Autoimmunity Report

Introduction

The Cardiovascular Test is based on Whole Genome Sequencing Test. As such, it analyzes all Common and Rare Variants associated with Cardiovascular Diseases instead of a limited set of genes, like old genetic target panels. Cardiovascular Diseases affect the heart and blood vessels and include Coronary Heart Disease, Cerebrovascular Disease, Peripheral Arterial Disease, Congenital Heart Disease, Deep Vein Thrombosis, Pulmonary Embolism, Rheumatic Heart Disease. Along with environmental factors, Genetics plays a key role in the etiology of several forms of Cardiovascular Diseases.

In our analysis, we found pathogenic or likely pathogenic variants related to:

- Corneal endothelial dystrophy type 2
- Prostate cancer
- Rheumatoid arthritis

Genes/Locations included in report:

C2 (0)	ADA (0)	BTK (0)	C1R (0)	C1S (0)	C4A (0)	C8A (0)
CR2 (0)	FAS (1)	GCK (0)	IL6 (0)	INS (0)	ITK (0)	LCK (0)
MIF (0)	NBN (0)	PNP (0)	WAS (0)	ACP5 (0)	ADA2 (0)	AGRN (0)
AIRE (0)	AKT2 (0)	C1QA (0)	C1QB (0)	C1QC (0)	CAV1 (0)	CD19 (0)
CD3G (0)	CD81 (0)	CHAT (0)	CHD7 (1)	COMT (2)	FADD (0)	GALC (0)
GNAS (0)	ICOS (0)	IL7R (0)	IRF5 (2)	ITCH (0)	KRAS (0)	LIG4 (0)
LRBA (0)	MMP2 (0)	NRAS (0)	PAX4 (0)	PDX1 (0)	PEPD (0)	POLG (0)
PTEN (0)	RAG1 (0)	RAG2 (0)	RMRP (1)	SYT2 (0)	TBX1 (0)	TRAC (0)
TSHR (0)	ABCC8 (1)	ALG14 (0)	BANK1 (1)	CD247 (0)	CTLA4 (1)	DDX41 (0)
FASLG (0)	FOXD3 (0)	FOXP3 (0)	GP1BB (0)	HLA-B (0)	HYMAI (0)	IL2RA (0)

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DANTE LABS™ TEST RESULTS

KIT ID: SAMPLE

IL2RG (0)	ITGAM (0)	KDM6A (0)	KMT2D (0)	LMNB2 (0)	MASP2 (0)	MS4A1 (0)
NFKB1 (0)	NFKB2 (0)	NHEJ1 (0)	NLRP1 (1)	PLCG2 (0)	PRKCD (0)	STAT1 (0)
STAT3 (0)	STAT4 (0)	STIM1 (0)	STX16 (0)	TREX1 (0)	TTC7A (1)	VAMP1 (0)
WIPF1 (0)	ZFP57 (0)	CASP10 (0)	DNASE1 (0)	FCGR2A (1)	FCGR2B (0)	FCGR2C (0)
KCNJ11 (1)	PLAGL1 (0)	PTPN22 (1)	SEC23B (0)	SLC5A7 (0)	SNAP25 (0)	COL13A1 (0)
DCLRE1C (0)	HLADRB1 (0)	SLC18A3 (0)	SLC25A1 (0)	TNFAIP3 (0)	DNASE1L3 (0)	HLA-DQB1 (0)
SERPING1 (0)	C1GALT1C1 (0)	TNFRSF13B (0)	TNFRSF13C (0)			

Variants Found:

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
IRF5	chr7:128578301	rs2004640	Rheumatoid arthritis	HET	G>T	0.41354	pathogenic	
COMT	chr22:19951271	rs4680	CATECHOL-O-METHYLTRANSFERASE POLYMORPHISM	HET	G>A	0.36921	drug response	★★★
FCGR2A	chr1:161479745	rs1801274	Lupus nephritis	HOM	A>G	0.44169	drug response	★★★
COMT	chr22:19929027	rs13306278	Selective serotonin reuptake inhibitors response - Efficacy	HET	C>T	0.07728	drug response	★★★
KCNJ11	chr11:17409572	rs5219	glibenclamide response - Efficacy	HET	T>C	0.73702	drug response	★★★
ABCC8	chr11:17409572	rs5219	glibenclamide response - Efficacy	HET	T>C	0.73702	drug response	★★★
TTC7A	chr2:47184149		Multiple gastrointestinal atresias	HET	A>G		uncertain significance	★
CHD7	chr8:61690321	rs4738824	Scoliosis	HOM	A>G	0.86062	uncertain significance	
BANK1	chr4:102751076	rs10516487	Systemic lupus erythmatosus	HOM	G>A	0.21845	uncertain significance	
PTPN22	chr1:114415368	rs2488457	Diabetes mellitus	HOM	G>C	0.74701	risk factor	
CTLA4	chr2:204738919	rs3087243	Hashimoto thyroiditis	HET	G>A	0.36901	risk factor	
FAS	chr10:90749256	rs2234767	LUNG CANCER	HET	G>A	0.18411	risk factor	
IRF5	chr7:128589427	rs10954213	Systemic lupus erythematosus 10	HET	G>A	0.53594	risk factor	

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
NLRP1	chr17:5485367	rs12150220	Vitiligo-associated multiple autoimmune disease susceptibility 1	HOM	A>T	0.19209	risk factor	
RMRP Rare	chr9:35658011	rs772443941	Metaphyseal chondrodysplasia	HET	G>A	0.00031	conflicting interpretations of pathogenicity	

Individual Variant Interpretations:

rs721048 - NM_001142615.3(EHBP1):c.1185+30064G>A

In a genomewide association study of prostate cancer, Gudmundsson et al. (2008) identified a novel variant in an intron of the EHBP1 gene, rs721048 that was associated with prostate cancer (HPC12; 611868) (P = 7.7 x 10(-9)). The rs721048 A allele showed a significantly stronger association with more aggressive, rather than less aggressive, forms of the disease.

Prostate cancer is a common disease that affects men, usually in middle age or later. In this disorder, certain cells in the prostate become abnormal and multiply without control or order to form a tumor. The prostate is a gland that surrounds the male urethra and helps produce semen, the fluid that carries sperm.Early prostate cancer usually does not cause pain, and most affected men exhibit no noticeable symptoms. Men are often diagnosed as the result of health screenings, such as a blood test for a substance called prostate specific antigen (PSA) or a medical procedure called a digital rectal exam. As the tumor grows larger, signs and symptoms can include difficulty starting or stopping the flow of urine, a feeling of not being able to empty the bladder completely, blood in the urine or semen, or pain with ejaculation. However, these changes can also occur with many other genitourinary conditions. Having one or more of these symptoms does not necessarily mean that a man has prostate cancer.The severity and outcome of prostate cancer varies widely. Early-stage prostate cancer can usually be treated successfully, and some older men have prostate tumors that grow so slowly that they may never cause health problems during their lifetime, even without treatment. In other men, however, the cancer is much more aggressive; in these cases, prostate cancer can be life-threatening.Some cancerous tumors can invade surrounding tissue and spread to other parts of the body. Tumors that begin at one site and then spread to other areas of the body are called metastatic cancers. The signs and symptoms of metastatic cancer depend on where the disease has spread. If prostate cancer spreads, cancerous cells most often appear in the lymph nodes, bones, lungs, liver, or brain. Bone metastases of prostate cancer most often cause pain in the lower back, pelvis, or hips.A small percentage of all prostate cancers cluster in families. These hereditary cancers are associated with inherited gene mutations. Hereditary prostate cancers tend to develop earlier in life than non-inherited (sporadic) cases.

PubMed PMID: 18264098

rs2004640 - NM_001098629.3(IRF5):c.-12+198=

In an analysis of SNPs in genes of the type I interferon pathway in cases and controls, Sigurdsson et al. (2005) identified SNPs in the IRF5 gene that displayed strong signals in joint analysis of linkage and association with SLE (SLEB10; 612251). In joint linkage and association analysis, the SNP rs2004640 achieved a combined P of 2.4 x 10(-7).

Graham et al. (2006) replicated the association of the IRF5 T allele of rs2004640 with SLE found by Sigurdsson et al. (2005) in 4 independent case-control cohorts and by family-based transmission disequilibrium test analysis. The T allele creates a 5-prime donor splice site in exon 1B of the IRF5 gene, allowing expression of several unique IRF5 isoforms.

In a study of IRF5 SNPs in Swedish patients with rheumatoid arthritis (RA; 180300), Sigurdsson et al. (2007) found association with rs2004640 (p = 0.0067) and an even stronger association (p = 0.00063) with rs3807306, which was in linkage disequilibrium (r(2) = 0.67) with rs2004640. The authors noted that the minor alleles of these 2 SNPs are on the same protective haplotype in both SLE and RA.

In a study of 485 Swedish SLE patients and 563 controls, Sigurdsson et al. (2008) performed logistic regression analysis conditioned on the CGGGG indel polymorphism in the promoter of the IRF5 gene (607218.0001), and found that the CGGGG indel accounts for the association signal previously observed with rs2004640.

PubMed PMID: 15657875
PubMed PMID: 16642019
PubMed PMID: 17599733
PubMed PMID: 18063667

rs1801253 - NM_000684.3(ADRB1):c.1165G>C (p.Gly389Arg)

The beta-1-adrenergic receptor, a key cell surface signaling protein expressed in the heart and other organs, mediates the actions of catecholamines in the sympathetic nervous system. Mason et al. (1999) identified a C-to-G transversion in the intracellular cytoplasmic tail near the seventh transmembrane-spanning segment of the human ADRB1 gene, resulting in an arg389-to-gly substitution (R389G). Allele frequencies for gly389 and arg389 residues were 0.26 and 0.74, respectively (the former had previously been considered as the human wildtype ADRB1 allele). Using site-directed mutagenesis to mimic the 2 variants, cultured cells were permanently transfected to express the gly389 and arg389 receptors. In functional studies with matched expression, the arg389 receptors had slightly higher basal levels of adenylyl cyclase activities. However, maximal isoproterenol-stimulated levels were markedly higher for the arg389 receptor as compared with the gly389 receptor. Agonist-promoted binding was also increased for the arg389 receptor, consistent with enhanced coupling to stimulatory G protein (Gs; see 139320) and increased adenylyl cyclase activation. These and other studies indicated that this polymorphic variation of the human ADRB1 gene results in alterations of receptor-Gs interaction with functional consequences on signal transduction, consistent with its localization in a putative G-protein binding domain. Mason et al. (1999) suggested that the genetic variation of the ADRB1 gene may be the basis of interindividual differences in pathophysiologic characteristics or in the response to therapeutic beta-adrenergic receptor agonists and antagonists in cardiovascular and other diseases.

Among black subjects, Small et al. (2002) found an adjusted odds ratio for heart failure (10.11) in persons who were homozygous for both arg389 of the ADRB1 gene and for a 4-bp deletion (322-325del; 104250.0001) in the ADRA2C gene. Small et al. (2002) reasoned that the decreased function of the deletion polymorphism would reduce the control of norepinephrine by negative feedback from presynaptic alpha-2-adrenergic receptors, and that the increased function of the arg389 form of the beta-1-adrenergic receptor on myocytes would in combination result in increased synaptic norepinephrine release and enhanced receptor function at the myocyte, thus predisposing persons to heart failure. They found no increased risk with the arg389 allele alone.

Liggett et al. (2006) studied isolated right ventricular trabeculae from failing and nonfailing human hearts and observed that arg389 receptors had approximately 3- and 4-fold greater agonist-promoted contractility compared to gly389 receptors, respectively. The beta-blocker, bucindolol, was an inverse agonist in failing arg389, but not gly389, ventricles. In transfected cells, bucindolol antagonized agonist-stimulated cAMP, with a greater absolute decrease for arg389. In a placebo-controlled trial of bucindolol in 1,040 heart failure patients, no outcome was associated with genotype in the placebo group, indicating little impact on the natural course of heart failure. However, arg389 homozygotes treated with bucindolol had an age-, sex-, and race-adjusted 38% reduction in mortality (p = 0.03) and a 34% reduction in mortality or hospitalization (p = 0.004) versus placebo. Gly389 carriers had no clinical response to bucindolol compared with placebo. Liggett et al. (2006) concluded that the R389G variation alters signaling in multiple models and affects the therapeutic response to beta-blockers.

Lobmeyer et al. (2007) genotyped 54 patients with congestive heart failure for the R389G and del322-325 polymorphisms in the ADRB1 and ADRA2C genes, respectively, and performed echocardiography before and after treatment with the beta-blocker metoprolol. The authors found that patients homozygous for R389 who also carried del322-325 showed a significantly higher ejection fraction increase with metoprolol than all the other genotype combination groups, and concluded that the ADRB1 and ADRA2C polymorphisms synergistically influence the ejection fraction response to beta-blocker therapy of heart failure patients.

PubMed PMID: 10212248
PubMed PMID: 12374873
PubMed PMID: 16844790
PubMed PMID: 17496726

rs4738824 - NM_017780.4(CHD7):c.1666-3238A>G

This variant, formerly titled SCOLIOSIS, IDIOPATHIC, SUSCEPTIBILITY TO, 3, has been reclassified based on the findings of Tilley et al. (2013).

To search for genes underlying susceptibility to idiopathic scoliosis (see IS3, 608765), Gao et al. (2007) ascertained a cohort of 52 families and conducted a study by genomewide scans, which produced evidence of linkage in association with 8q12 loci (multipoint lod = 2.77; p = 0.0028). Further mapping in the region showed significant evidence of disease-associated haplotypes centering over exons 2 through 4 of the CHD7 gene, which is associated with the CHARGE syndrome of multiple developmental anomalies. In 25 affected probands with idiopathic scoliosis (see IS3, 608765) and 44 parental controls, Gao et al. (2007) identified a single-nucleotide polymorphism, SNP rs4738824, an A-to-G change in intron 2 of the CHD7 gene that was predicted to disrupt a caudal-type (cdx) transcription factor binding site. The A nucleotide of this SNP appears to be perfectly conserved across 9 vertebrate species. In the 27 remaining families in the study, Gao et al. (2007) found significant overtransmission of the G allele, which was predicted to disrupt a caudal-type (cdx) transcription factor binding site, to affected offspring (p = 0.005).

Tilley et al. (2013) performed model-independent linkage analysis and tests of association for 22 single-nucleotide polymorphisms in the CHD7 gene in 244 families of European descent with familial idiopathic scoliosis. Linkage analysis identified 3 marginally significant results. However, their results were not significant for tests of association to the CHD7 gene (p less than 0.01). In addition, no significant results (p less than 0.01) were found from a metaanalysis of the results from the tests of association from their sample and that of Gao et al. (2007).

PubMed PMID: 23883829
PubMed PMID: 17436250

rs10516487 - NM_017935.5(BANK1):c.182G>A (p.Arg61His)

This variant, formerly titled SYSTEMIC LUPUS ERYTHMATOSUS, ASSOCIATION WITH, has been reclassified because its contribution to the phenotype has not been confirmed.

Kozyrev et al. (2008) identified an association between systemic lupus erythematosus (SLE; 152700) and a nonsynonymous substitution, rs10516487, in the BANK1 gene. This SNP consists of a G-to-A transition that results in substitution of his for arg at codon 61, with the G allele conferring risk.

PubMed PMID: 18204447

rs4950928 - NM_001276.2(CHI3L1):c.-131C>G

In a genomewide association study of serum YKL-40 levels in 632 Hutterites, Ober et al. (2008) identified a polymorphism (-131C-G; rs4950928) in the promoter of the CHI3L1 gene that was significantly associated with elevated YKL-40 levels (p = 1.1 x 10(-13)) and asthma-related traits (611960), including asthma (p = 0.047), bronchial hyperresponsiveness (p = 0.002), and measures of pulmonary function (p = 0.046 to 0.002). The -131C-G polymorphism also predicted the presence of asthma in 2 case-control populations (combined p = 1.2 x 10 (-5)) and serum YKL-40 levels at birth through 5 years of age in a birth cohort (p = 8.9 x 10(-13) to 2.5 x 10(-4)). The authors stated that although they could not statistically distinguish between implicated SNPs in perfect linkage disequilibrium, -131C-G, located within a binding site for the MYC (190080) and MAX (154950) transcription factors, seemed likely to be the causal SNP.

PubMed PMID: 18403759

rs7794745 - NM_014141.6(CNTNAP2):c.208+18133A>T

In 2 independent family-based samples, Arking et al. (2008) identified a common variant in the CNTNAP2 gene, rs7794745, that was associated with increased risk for autism (AUTS15; 612100). This SNP resides in intron 2 of the CNTNAP2 gene. In the combined sample, overall transmission frequency of the T allele to affected children (tau = 0.55, p less than 7.35 x 10(05)) was significantly greater from mothers (tau = 0.61) than from fathers (tau = 0.53), and this parent-of-origin difference was significant (P less than 0.001).

PubMed PMID: 18179894

rs2488457 - NM_015967.6(PTPN22):c.-1123C>G

By sequencing both strands of genomic DNA from 35 healthy Japanese individuals, Kawasaki et al. (2006) identified a -1123C-G promoter SNP (rs2488457) in the PTPN22 gene. In a study of 484 Japanese patients with type I diabetes (IDDM; 222100), 317 of whom had acute-onset diabetes, and 492 healthy controls, the authors found that the heterozygous C/G genotype was associated with susceptibility to acute-onset but not slow-onset type I diabetes (OR = 1.42, p = 0.015). A similar tendency was observed in 69 Korean patients with acute-onset type I diabetes (p = 0.0105, combined OR = 1.41).

PubMed PMID: 16470599

rs3087243 - NM_005214.5(CTLA4):c.*1148+236G>A

Ueda et al. (2003) identified a series of single-nucleotide polymorphisms (SNPs) between 0.2 and 6.3 kb 3-prime of the end of the CTLA4 transcript. One was termed CT60 and encodes either a protective A/A genotype or a predisposing G/G genotype for autoimmune disease (rs3087243). CT60 is a common SNP, with 63.4% of 1,316 Graves disease (275000) patient chromosomes and 53.2% of 1,646 control chromosomes having the susceptible G allele. Compared with the protective CT60 A/A genotype, the A/G and G/G genotypes had odds ratios of 1.59 (1.19-2.13) and 2.32 (1.71-3.15), respectively. In controls, the A/A, A/G, and G/G genotypes had frequencies of 22.8%, 48.0%, and 29.2%, and in Graves disease cases, 13.7%, 45.7%, and 40.6%, respectively. Conversely, relative to the disease-predisposing G/G genotype, A/G and A/A had odds ratios of 0.68 (0.54-0.86) and 0.43 (0.32-0.59), respectively. The CT60 SNP was also associated with autoimmune hypothyroidism, or Hashimoto thyroiditis (140300) to the same degree as Graves disease (odds ratio = 1.45 (1.17-1.80); p = 0.0005). However, the effect was much weaker in type I diabetes. Ueda et al. (2003) suggested the presence of a common Graves disease, type I diabetes (IDDM12; 601388), and autoimmune hypothyroidism locus in the 6.1-kb 3-prime region of CTLA4. Using a real-time PCR assay, Ueda et al. (2003) showed that the CT60 polymorphism determines the efficiency of the splicing and production of soluble CTLA4, with the CT60G disease-susceptibility haplotype producing less soluble CTLA4 transcript than the resistant CT60A haplotype. In a mouse model of type I diabetes, susceptibility was also associated with variation in CTLA4 gene splicing with reduced production of a splice form encoding a molecule lacking the CD80/CD86 ligand-binding domain.

Van Belzen et al. (2004) genotyped 215 Dutch patients with celiac disease (609755) and 213 controls for the 49A-G (123890.0001) and CT60 polymorphisms in the CTLA4 gene. They found no significant difference between patients and controls in the frequency of the 49G allele, but did find an increase in the frequency of the CT60 G allele in patients (p = 0.048). Van Belzen et al. (2004) concluded that CTLA4 is involved in the development of celiac disease.

PubMed PMID: 12724780
PubMed PMID: 15199380

rs2234767 - NM_001141945.2(ACTA2):c.-24+1440C>T

Zhang et al. (2005) genotyped 1,000 Han Chinese lung cancer (211980) patients and 1,270 controls for 2 functional polymorphisms in the promoter regions of the FAS and FASL genes, -1377G-A and -844T-C (134638.0002), respectively. Compared to noncarriers, there was a 1.6-fold increased risk of developing lung cancer for carriers of the FAS -1377AA genotype and a 1.8-fold increased risk for carriers of the FASL -844CC genotype. Carriers of both homozygous genotypes had a more than 4-fold increased risk, indicative of multiplicative gene-gene interaction.

PubMed PMID: 15937082

rs4833095 - NM_003263.4(TLR1):c.743A>G (p.Asn248Ser)

Schuring et al. (2009) studied association of an asn248-to-ser (N248S) SNP in the TLR1 gene and leprosy (LPRS5; 613223) in a Bangladeshi population consisting of 842 patients and 543 controls. They found that the S allele was slightly more frequent among patients than controls (54% vs 51%; OR = 1.12). Homozygosity for S248 was significantly associated with leprosy per se (OR = 1.34), whereas heterozygosity was found to be protective against leprosy (OR = 0.78). In contrast, the homozygous N248 genotype was equally distributed among patients and controls. No difference in allele frequency or genotype was associated with leprosy classification or serologic status. However, patients who experienced erythema nodosum leprosum reactions were more likely to have the N248 allele (68%) than were patients who had no reactions (46%). Schuring et al. (2009) noted that amino acid 248 of TLR1 is located in the external ligand-binding site of the receptor, and that Omueti et al. (2007) had shown that the S248 variant enabled normal function, whereas the N248 variant diminished the response of TLR1 to bacterial agonists.

Leprosy, also called Hansen disease, is a disorder known since ancient times. It is caused by bacteria called Mycobacterium leprae and is contagious, which means that it can be passed from person to person. It is usually contracted by breathing airborne droplets from affected individuals' coughs and sneezes, or by coming into contact with their nasal fluids. However, it is not highly transmissible, and approximately 95 percent of individuals who are exposed to Mycobacterium leprae never develop leprosy. The infection can be contracted at any age, and signs and symptoms can take anywhere from several months to 20 years to appear.Leprosy affects the skin and the peripheral nerves, which connect the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, and heat. Most affected individuals have areas of skin damage (cutaneous lesions) and problems with nerve function (peripheral neuropathy); however, the severity and extent of the problems vary widely. Leprosy occurs on a spectrum, in which the most severe form is called multibacillary or lepromatous, and the least severe form is called paucibacillary or tuberculoid. Patterns of signs and symptoms intermediate between these forms are sometimes called borderline forms.Multibacillary leprosy usually involves a large number of cutaneous lesions, including both surface damage and lumps under the skin (nodules). The moist tissues that line body openings such as the eyelids and the inside of the nose and mouth (mucous membranes) can also be affected, which can lead to vision loss, destruction of nasal tissue, or impaired speech. Some affected individuals have damage to internal organs and tissues. The nerve damage that occurs in multibacillary leprosy often results in a lack of sensation in the hands and feet. Repeated injuries that go unnoticed and untreated because of this lack of sensation can lead to reabsorption of affected fingers or toes by the body, resulting in the shortening or loss of these digits.Paucibacillary leprosy typically involves a small number of surface lesions on the skin. There is generally loss of sensation in these areas, but the other signs and symptoms that occur in multibacillary leprosy are less likely to develop in this form of the disorder.In any form of leprosy, episodes called reactions can occur, and can lead to further nerve damage. These episodes can include reversal reactions, which involve pain and swelling of the skin lesions and the nerves in the hands and feet. People with the more severe forms of leprosy can develop a type of reaction called erythema nodosum leprosum (ENL). These episodes involve fever and painful skin nodules. In addition, painful, swollen nerves can occur. ENL can also lead to inflammation of the joints, eyes, and the testicles in men.Leprosy has long been stigmatized because of its infectious nature and the disfigurement it can cause. This stigma can cause social and emotional problems for affected individuals. However, modern treatments can prevent leprosy from getting worse and spreading to other people. While the infection is curable, nerve and tissue damage that occurred before treatment is generally permanent.

PubMed PMID: 17475868
PubMed PMID: 19456232

rs9406328 - NM_003247.3(THBS2):c.1478-8C>T

In an association study of 2 independent Japanese populations involving a total of 847 patients with lumbar disc herniation (LDH; 603932) and 896 controls, Hirose et al. (2008) found a significant association (corrected p = 0.000045) between LDH and a -8C-T polymorphism (rs9406328) located in a polypyrimidine tract upstream of the 3-prime splice site in intron 10 of the THBS2 gene. In vivo studies demonstrated increased skipping of exon 11 with the susceptibility (T) allele; solid-phase binding assays showed that skipping of exon 11 results in decreased THBS2 interaction with MMP2 (120360) and MMP9 (120361). Hirose et al. (2008) found that a missense SNP in the MMP9 gene (120361.0001) was also strongly associated with LDH in the Japanese population and showed a combinatorial effect with THBS2, with an odds ratio of 3.03 for the genotype that was homozygous for the susceptibility alleles of both SNPs.

PubMed PMID: 18455130

rs2010963 - NM_001025366.3(VEGFA):c.-94C>G

Awata et al. (2002) studied the -634G-C polymorphism of the VEGF gene in type 2 diabetes (125853) patients with proliferative and nonproliferative diabetic retinopathy (MVCD1; 603933) and compared the genotype frequencies with controls (patients without retinopathy). The odds ratio for the CC genotype to the GG genotype was 3.20 (95% CI, 1.45-7.05; p = 0.0046). The -634C allele was significantly increased in patients with nonproliferative diabetic retinopathy (p = 0.0026) and was insignificantly increased in patients with proliferative diabetic retinopathy compared with patients without retinopathy, although frequencies of the allele did not differ significantly between the nonproliferative and proliferative diabetic retinopathy groups. Logistic regression analysis revealed that the -634G-C polymorphism was strongly associated with an increased risk of retinopathy. Furthermore, VEGF serum levels were significantly higher in healthy subjects with the CC genotype of the polymorphism than in those with other genotypes.

PubMed PMID: 11978667

rs1617640 - NM_000799.3(EPO):c.-1306C>A

In a cohort of 374 patients with type 2 diabetes (125853) and microvascular complications of diabetes, including proliferative diabetic retinopathy (PDR) and end-stage renal disease (ESRD) (MVCD2, 612623), and 239 age- and ethnicity-matched diabetic controls, Tong et al. (2008) found significant association between the T allele of rs1617640, a SNP in the promoter of the EPO gene, and PDR and ESDR (corrected p = 0.036). The association with diabetic microvascular complications was confirmed in 365 patients with type 1 diabetes (222100) with both PDR and ESRD, 500 with nephropathy and retinopathy without progression to PDR and ESRD, and 574 type 1 diabetic control patients without nephropathy or retinopathy (p = 2.66 x 10(-8)), as well as in a third cohort involving 379 type 1 diabetics with both PDR and nephropathy and 141 diabetic controls (p = 0.021). The EPO concentration in vitreous samples was 7.5-fold higher in normal subjects with the TT risk genotype than in those with the GG genotype, and studies in cultured HEK293 cells showed that the T allele enhanced luciferase reporter expression by 25-fold compared with that of the G allele (p = 4.7 x 10(-29)).

PubMed PMID: 18458324

rs10954213 - NM_001098629.3(IRF5):c.*555G>A

Cunninghame Graham et al. (2007) identified 2 overtransmitted IRF5 haplotypes and a single undertransmitted haplotype among 380 UK SLE (SLEB10; 612251) nuclear families. The strongest association was with a TCTAACT haplotype, which carried all the overtransmitted alleles in the study. The TAT haplotype showed a dose-dependent relationship with mRNA expression. A differential expression pattern was seen between 2 expression probes located on each side of rs10954213 in the 3-prime untranslated region (UTR). rs10954213 showed the strongest association with RNA expression levels. The A allele of rs10954213 created a functional polyadenylation site, and the A genotype correlated with increased expression of a transcript variant containing a shorter 3-prime UTR. Expression levels of transcript variants with the shorter or longer 3-prime UTRs were inversely correlated. The authors proposed a new mechanism by which an IRF5 polymorphism may control the expression of alternate transcript variants, which may have different effects on interferon signaling.

In a study of 485 Swedish SLE patients and 563 controls, Sigurdsson et al. (2008) performed logistic regression analysis conditioned on the CGGGG indel polymorphism in the promoter of the IRF5 gene (607218.0001), and found that the CGGGG indel accounts for the association signal previously observed with rs10954213.

Systemic lupus erythematosus (SLE) is a chronic disease that causes inflammation in connective tissues, such as cartilage and the lining of blood vessels, which provide strength and flexibility to structures throughout the body. The signs and symptoms of SLE vary among affected individuals, and can involve many organs and systems, including the skin, joints, kidneys, lungs, central nervous system, and blood-forming (hematopoietic) system. SLE is one of a large group of conditions called autoimmune disorders that occur when the immune system attacks the body's own tissues and organs.SLE may first appear as extreme tiredness (fatigue), a vague feeling of discomfort or illness (malaise), fever, loss of appetite, and weight loss. Most affected individuals also have joint pain, typically affecting the same joints on both sides of the body, and muscle pain and weakness. Skin problems are common in SLE. A characteristic feature is a flat red rash across the cheeks and bridge of the nose, called a "butterfly rash" because of its shape. The rash, which generally does not hurt or itch, often appears or becomes more pronounced when exposed to sunlight. Other skin problems that may occur in SLE include calcium deposits under the skin (calcinosis), damaged blood vessels (vasculitis) in the skin, and tiny red spots called petechiae. Petechiae are caused by a shortage of cell fragments involved in clotting (platelets), which leads to bleeding under the skin. Affected individuals may also have hair loss (alopecia) and open sores (ulcerations) in the moist lining (mucosae) of the mouth, nose, or, less commonly, the genitals.About a third of people with SLE develop kidney disease (nephritis). Heart problems may also occur in SLE, including inflammation of the sac-like membrane around the heart (pericarditis) and abnormalities of the heart valves, which control blood flow in the heart. Heart disease caused by fatty buildup in the blood vessels (atherosclerosis), which is very common in the general population, is even more common in people with SLE. The inflammation characteristic of SLE can also damage the nervous system, and may result in abnormal sensation and weakness in the limbs (peripheral neuropathy); seizures; stroke; and difficulty processing, learning, and remembering information (cognitive impairment). Anxiety and depression are also common in SLE.People with SLE have episodes in which the condition gets worse (exacerbations) and other times when it gets better (remissions). Overall, SLE gradually gets worse over time, and damage to the major organs of the body can be life-threatening.

PubMed PMID: 17189288
PubMed PMID: 18063667

rs12150220 - NM_033004.4(NLRP1):c.464T>A (p.Leu155His)

In a study of families with vitiligo-associated multiple autoimmune disease (VAMAS1; 606579), Jin et al. (2007) identified association of a nonsynonymous change in the coding region of the NALP1 gene, leu155 to his (L155H; rs12150220), with susceptibility both to vitiligo alone and to autoimmune and autoinflammatory diseases. The L155H substitution occurs between the N-terminal pyrin and NACHT domains of the NALP1 polypeptide, within a region highly conserved through primate evolution. An association was also identified with another SNP in the promoter region.

PubMed PMID: 17377159

rs916977 - NM_004667.5(HERC2):c.1598+247A>G

In 3 independent genomewide association studies of a total of 1,406 persons and a genomewide linkage study of 1,292 relatives, all from the Netherlands, Kayser et al. (2008) found that the HERC2 variant rs916977 showed a gradient-wise (clinal) allele distribution across 23 European populations that was significantly correlated to iris color variation (227220), with the C allele, associated with blue eyes, being more common in northern Europe and the T allele, associated with brown eyes, more common in southern Europe. Analysis of rs916977 together with the 3 SNPs in intron 1 of the OCA2 gene identified by Duffy et al. (2007) (611409.0013) revealed significant genomewide association for only the HERC2 SNP (P = 3.53 x 10(-18)).

PubMed PMID: 17236130
PubMed PMID: 18252221

rs854560 - NM_000446.7(PON1):c.163T>A (p.Leu55Met)

This polymorphism was originally designated MET54LEU (M54L; Garin et al., 1997) and has also been designated MET55LEU (M55L; e.g., Kao et al., 1998, 2002). It is referred to here as LEU55MET (L55M) because Brophy et al. (2001) noted that leucine is the more frequent amino acid at position 55 (or 54, depending on the numbering system).

Garin et al. (1997) investigated this polymorphism in 408 diabetic patients with or without vascular disease. There were highly significant differences in plasma concentrations and activities of paraoxonase between genotypes defined by the met54-to-leu polymorphism. On the other hand, the arg191 variant (168820.0001) had little impact on paraoxonase concentration. Homozygosity for the leu54 allele was an independent risk factor for cardiovascular disease. A linkage disequilibrium was apparent between the mutations giving rise to leu54 and arg191. Garin et al. (1997) stated that their study underlined the fact that susceptibility to cardiovascular disease correlated with high-activity paraoxonase alleles. The M54L polymorphism appeared to be of central importance to paraoxonase function by virtue of its association with modulated concentrations. Linkage disequilibrium could explain the association between both the leu54 and the arg191 polymorphisms and CVD.

Brophy et al. (2001) presented evidence that the L55M effect of lowered activity is not due primarily to the amino acid change itself but to linkage disequilibrium with the -108 regulatory region polymorphism (168820.0003). The -108C/T polymorphism accounted for 22.8% of the observed variability in PON1 expression levels, which was much greater than that attributable to other PON1 polymorphisms.

Deakin et al. (2002) analyzed glucose metabolism as a function of PON1 polymorphisms in young healthy nondiabetic men from families with premature coronary heart disease (CHD) and matched controls. The L55M PON1 polymorphism was independently associated with the glucose response to an oral glucose tolerance test. LL homozygotes had significantly impaired glucose disposal ($p = 0.0007$) compared with LM and MM genotypes. It was particularly marked for subjects from high CHD risk families and differentiated them from matched controls ($p = 0.049$). The area under the glucose curve ($p = 0.0036$) and the time to peak glucose value ($p = 0.026$) were significantly higher in the LL carriers, whereas the insulin response was slower ($p = 0.013$). The results showed that an association exists between PON1 gene polymorphisms and glucose metabolism. The authors also concluded that the L55M-glucose interaction differentiated offspring of high CHD risk families, suggesting that it may be of particular relevance for vascular disease and possibly other diabetic complications.

Barbieri et al. (2002) investigated association of the M54L polymorphism with the degree of insulin resistance (IR) in 213 healthy subjects by the homeostasis model assessment. The frequency was 0.366 for the LL genotype, 0.469 for the LM genotype, and 0.164 for the MM genotype. Comparing the 3 genotype groups, LL genotype had the more severe degree of IR. Subjects carrying the LL genotype were associated with the IR syndrome picture more than individuals carrying the M allele because they were more overweight and had the highest levels of triglycerides and blood pressure and the lowest values of plasma high density lipoprotein cholesterol. In a multivariate stepwise regression analysis, LL genotype was a significant predictor of IR, independent of age, sex, body mass index, fasting plasma triglycerides, and high density lipoprotein cholesterol. The authors concluded that the presence of LL PON genotype is associated with a more severe degree of IR. Thus, IR might be the possible missing link between the M54L polymorphism and the increased cardiovascular risk.

Kao et al. (1998) investigated the potential significance of these PON1 polymorphisms in the pathogenesis of diabetic retinopathy in IDDM (MVCD5; 612633). They analyzed samples from 80 patients with diabetic retinopathy and 119 controls. The allelic frequency of the leu54 (L) polymorphism was significantly higher in the group with retinopathy than in the group without retinopathy (73% vs 57%, p less than 0.001). Kao et al. (1998) concluded that the genotype L/L was strongly associated with the development of diabetic retinopathy (p less than 0.001), but a similar association was not found with the arg192 polymorphism.

Kao et al. (2002) analyzed the M54L PON1 polymorphism in 372 adolescents with type 1 diabetes (222100) and confirmed increased susceptibility to diabetic retinopathy with the leu/leu genotype (odds ratio, 3.4; p less than 0.0001) independent of age, duration of disease, and cholesterol.

PubMed PMID: 11335891
PubMed PMID: 9011577
PubMed PMID: 11889198
PubMed PMID: 11788650
PubMed PMID: 9661650
PubMed PMID: 11918623

rs1260326 - NM_001486.4(GCKR):c.1337T>C (p.Leu446Pro)

Beer et al. (2009) noted that the 1403C-T transition (rs1260326) in the GCKR gene results in a pro446-to-leu (P446L) substitution at a conserved residue in the glucokinase regulatory protein. Residue 446 lies between 2 motifs thought to be directly involved in binding of phosphate esters.

By genomewide association studies, Orho-Melander et al. (2008) showed that the intronic rs780094 variant of the GCKR gene was associated with higher plasma triglyceride levels (p = 3 x 10(-56)) but lower fasting plasma glucose levels (p = 1 x 10(-13)) (FGQTL5; 613463). Fine-mapping by genotyping and imputing SNPs across the GCKR locus identified a common 1403C-T transition, resulting in a pro446-to-leu (P446L; rs1260326) substitution, as the strongest signal for association with triglycerides. The rs1260326 SNP shows strong linkage disequilibrium (r(2) = 0.93) with rs780094 and has a minor allele frequency of 0.34.

In 4,833 middle-aged French individuals, Vaxillaire et al. (2008) found that the minor T allele of the P446L (rs1260326) SNP was strongly associated with lower fasting glucose levels and fasting insulin levels, and conversely, higher triglyceride levels.

Dupuis et al. (2010) performed metaanalyses of 21 genomewide association studies informative for fasting glucose, fasting insulin, and indices of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) in up to 46,186 nondiabetic participants. Follow-up of 25 loci in up to 76,558 additional subjects identified 16 loci associated with fasting glucose and HOMA-B and 2 loci associated with fasting insulin and HOMA-IR. Dupuis et al. (2010) identified association of elevation of fasting blood glucose (p = 5.6 x 10(-38)) and decreased triglyceride levels (p = 9.6 x 10(-17)) with the C allele of the intronic C-T SNP (rs780094) in the GCKR gene on chromosome 2p23.3-p23.2. This variant was also associated with fasting insulin levels (3.0 x 10(-24)).

In a series of transfection experiments using wildtype and P446L-GKRP, Beer et al. (2009) reported reduced regulation by physiologic concentrations of F6P in the presence of P446L-GKRP, resulting indirectly in increased GCK activity. Assays matched for GKRP activity demonstrated no difference in dose-dependent inhibition of GCK activity or F1P-mediated regulation. Quantitative RT-PCR analysis showed that GCKR is highly expressed relative to GCK in human liver and has very low expression in human pancreatic islets relative to GCK. The authors noted that altered GCK regulation in liver is predicted to enhance glycolytic flux, promoting hepatic glucose metabolism and elevating concentrations of malonyl-CoA (a substrate for de novo lipogenesis). Beer et al. (2009) proposed this as a mutational mechanism for the association of the leu446 allele with raised triglycerides and lower glucose levels.

PubMed PMID: 19643913
PubMed PMID: 18678614
PubMed PMID: 18556336
PubMed PMID: 20081858

rs2228145 - NM_000565.4(IL6R):c.1073A>C (p.Asp358Ala)

In a study using admixture mapping to locate regions of the genome associated with acute-phase inflammatory markers and soluble receptors, Reich et al. (2007) identified a missense SNP, rs8192284, that was significantly associated with circulating levels of IL6SR (614689). This SNP, an A-to-C transversion that results in an asp358-to-ala (D358A) amino acid substitution, is present in approximately 35% of Europeans and 4% of West Africans and accounted for the admixture peak within a 40-kb segment on chromosome 1q21.3. Galicia et al. (2004), who had identified the association of rs8192284 with IL6SR in Japanese, noted that this SNP occurs at the proteolytic cleavage site of IL6R and that consequently, variability could affect the level of the circulating soluble receptor. Reich et al. (2007) also identified an association between this SNP and IL6 (147620) levels (614752) in both European Americans and African Americans. After correction for covariates, there was a 1.09- to 1.13-fold increase in IL6SR levels with 1 copy of the C allele of rs8192284 and a 1.24- to 1.43-fold increase with 2 copies, and there was a 1.06- to 1.15-fold increase in IL6 levels with 1 copy of the C allele and a 1.22- to 1.43-fold increase with 2 copies. Surveying cell lines from several different ethnic groups showed no evidence of an association of surface IL6R with rs8192284, supporting the hypothesis of Galicia et al. (2004) that the mechanism of action of rs8192284 is to affect cleavage efficiency.

PubMed PMID: 15306846
PubMed PMID: 17357077

rs1670533 - NM_001131034.4(RNF212):c.362+1497C>T

In a genomewide scan for variants associated with recombination rate (612042), Kong et al. (2008) identified a SNP in the RNF212 gene, rs1670533, that was strongly associated. The SNP rs1670533 was strongly associated with female recombination rate (p = 1.9 x 10(-12)) and, relative to the TT homozygote, each copy of allele C was estimated to increase recombination rate by 88.2 cM. See also 612041.0001.

PubMed PMID: 18239089

rs6449213 - NM_020041.3(SLC2A9):c.410+4190G>A

In combined analysis of a genomewide association study and 3 replication samples, Doring et al. (2008) found strong association between serum uric acid concentration (UAQTL2; see 612076) and a SNP in intron 4 of the SLC2A9 gene, rs6449213 (P = 1.84 x 10(-47)). For gout, the odds ratio (OR) per risk allele was 0.61 (P = 9.59 x 10(-8)) in an analysis of the initial study German population and one of the replication samples.

Vitart et al. (2008) found association of this SNP with serum uric acid concentration in Croatian (1.98 x 10(-5)) and UK (Orkney) (P = 0.000084) population samples. In a metaanalysis of gout cases and controls from Croatian, German, and UK populations, the T allele of SNP rs6449213 achieved an odds ratio (OR) of 1.34, P = 3.77 x 10(-4). Both Doring et al. (2008) and Vitart et al. (2008) observed a strong SNP allele-by-sex interaction for serum uric acid concentration, such that in women the effects were much more significant than those in men.

PubMed PMID: 18327256
PubMed PMID: 18327257

rs1799864 - NM_001123041.2(CCR2):c.190G>A (p.Val64Ile)

Smith et al. (1997) demonstrated that the rarer 64I allele of a val64-to-ile polymorphism of CCR2 confers relative resistance to infection by HIV-1 (609423).

Mummidi et al. (1998) found that the CCR2-64I allele was associated with a delay in disease progression in African Americans but not in Caucasians.

PubMed PMID: 9252328
PubMed PMID: 9662369

rs5743618 - NM_003263.4(TLR1):c.1805G>T (p.Ser602Ile)

Protection Against Leprosy

Johnson et al. (2007) identified a nonsynonymous SNP in TLR1, 1805T-G (rs5743618), that results in an ile602-to-ser (I602S) substitution at the junction of the transmembrane and intracellular domains of TLR1. They found that 602S was associated with aberrant trafficking of TLR1 to the cell surface and diminished responses of blood monocytes to bacterial agonists. The 602S allele was more frequent in 66 Europeans (75% allele frequency) than in 27 Africans (26%) or in 21 East Asians, all of whom were homozygous for 602I. Johnson et al. (2007) found that the 602S allele was significantly underrepresented in 57 Turkish leprosy patients compared with 90 controls (odds ratio of 0.48). Leprosy patients were more frequently homozygous for 602I, whereas control subjects were more likely to be homozygous for 602S. The results suggested that TLR1 602S plays a protective role in the context of clinical leprosy (see 613223).

Using luciferase reporter analysis, Misch et al. (2008) observed reduced NFKB (see 164011) activity in embryonic kidney cells transfected with the 1805G TLR1 variant following stimulation with extracts of M. leprae compared with cells transfected with the 1805T TLR1 variant. Peripheral blood mononuclear cells from individuals homozygous for 1805G had significantly reduced proinflammatory cytokine responses following stimulation with whole M. leprae or cell wall extracts. In 933 Nepalese leprosy patients, including 238 with the inflammatory reversal reaction, the 1805G allele was associated with protection from reversal reaction (OR of 0.51). Misch et al. (2008) proposed that TLR1 may be associated with a Th1 response and that TLR1 deficiency due to 1805G influences adaptive immunity during leprosy infection and may affect clinical manifestations, such as nerve damage and disability.

Using flow cytometric analysis, Hart and Tapping (2012) demonstrated that monocytes and macrophages from individuals homozygous for 602S were resistant to downregulation of MHC class II, CD64 (see 146760), and IFNG (147570) responses when stimulated with a synthetic TLR1 agonist or mycobacterial membrane components compared with individuals carrying 602I. In addition, macrophages from individuals homozygous for 602S failed to upregulate expression of ARG1 (608313) when challenged with mycobacterial agonists. However, when cells expressing either variant were stimulated with whole mycobacteria, production of TNF and IL6 was similar, as was expression of MHC class II and ARG1. Hart and Tapping (2012) proposed that the TLR1 602S variant protects against mycobacterial disease by preventing soluble mycobacterial products, possibly released from granulomas, from disarming myeloid cells prior to encountering whole mycobacteria.

Association with Neutrophil Priming

Using agonists to TLR2 (603028)/TLR1 or TLR2/TLR6 (605403) heterodimers to stimulate polymorphonuclear leukocytes (PMNs) Whitmore et al. (2016) observed that all donors responded to TLR2/TLR6 priming, whereas only a subset responded to TLR2/TLR1 priming. Genotype analysis revealed that PMN responsiveness to TLR2/TLR1 priming was enhanced by the presence of the 1805G-T SNP in TLR1, which results in a ser602 to ile change. Surface expression of TLR1 was higher in high TLR2/TLR1 primers compared with low primers, and high primers showed an enhanced association of TLR1 with the endoplasmic reticulum chaperone GP96 (HSP90B1; 191175). Neutrophil priming responses in vitro did not differ between 1805GT heterozygotes and 1805TT homozygotes. Whitmore et al. (2016) concluded that the TLR1 1805G-T SNP leads to excessive PMN priming in response to cell stimulation.

Leprosy, also called Hansen disease, is a disorder known since ancient times. It is caused by bacteria called Mycobacterium leprae and is contagious, which means that it can be passed from person to person. It is usually contracted by breathing airborne droplets from affected individuals' coughs and sneezes, or by coming into contact with their nasal fluids. However, it is not highly transmissible, and approximately 95 percent of individuals who are exposed to Mycobacterium leprae never develop leprosy. The infection can be contracted at any age, and signs and symptoms can take anywhere from several months to 20 years to appear.Leprosy affects the skin and the peripheral nerves, which connect the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, and heat. Most affected individuals have areas of skin damage (cutaneous lesions) and problems with nerve function (peripheral neuropathy); however, the severity and extent of the problems vary widely. Leprosy occurs on a spectrum, in which the most severe form is called multibacillary or lepromatous, and the least severe form is called paucibacillary or tuberculoid. Patterns of signs and symptoms intermediate between these forms are sometimes called borderline forms.Multibacillary leprosy usually involves a large number of cutaneous lesions, including both surface damage and lumps under the skin (nodules). The moist tissues that line body openings such as the eyelids and the inside of the nose and mouth (mucous membranes) can also be affected, which can lead to vision loss, destruction of nasal tissue, or impaired speech. Some affected individuals have damage to internal organs and tissues. The nerve damage that occurs in multibacillary leprosy often results in a lack of sensation in the hands and feet. Repeated injuries that go unnoticed and untreated because of this lack of sensation can lead to reabsorption of affected fingers or toes by the body, resulting in the shortening or loss of these digits.Paucibacillary leprosy typically involves a small number of surface lesions on the skin. There is generally loss of sensation in these areas, but the other signs and symptoms that occur in multibacillary leprosy are less likely to develop in this form of the disorder.In any form of leprosy, episodes called reactions can occur, and can lead to further nerve damage. These episodes can include reversal reactions, which involve pain and swelling of the skin lesions and the nerves in the hands and feet. People with the more severe forms of leprosy can develop a type of reaction called erythema nodosum leprosum (ENL). These episodes involve fever and painful skin nodules. In addition, painful, swollen nerves can occur. ENL can also lead to inflammation of the joints, eyes, and the testicles in men.Leprosy has long been stigmatized because of its infectious nature and the disfigurement it can

cause. This stigma can cause social and emotional problems for affected individuals. However, modern treatments can prevent leprosy from getting worse and spreading to other people. While the infection is curable, nerve and tissue damage that occurred before treatment is generally permanent.

PubMed PMID: 17548585
PubMed PMID: 18461142
PubMed PMID: 23105135
PubMed PMID: 26729809

List of Conditions:

- Corneal endothelial dystrophy type 2
- Prostate cancer
- Rheumatoid arthritis

Methods

Extraction

Before sequencing, DNA extraction and library preparation processes were carried-out by automated liquid handling robots. Sequencing was completed using the NovaSeq 6000 instrument (Illumina).

The Nextera DNA Flex (Illumina) library was used during sequencing.

Analysis

Primary and secondary analysis was performed on the Illumina DRAGEN platform. Our secondary analysis extends the GATK 'best practices' pipeline. This includes Variant Quality Score Recalibration

It is important to note that applying a filter will not remove any data from the VCF file; it will just annotate the "FILTER" column. Variants with the "PASS" annotation are considered high quality and may, therefore, be used for advanced downstream analysis.

Sequence data is primarily aligned to the GATK GRCh37 reference genome and mitochondria is aligned to the Revised Cambridge Reference Sequence (NC_012920.1). Additional references may have been requested though tertiary analysis is not conducted on variant calls using references other than GRCh37.

Limitations

Test results are not interpretations. All variants reported in the genes included in the panel are reported.

Rare polymorphisms may lead to false-negative or false-positive results.

Due to limited read length and other contributing technical limitations, repeat expansions (e.g. in the Huntington gene, the SCA-genes, the myotonic dystrophy repeat region, and other similar regions) cannot be assessed with the applied method

Disclaimer

Any preparation and processing of a sample from saliva collection kit to Dante Labs by a customer is assumed to belong to the email used by the customer at the moment of kit registration on the Dante Labs Genome Manager platform before the shipment of the specimen to the laboratory.

The analysis and reporting conducted by Dante Labs are based on information from one or more published third-party scientific and medical studies.

Because of scientific and medical information changes over time, your risk assessment for one or more of the conditions contained within this report may also change over time. For example, opinions differ on the importance and relative weights given to genetic factors. Also, epidemiological data isn't available for some conditions, and this report may not be able to provide definitive information about the severity of a particular condition. We recommend asking your healthcare provider to correctly interpret them. Therefore, this report may not be 100% accurate (e.g., new research could mean different results) and may not predict actual results or outcomes.

This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The US Food and Drug Administration (FDA) has determined that clearance or approval of this method is not necessary and thus neither have been obtained.

Contact

Please contact contact@dantelabs.com for more information on the contents of this report, our analysis methodology, and the limitations of this process.