to be independent. The same region has also been associated with type 2 diabetes,[9] suggesting that there may be a shared mechanism involved in susceptibility for the diseases.

The U.K. study, among other studies, also identified additional markers included in the test. Of these, the MTHFD1L (methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like) gene (rs6922269) encodes a protein that affects serum levels of homocysteine, which is a known risk factor for cardiovascular disease.[4]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
Intergenic_9p21	rs1333049	C	1.30	Asian	51.2%	Validated	18264662
Intergenic_9p21	rs1333049	C	1.29	Caucasian	45.6%	Validated	18362232
HNF1A	rs2259816	A	1.08	Caucasian	38.1%	Validated	19198612
Intergenic_1q41	rs3008621	G	1.10	Caucasian	87.8%	Validated	19164808
Intergenic_10q11	rs501120	T[i]	1.11	Caucasian	83.3%	Validated	19164808
MTHFD1L	rs6922269	A	1.17	Caucasian	26.1%	Validated	17554300
MRAS	rs9818870	T	1.15	Caucasian	16.8%	Validated	19198612
SMAD3	rs17228212	C	1.19	Caucasian	33.9%	Preliminary	17634449
Intergenic_8p22	rs17411031	G	0.86	Caucasian	27.4%	Preliminary	17634449
Intergenic_2q36	rs2943634	C	1.22	Caucasian	65.5%	Preliminary	17634449
Intergenic_5q21	rs383830	A	1.60	Caucasian	79.2%	Preliminary	17554300
SEZ6L	rs688034	T	1.27	Caucasian	33.2%	Preliminary	17554300
CDH13	rs8055236	G	1.91	Caucasian	80.5%	Preliminary	17554300

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

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[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
414.0 Coronary atherosclerosis Applies to: • Arteriosclerotic heart disease [ASHD] • Atherosclerotic heart disease • Coronary (artery): ◦ arteriosclerosis ◦ arteritis or endarteritis ◦ atheroma ◦ sclerosis ◦ stricture	N/A

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Diabetes, type 1

Report Type: Health Conditions

About: Type 1 Diabetes (T1D) is a chronic disease that is characterized by the autoimmune destruction of pancreatic beta cells.[1] Symptoms include thirst, frequent urination, hunger, fatigue, weight loss, itchy skin and blurry eyesight, among others.[2] Individuals with T1D are unable to produce sufficient insulin to control blood glucose levels and as a result, require insulin. T1D is caused primarily by genetic factors that control the immune system and interact with environmental triggers.[1]

Genetics: The majority of the genetic susceptibility to T1D lies in the Human Leukocyte Antigen complex (HLA) on chromosome 6.[3,4] It is estimated that the HLA region accounts for about 40% of the observed familial clustering of T1D, while the currently known non-HLA genes account for about 7% to 8%.[5,6]

The HLA Class II genes encode molecules that present “non-self”-derived proteins to T-cells. This group includes HLA-DRB1, HLA-DQA1 and HLA-DQB1, which represent the primary determinants of T1D risk. Risk is calculated based on the presence or absence of alleles in markers rs2187668 (A) and rs7454108 (C), which together tag the highest T1D risk genotype combination in Caucasians (HLA-DRB1*0301-DQA1*0501-DQB1*0201/HLA-DRB1*04-DQA1*0301-DQB1*0302).[7,8] In addition, there are alleles at HLA Class I and Class III genes that have been implicated in T1D risk, but these have not been as well characterized.[9]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
ERBB3	rs11171739	C	1.34	Caucasian	40.7%	Validated	17554300
IL2RA	rs12251307	C	1.33	Caucasian	89.8%	Validated	18978792
CLEC16A	rs12708716	A	1.89	Asian	76.2%	Validated	19178520
CLEC16A	rs12708716	A	1.23	Caucasian	68.1%	Validated	17554260
PTPN2	rs1893217	C	1.30	Caucasian	11.5%	Validated	17554260
IFIH1	rs1990760	T	1.18	Caucasian	62.5%	Validated	17554260
Intergenic_4q27	rs2069763	T	1.13	Caucasian	32.9%	Validated	19073967
HLA	rs2187668	A	3.64	Caucasian	8.0%	Validated	18252895
PTPN22	rs2476601	A	1.96	Caucasian	11.7%	Validated	17554260
CTLA4	rs3087243	G	1.18	Caucasian	54.0%	Validated	17554260
SH2B3	rs3184504	T	1.35	Caucasian	44.5%	Validated	19073967
INS	rs3741208	T	1.25	Caucasian	35.7%	Validated	17554260
HLA	rs7454108	C	7.23	Caucasian	18.1%	Validated	18252895
PTPN22	rs2488457	G	1.41	Asian	67.3%	Preliminary	16470599
IL2RA	rs3118470	C	1.18	Asian	54.8%	Preliminary	19106270

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

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Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
250.01 Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled	V77.1

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Diabetes, type 2

Report Type: Health Conditions

About: Type 2 diabetes (T2D) accounts for approximately 90% of individuals with diabetes. It is estimated that over 6% of individuals in the world between the ages of 20 and 79 have the condition.[1] This chronic disease is characterized by high blood glucose levels that are caused by a defect in the insulin signaling pathway.[2] Risk factors for T2D include family history and obesity, and research indicates that multiple genetic factors are also associated with the disease.[1]

Genetics: T2D arises from a combination of genetic and environmental factors.[1] The hereditability of T2D is well-established by familial studies, yet environmental and lifestyle factors must also play a role in the development of T2D because the prevalence of T2D has increased dramatically in the last 50 years, a period of time too brief to be explained by changes in gene frequencies. Most of the genetic variants associated with an increased risk for T2D impact the development or function of pancreatic beta-cells, which produce, store and secrete the hormone insulin.[3] In addition, genetic factors associated with fat mass and increased risk for obesity also contribute to the development of T2D.[1]

Genes in the T2D test that affect pancreatic beta-cells include CDKAL1,[4] CDKN2B,[5] HHEX,[6,7,8] HNF1B,[9] JAZF1,[10] KCNJ11,[11,12] KCNQ1,[13] NOTCH2,[14] SLC30A8,[6,7,15,16] TCF7L2[17,18,19] and WFS1.[20]

The T2D test also includes genes associated with fat mass and obesity risk, such as FTO,[21] IGF2BP2,[22,23] PPARG,[24,25] ADIPOQ[26] and ESR1.[27,28]

The most consistent evidence for the association of genetic markers with T2D has come from large-scale T2D genetic studies in European populations.

Individuals of African American ancestry are twice as likely to develop Type 2 Diabetes (T2D) as those of Caucasian ancestry, particularly African American women. African American populations have been studied for most of the Caucasian T2D-associated gene markers. Due to differences in allele frequencies in the two ethnic population and the smaller number of African Americans studied, only a few of the Caucasian markers have been found to be associated with T2D in Africans.

Recently, many studies initially conducted in Caucasian populations have been replicated in Japanese populations, and an overlap in disease variants has been discovered. In addition, the shared variants appear to confer a higher disease risk in Japanese versus Caucasians. This may be due to the fact that the Japanese (in Japan) are a leaner and more homogenous population in comparison. A large proportion of Asian type 2 diabetics are non-obese, and studies have shown that non-obese T2D patients progress to insulin dependence faster. Non-obese T2D Europeans or Japanese-Americans have a higher prevalence of TCF7L2 and PPARG risk alleles, respectively, compared to individuals who do not have T2D.[29,30,31] Furthermore, it has been shown that although they are not obese, the fat distribution of non-obese type 2 diabetics tends to be abdominal. The gene variants repeatedly showing the highest odds ratios associated with T2D in Japanese are TCF7L2, CDKAL1, CDKN2B and KCNQ1. As with other populations, recently replicated studies in Chinese populations show an overlap in disease variants compared to those discovered in Caucasian populations.[32]

Recommendations: The U.S. Preventative Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mmHg.[33]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
WFS1	rs10010131	G	1.12	Caucasian	67.7%	Validated	18040659
CDKN2B	rs10811661	T	1.27	Asian	57.7%	Validated	18477659
CDKN2B	rs10811661	T	1.20	Caucasian	80.1%	Validated	17463246
MTNR1B	rs10830963	G	1.16	Asian	41.7%	Validated	19241057
MTNR1B	rs10830963	G	1.09	Caucasian	30.0%	Validated	19060907
NOTCH2	rs10923931	T	1.13	Caucasian	9.3%	Validated	18372903
CDKAL1	rs10946398	C	1.16	Caucasian	33.6%	Validated	17463249
HHEX	rs1111875	G	1.27	Asian	31.5%	Validated	18477659
HHEX	rs1111875	G	1.15	Caucasian	58.4%	Validated	17463246
SLC30A8	rs13266634	C	1.17	Asian	53.0%	Validated	18469204
SLC30A8	rs13266634	C	1.12	Caucasian	76.1%	Validated	17463249
IGF2BP2	rs1470579	C	1.18	Asian	26.2%	Validated	18477659
IGF2BP2	rs1470579	C	1.19	Caucasian	29.6%	Validated	17463246
PPARG	rs1801282	C	1.75	Asian	95.2%	Validated	11289058
PPARG	rs1801282	C	1.23	Caucasian	90.3%	Validated	17463249
KCNQ1	rs2237892	C	1.43	Asian	65.5%	Validated	18711367
KCNQ1	rs2237892	C	1.29	Caucasian	92.5%	Validated	18711367
KCNJ11	rs5219	T	1.25	Asian	35.5%	Validated	18162508
KCNJ11	rs5219	T	1.15	Caucasian	36.0%	Validated	17463246
HNF1B	rs7501939	T	1.15	Caucasian	43.4%	Validated	17603484
CDKAL1	rs7754840	C	1.27	Asian	42.3%	Validated	18766326
TCF7L2	rs7903146	T	1.51	African	33.7%	Validated	17601994
TCF7L2	rs7903146	T	1.59	Asian	2.4%	Validated	19012045
TCF7L2	rs7903146	T	1.38	Caucasian	27.9%	Validated	17463246
FTO	rs8050136	A	1.27	Caucasian	46.0%	Validated	17463249
JAZF1	rs864745	T[i]	1.10	Caucasian	48.7%	Validated	18372903
ESR1	rs1569788	C	1.25	African	52.9%	Preliminary	18305958
ADIPOQ	rs182052	A	1.24	African	38.7%	Preliminary	19056609
ESR1	rs3020314	C	1.23	Caucasian	25.7%	Preliminary	18854778
Intergenic_6q24	rs4897081	A	1.28	African	51.0%	Preliminary	18560894

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
250.00 Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	V77.1 Screen-diabetes mellitus

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Exfoliation glaucoma

Report Type: Health Conditions

About: Exfoliation glaucoma (XFG), also known as pseudoexfoliation glaucoma, accounts for about 12% of glaucoma cases and mainly affects older people.[1] Clinically, XFG is considered a symptom of a systemic condition called exfoliation syndrome (XFS), also known as pseudoexfoliation syndrome. One risk factor for XFS is a family history of the condition,[2] and research indicates that genetic factors, such as variants in the LOXL gene, are also associated with XFG.[3]

Genetics: The genetic contribution to different forms of glaucoma is believed to include both rare Mendelian mutations and common susceptibility alleles.[4] For XFG, a common susceptibility allele has been identified.

The genetic marker rs2165241 in the LOXL1 gene, which encodes lysyl oxidase-like protein 1, was found to be associated with XFS in a large study of Caucasians from Iceland and Sweden.[3] The LOXL1 protein is believed to assist in the construction and maintenance of the extracellular matrix, which provides structural support to cells. LOXL1 is expressed by many cell types in the eye, and changes in the LOXL1 gene may lead to defective processing of extracellular matrix proteins.[3] Approximately 35% of people with European ancestry carry one copy of the risk allele of rs2165241 and about 22% carry two copies. However, the prevalence of XFS in most countries is much lower than the frequency of this allele, indicating that other genetic and environmental factors contribute to risk for XLS. Interestingly, the amount of risk associated with rs2165241 has been observed to be lower in Caucasians in Australia compared to Caucasians in Nordic countries.[5] The rs2165241 marker is not associated with the risk of developing non-XFS types of glaucoma.[3]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
LOXL1	rs2165241	T	3.62	Caucasian	43.8%	Preliminary	17690259

[a]Gene or locus containing the tested marker
[b]Marker tested
[c]Allele associated with disease risk
[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele
[e]Ethnicity of the population in the corresponding study
[f]Percentage of people who have the associated allele in the population studied
[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

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Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
365.9 Unspecified glaucoma	V80.1 Screening for glaucoma

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Hypertension

Report Type: Health Conditions

About: The prevalence of hypertension, also known as high blood pressure, is estimated to be 29% in the U.S.[1] This condition can lead to stroke, heart attack and kidney failure. Risk factors for hypertension include high salt intake, being overweight and high alcohol consumption.[2] Research indicates that genetic factors are also associated with risk for the condition.[3,4,5,6]

Genetics: Over 90% of individuals who develop hypertension are considered to have essential or primary hypertension, meaning that no underlying medical cause can be identified. Hypertension can also be secondary to existing medical problems, such as kidney disease. Some rare forms of hypertension are caused by mutations in single genes. Individuals with these mutations usually have a family history of the disease and hypertension occurs at a younger age. This genetic test focuses on essential hypertension, for which several susceptibility alleles have been identified through large population studies.[3,4,5,6]

Because of the complex interactions of different physiologic pathways regulating blood pressure, it has been difficult to definitively identify risk alleles in candidate genes for hypertension. Contradictory results have been reported for many genes identified in an early study but not replicated in further research. A few large population-based genome-wide scans and candidate gene association studies have identified two genes as risk factors for hypertension: PPARGC1A and BCAT1.[3,4,5,6]

The PPARGC1A gene encodes the protein PPAR-gamma coactivator 1,[7] which regulates the expression of genes involved in several metabolic processes related to blood pressure homeostasis. The Gly482Ser (rs7961152) allele causes an amino acid change in the protein, but the functional consequence of this change is unknown. The Ser allele was associated with decreased risk for essential hypertension in a Danish population.[5] The same allele was also modestly associated with decreased risk for severe essential hypertension in a Chinese population.[6]

The BCAT1 gene encodes branched-chain aminotransferase 1, which catalyzes the first reaction in the catabolism of the essential branched-chain amino acids leucine, isoleucine and valine. The rs7961152 marker is in a non-coding region of the BCAT1 gene, making it difficult to discern the functional impact of a nucleotide change. The variant may be linked to another causative mutation in the same gene or a neighboring gene. The A allele of the rs7961152 marker was associated with an increased risk for essential hypertension in a study of a British Caucasian population.[4] In a Korean population, the same allele was moderately associated with increased blood pressure.[3]

Recommendations: The U.S. Preventive Services Task Force recommends screening for high blood pressure in adults aged 18 and older.[8]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
BCAT1	rs7961152	A	1.29	Asian	16.9%	Preliminary	19424278
BCAT1	rs7961152	A	1.16	Caucasian	46.5%	Preliminary	17554300
PPARGC1A	rs8192678	A	0.60	Asian	40.5%	Preliminary	17971240
PPARGC1A	rs8192678	A	0.70	Caucasian	35.0%	Preliminary	15738346

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
401.1 Benign essential hypertension	N/A

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Multiple sclerosis

Report Type: Health Conditions

About: Multiple sclerosis is a chronic inflammatory disease that is presumed to be an autoimmune disorder.[1,2] This neurodegenerative disease damages the myelin sheaths surrounding neurons, which leads to muscle weakness,difficulties with balance and numbness, among others.[3] Though the cause of multiple sclerosis is unknown, genetic factors are associated with the disease.[2,4]

Genetics: Genetic variation in the major histocompatibility complex region of Chromosome 6 has long been known to play a role in susceptibility to multiple sclerosis. The human leukocyte antigen (HLA) region, a set of genes within the major histocompatibility complex, has been associated with an increased risk for multiple sclerosis in people of European descent.[2] The HLA region is also associated with other auto-immune conditions, such as type 1 diabetes and rheumatoid arthritis.[5,6] Two other genes, interleukin 2 receptor alpha (IL2RA) and interleukin 7 receptor (IL7R), are also involved in the immune system and associated with the risk for multiple sclerosis.[2] Variants in these genes were examined in families of European descent from the U.S. and U.K. While HLA had the strongest association, both IL2RA and IL7R also appeared to play a role in susceptibility to multiple sclerosis.[2] The test includes variants in the HLA region, as well as the IL2RA and IL7R genes.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
IL2RA	rs12722489	G	1.25	Caucasian	82.7%	Validated	17660530
HLA	rs3135388	T	1.99	Caucasian	19.0%	Validated	17660530
IL7RA	rs6897932	C	1.18	Caucasian	75.7%	Validated	17660530
KIF1B	rs10492972	C	1.34	Caucasian	33.6%	Preliminary	18997785
EVI5	rs10735781	G	1.11	Caucasian	34.5%	Preliminary	17660530
ANKRD15	rs10975200	G	1.14	Caucasian	16.4%	Preliminary	17660530
FAM69A	rs11164838	C	1.11	Caucasian	58.4%	Preliminary	17660530
CD58	rs12044852	C	1.24	Caucasian	87.2%	Preliminary	17660530
CBLB	rs12487066	T	1.09	Caucasian	67.7%	Preliminary	17660530
PDE4B	rs1321172	G	1.08	Caucasian	54.9%	Preliminary	17660530
KLRB1	rs4763655	A	1.10	Caucasian	33.2%	Preliminary	17660530

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: Multiple sclerosis is rare in non-European populations and, thus, has not been widely studied in people of African or Asian descent. Therefore, only data from studies using large populations of European descent are represented. Genetic risk factors found in Caucasians may well apply to people of other ethnicities, but this has not been proven. Only the most common relapsing-remitting form of multiple sclerosis has been well studied, and all the information provided here relates to relapsing-remitting multiple sclerosis.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
340 Multiple sclerosis Applies to: • Disseminated or multiple sclerosis: ◦ NOS ◦ brain stem ◦ cord ◦ generalized	V82.9 Screening for unspecified condition

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Myocardial infarction

Report Type: Health Conditions

About: Myocardial infarction (MI) kills approximately half a million people in the U.S. each year.[1] Symptoms of this condition include chest pain, shortness of breath and other symptoms.[1,2] Risk factors include a family history of MI, diabetes, hypertension and hypercholesteremia.[2] Research indicates that genetic factors are also associated with MI.[2,3]

Genetics: Genetic susceptibility factors contribute to the risk of MI. Their importance is highlighted by the fact that about 15% to 20% of individuals who have an MI lack conventional risk factors.[4] Studies suggest that many genetic variations associated with the disease are in genes involved in processes involving endothelial cell function, inflammation, lipid metabolism, thrombosis and fibrinolysis.[2,3]

Many SNPs associated with heart disease are in genes involved in inflammation. A marker in the CXCL12 gene, which encodes a chemokine molecule important for attracting lymphocytes,[5] was shown to be also associated with the risk for MI in a large study of Caucasians.[6] Additionally, in a large genome-wide association study identifying markers affecting eosinophil counts, a marker at 12q24 (rs3184504) in the SH2B3 gene, which encodes a protein important for cytokine pathway inhibition, was associated with risk for MI in six different populations.[7]

A number of high-impact studies have identified 9p21.3 as an important genetic region associated with risk for MI or coronary artery disease.[8] This region contains no annotated genes but lies close to the CDKN2A and CDKN2B genes, which regulate important cell cycle pathways. An allele of the rs10757278 marker in the 9p21.3 region is associated with MI in Icelandic, U.S. Caucasian, and Italian populations.[9,10,11] When the Italian patient group was subdivided into those with and without a family history of MI, only the individuals with a family history of MI still showed a significant association with the allele.[11] This research suggests that in cases with a family history of heart disease and heart attack, the relative risk for an individual carrying a risk allele can be significantly higher.

Another large study carried out by the Myocardial Infarction Genetics Consortium replicated the region of 9p21, as well as identified or replicated other markers in MIA3 (rs17465637), 1p13 (rs646776), 10q11 in CXCL12 (rs1746048), 21q22 (rs9982601), 6p24 in PHACTR1 (rs12526453), and 2q33 in WDR12 (rs6725887).[6]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
PSMA6	rs1048990	G	1.21	Asian	37.8%	Validated	16845397
Intergenic_9p21	rs10757278	G	1.28	Caucasian	50.0%	Validated	17478679
PCSK9	rs11206510	T	1.15	Caucasian	83.6%	Validated	19198609
PHACTR1	rs12526453	C	1.12	Caucasian	63.3%	Validated	19198609
CXCL12	rs1746048	C	1.17	Caucasian	85.4%	Validated	19198609
MIA3	rs17465637	C	1.14	Caucasian	26.8%	Validated	19198609
SH2B3	rs3184504	T	1.13	Caucasian	44.5%	Validated	19198610
Intergenic_1p13	rs646776	T[i]	1.19	Caucasian	74.6%	Validated	19198609
WDR12	rs6725887	C	1.17	Caucasian	15.9%	Validated	19198609
LGALS2	rs7291467	C[j]	1.23	Asian	73.3%	Validated	15129282
Intergenic_21q22	rs9982601	T	1.20	Caucasian	20.6%	Validated	19198609
LTA	rs1041981	A	1.78	Asian	43.5%	Preliminary	12426569
OR13G1	rs1151640	G	1.31	Caucasian	46.0%	Preliminary	16175505
PRR4	rs1376251	C	1.23	Caucasian	65.3%	Preliminary	16175505
MIAT	rs2331291	T	1.38	Asian	13.1%	Preliminary	17066261

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

[j]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either a C or a G in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
410.9 Acute myocardial infarction of unspecified site Applies to: • Acute myocardial infarction NOS • Coronary occlusion NOS • Myocardial infarction NOS	V81.2 Screening for other and unspecified cardiovascular conditions

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Obesity

Report Type: Health Conditions

About: Obesity (BMI > 30 kg/m2) affects at least 20% of individuals in Western countries, while 50% of people are classified as overweight (BMI > 25 kg/m2) or obese by the World Health Organization's definition. This condition is characterized by an increase in fat mass that can result in adverse health consequences. Obesity is associated with increased risks for cardiovascular disease, type 2 diabetes and various types of cancer. Risk factors for obesity include low physical activity and consumption of high-energy foods. Research indicates that genetic factors are also associated with the disease.[1]

Genetics: Some rare inherited forms of obesity are caused by a mutation in a single gene.[1] However, these monogenic forms of obesity only account for a small fraction of obesity cases. The genetic predisposition for obesity is thought to arise from multiple, common variants in several genes.[2,3] These common variants are referred to as low risk susceptibility alleles because they each contribute a relatively small amount of risk to developing obesity. Low risk susceptibility alleles for obesity have been successfully identified by screening large numbers of individuals in genome-wide association studies.[4,5]

The FTO gene was the first gene shown to be associated with common obesity in genome-wide association studies.[5] This association was quickly replicated in many other studies.[6,7] How FTO affects obesity is not understood,[8] but studies in rodents suggest that FTO has a role in regulating food intake. Mice genetically engineered to overexpress FTO show increased food intake, which leads to obesity.[9] The function of FTO in the central nervous system is also supported by the finding that human children carrying an obesity-associated FTO variant have increased energy intake.[10] Besides its effects in the brain, the FTO protein may also have functions in other tissues where it is also expressed.[8]

Genome-wide association studies have also implicated the MC4R gene in obesity.[4] The MC4R gene encodes the melanocortin 4 receptor, which is expressed in neurons that modulate food intake. Interestingly, rare mutations in this gene can cause monogenic obesity.

Recommendations: The U.S Preventative Services Task Force recommends screening all adults and children aged 6 years and older for obesity.[11]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
MC4R	rs17782313	C	1.12	Caucasian	26.5%	Validated	18454148
FTO	rs9939609	A	1.31	Caucasian	46.0%	Validated	17434869
PCSK1	rs6232	G	1.34	Caucasian	4.4%	Preliminary	18604207
INSIG2	rs7566605	C	1.29	Caucasian	26.5%	Preliminary	17465681
MC4R	rs17782313	C	1.24	Asian	24.4%	Validated	23049848
FTO	rs9939609	A	1.25	Asian	14.9%	Validated	22109280
PCSK1	rs6232	G	N/A	Asian	1.2%	Preliminary	19875984
INSIG2	rs7566605	C	N/A	Asian	33.7%	Preliminary	25028659

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation. The outcomes for this test are derived using genotype information from validated markers only.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
278.00 Obesity, unspecified Applies to: • Obesity NOS	V77.8 Screening for obesity

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Osteoarthritis

Report Type: Health Conditions

About: Osteoarthritis is the most common form of arthritis and is a major cause of disability in the U.S.[1] This progressive bone disease is characterized by cartilage loss, which can lead to pain and reduced joint function. Risk factors for osteoarthritis include age, obesity, gender and trauma. Research indicates that genetic factors are also associated with the disease.[2]

Genetics: Some rare forms of early-onset osteoarthritis (OA) are caused by mutations in single genes, but uncovering the genetic basis of the most common form of OA, which appears after age 45, has been more elusive. Variants in three genes that have been shown to increase the risk of developing OA are included on the test: GDF5, DVWA and PTGS2.

The GDF5 gene encodes a member of the transforming growth factor-beta superfamily and is involved in the development and maintenance of bone and cartilage. Mutations in GDF5 are known to cause disorders of skeletal development including chondrodysplasia, synphalangism and type C brachydactyly. In the largest meta-analysis study of OA to date, researchers found an association of a variant in the GDF5 gene with OA of the knee in Caucasian and Asian women.[3]

The DVWA gene encodes a protein that binds beta-tubulin, which is the building block of the microtubules that serve a structural and kinetic role in the cell. In Asians, a variant in the DVWA gene is associated with susceptibility to OA of the knee.[4]

The PTGS2 gene encodes prostaglandin G/H synthase 2, which is involved in a key step in the synthesis of prostaglandins. Prostaglandins are regulators of important biological processes such as inflammation, cell division, and formation of new blood vessels. In Caucasians, a variant in the PTGS2 gene is associated with OA in the knee.[5]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
GDF5	rs143383	T	1.55	Asian	77.9%	Preliminary	18299287
GDF5	rs143383	T	1.13	Caucasian	66.7%	Preliminary	19479880
PTGS2	rs4140564	C	1.55	Caucasian	8.0%	Preliminary	18471798
DVWA	rs7639618	G[i]	1.43	Asian	54.2%	Preliminary	19181678

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either a C or a G in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
715.89 Osteoarthrosis involving, or with mention of more than one site, but not specified as generalized, multiple sites	N/A

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Parkinson's disease

Report Type: Health Conditions

About: By the year 2030, the prevalence of Parkinson's disease (PD) is projected to double from numbers in 2005 (4.1 to 4.6 million).[1] This neurodegenerative disease is characterized by tremors, akinesia, bradykinesia and balance difficulties.[2] Risk factors include age and head trauma,[3] and research indicates that genetic factors, such as a variant in the LRRK2 gene, are also associated with the disease.[2]

Genetics: The genetic contribution to PD includes high-risk genetic mutations as well as low-risk susceptibility factors.[2] Familial PD, which accounts for 15% to 25% of individuals with PD, is caused by rare, high-penetrance mutations (LRRK2, SNCA, parkin, UCHL1, PINK1 and DJ-1). Most PD patients, however, do not have known high-risk mutations, have no family history of the disease and are classified as having sporadic or idiopathic PD. Compared to familial PD, individuals with sporadic PD tend to have a later age of onset but still exhibits similar clinical and pathological features.[4]

The test includes a common variant (rs34778348) in the LRRK2 gene that is associated with sporadic PD in Asians.[5,6] The LRRK2 (leucine-rich repeat kinase 2) gene, also known as dardarin, encodes a kinase that is found in the brain. High-risk genetic mutations in LRRK2 are pathogenic for familial PD in families of European descent.[7] In Asians, high risk PD-causing mutations of the LRRK2 gene appear to be extremely rare.

The A allele of rs34778348 in the LRRK2 gene has been found in PD patients in three Asian populations (Han Chinese, Japanese and Malay) but has not yet been found in other ethnic populations. This allele is associated with only a small increase in PD risk. Thus, rs34778348 is considered a low-risk susceptibility marker. Many people who carry the A allele may not develop PD. The A allele leads to an LRRK2 protein that causes cell death only when combined with oxidative stress.[8] This finding is consistent with the idea that the A allele may result in PD only when additional environmental, lifestyle or other personal risk factors are present.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
LRRK2	rs34778348	A	2.55	Asian	3.0%	Validated	19343804

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: The test does not include high-penetrance pathogenic mutations that cause PD and are inherited in a dominant manner. Most notably, the test does not include pathogenic mutations of the LRRK2 gene, which have been identified in PD families of European descent.[7]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
332.0 Paralysis agitans Applies to: • Parkinsonism or Parkinson's disease: ◦ NOS ◦ idiopathic ◦ primary	N/A

References

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Peripheral arterial disease

Report Type: Health Conditions

About: Peripheral arterial disease (PAD) affects 20% of individuals in the U.S. over the age of 55 and is strongly associated with a risk for myocardial infarction and stroke.[1] This progressive disease is characterized by the accumulation of plaque in the arterial system, especially the abdominal aorta and arteries in the legs.[1,2] Risk factors for PAD include age, sex, smoking, diabetes, hypertension and hyperlipidemia.[1] Research indicates that genetic factors are also associated with PAD.[3]

Genetics: Peripheral arterial disease (PAD) is caused by atherosclerosis, a complex disorder involving both genetic risk factors as well as traditional risk factors, such as cigarette smoking, cholesterol levels, hypertension and stress. Within various populations, genetic differences are thought to account for greater than 50% of the risk for atherosclerosis.[3] It is estimated that the genetic risk of atherosclerosis involves variants in hundreds of genes with a variety of functions in regulating blood pressure, lipid and cholesterol metabolism, pro-inflammatory processes, cell adhesion and migration.[3]

The CHRNA3 gene encodes a subunit of the nicotinic acetylcholine receptor, which binds to nicotine.[4] A large study of PAD in Caucasians from Iceland, New Zealand, Austria, Sweden and Italy[5] showed that a variant in CHRNA3 increased the risk for PAD by approximately 20%. No significant differences in risk were shown between males and females. The results from this study suggest that this variant may also partly confer a risk for cardiovascular disease indirectly through its relationship with exposure to nicotine as a function of smoking history.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
CHRNA3	rs1051730	T	1.19	Caucasian	38.5%	Validated	18385739

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
443.9 Peripheral vascular disease, unspecified Applies to: • Intermittent claudication NOS • Peripheral: ◦ angiopathy NOS ◦ vascular disease NOS • Spasm of artery	V81.2 Screening for other and unspecified cardiovascular conditions

References

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Psoriasis

Report Type: Health Conditions

About: Psoriasis is a common skin disease that is characterized by itchy, scaly skin and is caused by a defect in the immune system.[1] Risk factors for psoriasis include smoking, alcohol consumption, family history, diet, BMI, infections and stress.[2] Research indicates that genetic factors are also associated with the disease.[3]

Genetics: Psoriasis has long been known to have a heritable component, with the siblings of an individual with psoriasis having a significantly greater likelihood of also developing the condition compared to unrelated individuals. For example, a study in Australia looked at psoriasis in almost 4,000 twins.[4] They found that if one twin had psoriasis, the probability that the second twin also had the condition was 35% if they were identical, but only 12% if they were fraternal twins.

As with other autoimmune conditions, the genes in the HLA (human leukocyte antigen) region of chromosome 6 strongly influence susceptibility to psoriasis. Variants in other genes related to the immune system have also been implicated in the risk of developing the disorder.

One of the largest studies looking at HLA and psoriasis identified an association between variants in the HLA region of Chromosome 6 and susceptibility to psoriasis. HLA was also found to play a role in susceptibility to psoriatic arthritis, a subtype of psoriasis.[3] The study also revealed associations between psoriasis and genes involved in the body's immune response, namely interleukin genes IL12B and IL23R. A study by a consortium of academic groups in the US and Germany that specifically looked at interleukin genes confirmed the association with psoriasis.[5] This report also examined whether the interleukin genes were interacting with genes in the HLA region but found no evidence of such an interaction, suggesting that the HLA and the interleukin genes act as independent risk factors for psoriasis.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
HLA	rs10484554	T	2.80	Caucasian	13.4%	Validated	18369459
IL23R	rs11209026	G	1.40	Caucasian	95.9%	Validated	18219280
TNIP1	rs17728338	A	1.59	Caucasian	8.0%	Validated	19169254
STAT2	rs2066808	A[i]	1.34	Caucasian	92.9%	Validated	19169254
IL12B	rs3212227	A	1.62	Caucasian	81.0%	Validated	18219280
TNFAIP3	rs610604	G[j]	1.19	Caucasian	42.5%	Validated	19169254
Intergenic_1q21	rs4112788	C	1.41	Caucasian	59.7%	Preliminary	19169253
SPATA2	rs495337	C	1.25	Caucasian	57.0%	Preliminary	18364390

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

[j]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either a C or a G in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
696.1 Other psoriasis Applies to: • Acrodermatitis continua • Dermatitis repens • Psoriasis: ◦ NOS ◦ any type, except arthropathic	N/A

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Rheumatoid arthritis

Report Type: Health Conditions

About: Rheumatoid arthritis (RA) affects approximately 1% of the general population in the U.S.[1] Symptoms of this autoimmune disease include joint pain, stiffness and swelling.[2] Risk factors for RA include diet, smoking and age, among others.[3] Research indicates that genetic factors are also associated with the disease.[4,5]

Genetics: RA is known to have a heritable component. As with other auto-immune conditions, the genes in the HLA (human leukocyte antigen) region of chromosome 6, strongly influence susceptibility to rheumatoid arthritis. The HLA Class II region contains genes that are part of the major histocompatibility complex. HLA Class II molecules are strongly associated with development of RA in all ethnic groups and account for 30% to 50% of the overall genetic risk in RA.[6]

Other genes shown to be associated with RA are also involved in the immune response. Among these, the CTLA4 (Cytotoxic T-Lymphocyte Antigen 4) gene encodes a protein that plays a key regulatory role in the immune system, particularly in T-cells. A variant in the rs3087243 marker is associated with decreased production of soluble CTLA-4.[4,5] Abatacept is a drug used to treat RA that mimics the function of CTLA-4 by binding and inhibiting receptors on T-cells.[7] The CTLA-4 variant and RA is rare in African populations.[8]

The CD40 and TRAF1 genes encode proteins that act together to inhibit T-cells through intracellular signaling pathways. CD40 is also involved in the development of “memory” in B-cells and is found in the synovial fluid of RA patients. A variant of the rs4810485 marker is associated with a change in the efficiency of CD40 protein production.[4] A variant of the rs3761847 marker may impact TRAF1 protein levels.[9]

The FCRL3 gene encodes an immune receptor that has activating and inhibitory functions. Mutations in this gene are associated with RA, systemic lupus erythematosus and autoimmune thyroid disease. A variant in the rs7528684 marker may regulate FCRL3 protein levels in Asians. Evidence of a similar association has been found for some Caucasian subgroups.[10]

The CD244 gene encodes a receptor found on T-cells that regulates their cell-killing function. A variant in the rs3766379 marker is associated with RA in Asians.[11] The marker is located in a non-coding region of the gene, and the effect of the variant on protein function is unknown.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
PADI4	rs2240340	A	1.31	Asian	41.1%	Validated	18087673
PTPN22	rs2476601	A	1.53	Caucasian	11.7%	Validated	17982455
CTLA4	rs3087243	G	1.22	Asian	80.4%	Validated	19404967
CTLA4	rs3087243	G	1.11	Caucasian	54.0%	Validated	18794853
TRAF1	rs3761847	G	1.32	Caucasian	47.8%	Validated	17804836
CD244	rs3766379	T	1.31	Asian	48.2%	Validated	18794858
MMEL1	rs3890745	T[i]	1.12	Caucasian	66.8%	Validated	18794853
CD40	rs4810485	G	1.15	Caucasian	75.2%	Validated	18794853
HLA	rs6457617	T	2.36	Caucasian	52.2%	Validated	17554300
Intergenic_4q27	rs6822844	G	1.28	Caucasian	85.4%	Validated	19404967
Intergenic_6q23	rs6920220	A	1.24	Caucasian	16.5%	Validated	18794853
STAT4	rs7574865	T	1.27	Asian	35.2%	Validated	19404967
STAT4	rs7574865	T	1.24	Caucasian	23.4%	Validated	19404967
IL1B	rs16944	G	1.10	Caucasian	64.2%	Preliminary	18838388
FCRL3	rs7528684	G	1.16	Asian	40.5%	Preliminary	18087673

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
714.0 Rheumatoid arthritis Applies to: • Arthritis or polyarthritis: ◦ atrophic ◦ rheumatic (chronic)	V82.1 Screening for rheumatoid arthritis

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Systemic lupus erythematosus

Report Type: Health Conditions

About: Systemic lupus erythematosus (SLE) is the most common form of lupus.[1] This chronic autoimmune disease is characterized by the production of autoantibodies that can cause renal failure, arthritis, thrombosis, vasculitis and seizures.[2] Risk factors for SLE include exposure to silica dust, hormonal and reproductive factors and cigarette smoke.[2,3] Research indicates that genetic factors are also associated with the disease[4,5,6]

Genetics: Systemic lupus erythematosus (SLE or lupus) can occur either sporadically or be recurrent in families. Genes connected to the immune system are associated with the development of SLE, including the HLA Class II molecules of the major histocompatibility complex (MHC) and genes involved in the complement system.

The rs2187668 marker is located in the HLA Class II region and is linked to a high-risk set of alleles in three tightly linked genes in Caucasians.[4] The high risk alleles are HLA-DRB1*0301-HLA-DQA1*0501-DQB1*0201. This combination of alleles is very common, but it is the pairing of these alleles with others that can initiate SLE as well as other autoimmune diseases. The minor allele, "A", of rs2187668 has been associated with increased SLE risk in Caucasians.

Other genes included in the test are also involved in the immune system. Among these, the FCGR2A gene encodes a receptor that is expressed on immune cells and interacts with antibody complexes. The T allele of the rs1801274 marker causes an altered interaction with IgG and is thought to perpetuate autoimmune responses in SLE in Caucasians and Asians.[5,6]

In another example, the IRF5 gene encodes a transcription factor that regulates other genes that respond to interferon-alpha (IFN alpha). IFN alpha is normally produced in response to viral infections, but its levels are abnormally high in SLE patients. Increased IFN alpha levels result in increased IRF5 levels. The T allele of the rs2004640 marker encodes an alternative form of IRF5 and is associated with increased risk for SLE in individuals of Caucasian, Asian, African and Hispanic descent.[7] IRF5 has also been shown to have additive effects with STAT4 for increased risk for SLE.

The STAT4 gene encodes a transcription factor that regulates inflammatory gene expression. The T allele of the rs7574865 marker is associated with increased STAT4 expression and is thought to contribute to earlier onset and more severe disease in Caucasians, Asians and people of Hispanic ancestry.[8,9,10]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
ITGAM	rs1143679	A	1.55	African	11.0%	Validated	18204448
ITGAM	rs1143679	A	1.78	Caucasian	10.0%	Validated	18204448
ITGAM	rs1143679	A	2.26	Hispanic	9.0%	Validated	19129174
TNFSF4	rs1234314	G	1.26	Caucasian	42.5%	Validated	19092840
BLK	rs13277113	A	1.30	Asian	75.0%	Validated	19225526
BLK	rs13277113	A	1.39	Caucasian	23.5%	Validated	18204098
BANK1	rs17266594	T	1.64	Asian	84.5%	Validated	19357697
BANK1	rs17266594	T	1.42	Caucasian	73.9%	Validated	18204447
MECP2	rs1734787	C	1.55	Asian	88.5%	Validated	18320046
MECP2	rs1734787	C	1.35	Caucasian	18.5%	Validated	19333917
FCGR2A	rs1801274	C	1.87	African	45.3%	Validated	12115187
FCGR2A	rs1801274	C	1.61	Asian	31.5%	Validated	12867584
FCGR2A	rs1801274	C	1.24	Caucasian	50.9%	Validated	12115187
HLA	rs2187668	A	1.76	Caucasian	8.0%	Validated	19493061
CTLA4	rs231775	G	1.25	Asian	69.6%	Validated	15688186
PTPN22	rs2476601	A	1.35	Caucasian	11.7%	Validated	19493061
PTPN22	rs2476601	A	2.06	Hispanic	5.2%	Validated	16868974
CTLA4	rs3087243	G	1.32	Caucasian	54.0%	Validated	15248219
TNFAIP3	rs5029939	G	2.09	Caucasian	2.7%	Validated	19387456
STAT4	rs7574865	T	1.71	Asian	35.2%	Validated	19225526
STAT4	rs7574865	T	1.56	Caucasian	23.4%	Validated	18516230
STAT4	rs7574865	T	1.62	Hispanic	40.0%	Validated	18432273
CRP	rs3093062	G	1.45	African	79.9%	Preliminary	18182444

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
710.0 Systemic lupus erythematosus Applies to: • Disseminated lupus erythematosus • Libman-Sacks disease	V82.9 Screening for unspecified condition

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Ulcerative colitis

Report Type: Health Conditions

About: Ulcerative colitis (UC) has been on the rise for the past 50 years, but incidence rates seem to be plateauing.[1] This chronic, idiopathic condition is characterized by ulcers in the rectum and colon that can cause pain and bloody diarrhea.[2] Risk factors include a family history of the disease and smoking.[3,4] Research indicates that genetic factors are also associated with UC.[5,6,7]

Genetics: Both genetics and environmental factors are known to contribute to the risk of developing UC. A role for genetics is shown by the observation that people with a family history of UC have an increased risk of developing the disease. Up to 20% of UC cases occur in families, with a higher incidence in those of northern European and Jewish ancestry.[8] The genetic contribution to ulcerative colitis (UC) can be divided into two groups: HLA (human leukocyte antigen) and non-HLA susceptibility loci.

Like other autoimmune conditions, there is a strong association between susceptibility to UC and variants of the HLA region on Chromosome 6.[5] The involvement of HLA genes in UC has long been known, but the exact mechanisms are not well understood. The HLA-associated UC susceptibility loci in the test include the rs2395185 marker in the HLA Class II region[9] and the rs1800629 marker in the TNFA gene, which encodes the immune stimulatory TNF-alpha protein.[10] The genetic association to TNFA alleles has only been reliably demonstrated in Asians. TNF-alpha is a target of antibody drugs used to treat ulcerative colitis.[11]

Non-HLA UC susceptibility genes in the test include IL10 (interleukin 10)[6] and IL23R (interleukin 23 receptor),[7] among others. Several pro-inflammatory interleukin proteins, including IL10 and IL23, are targets for ulcerative colitis drug therapies that are either available or in clinical development.[11]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
NKX2-3	rs10883365	G	1.20	Caucasian	45.6%	Validated	18438406
IL23R	rs11209026	G	1.81	Caucasian	95.9%	Validated	19122664
IFNG	rs1558744	A	1.35	Caucasian	40.3%	Validated	19122664
HLA	rs2395185	G	1.77	Caucasian	56.7%	Validated	19122664
IL10	rs3024505	T	1.46	Caucasian	18.1%	Validated	18836448
MST1	rs3197999	T	1.20	Caucasian	26.1%	Validated	18438406
RNF186	rs3806308	G	1.37	Caucasian	60.2%	Validated	19122664
Intergenic_1p36	rs6426833	A	1.45	Caucasian	50.9%	Validated	19122664
BSN	rs9858542	A	1.31	Caucasian	25.7%	Validated	18438406
TNFa	rs1800629	A	2.27	Asian	8.9%	Preliminary	18827481

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
556.6 Universal ulcerative (chronic) colitis Applies to: • Pancolitis	N/A

References

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