dante labs

DANTE LABS™ TEST RESULTS

KIT ID: SAMPLE

Hereditary Cancer Test

Introduction

The Hereditary Cancer Test is based on Whole Genome Sequencing Test. As such, it analyzes all Common and Rare Variants associated with Hereditary Cancers instead of a limited set of genes, like old genetic target panels. Hereditary Cancers are a group of several types of cancer caused by a genetic defect that determine a higher-than-normal risk of developing cancer, including hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, Cowden syndrome, and Lynch syndrome. Along with environmental factors, Genetics plays a key role in the regulation of Hereditary Cancers

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

- Leanness
- Congenital heart disease
- Preeclampsia/eclampsia 4
- Unknown
- Hyperglycinuria
- Cancer progression and tumor cell motility
- Carcinoma of colon
- Legius syndrome

dante labs

DANTE LABS™ TEST RESULTS

KIT ID: SAMPLE

Genes/Locations included in report:

AR (3)	FH (2)	AIP (0)	ALK (0)	APC (0)	ATM (0)	ATR (0)
AXL (0)	BCR (0)	BLM (1)	BTK (0)	CBL (0)	ERG (0)	FAS (1)
HGF (0)	JUN (0)	KDR (0)	KEL (0)	KIT (0)	LYN (0)	MAX (0)
MET (0)	MYB (0)	MYC (0)	NBN (0)	NF1 (0)	NF2 (1)	QKI (0)
SMO (0)	SRC (0)	SYK (0)	VHL (1)	WRN (0)	WT1 (0)	XPA (0)
XPC (0)	ABL1 (0)	ABL2 (0)	AKT2 (0)	AKT3 (0)	ARAF (0)	ATK1 (0)
ATRX (0)	BAP1 (0)	BCL2 (0)	BCL6 (0)	BRAF (1)	BRD4 (0)	BTG1 (0)
CBFB (0)	CD70 (0)	CDH1 (1)	CDK4 (0)	CDK6 (0)	CDK8 (0)	CHD2 (0)
CHD4 (0)	CST3 (0)	CTCF (0)	CUL3 (0)	CYLD (1)	DAXX (0)	DDB2 (0)
DDR2 (1)	DKC1 (0)	EGFR (0)	EMSY (0)	ESR1 (1)	ETV1 (0)	ETV4 (0)

ETV6 (0)	ETVS (0)	EXT1 (0)	EZH2 (0)	FAT1 (0)	FGF3 (0)	FGF4 (0)
FGF6 (0)	FLCN (1)	FLT1 (0)	FLT3 (0)	FLT4 (0)	GID4 (0)	GLI1 (0)
GNAQ (0)	GNAS (0)	GPC3 (0)	GRM3 (0)	HRAS (0)	IDH1 (0)	IDH2 (0)
IGF2 (0)	IL7R (0)	IRF2 (0)	IRF4 (0)	IRS2 (0)	JAK1 (0)	JAK2 (3)
JAK3 (0)	KRAS (0)	LMO1 (0)	MCL1 (0)	MDM2 (1)	MDM4 (0)	MEN1 (0)
MITF (0)	MLH1 (0)	MLH3 (0)	MTOR (0)	MYCL (0)	MYCN (0)	NPM1 (0)
NRAS (0)	NSD1 (0)	PAK3 (0)	PAX5 (0)	PKD1 (0)	PMS1 (0)	PMS2 (0)
POLE (0)	POLH (0)	POT1 (0)	PRF1 (0)	PTEN (3)	RAC1 (0)	RAF1 (0)
RARA (0)	RIT1 (0)	ROS1 (0)	RRAS (0)	SBDS (0)	SDHA (1)	SDHB (0)
SDHC (0)	SDHD (0)	SLX4 (0)	SOS1 (0)	SOS2 (0)	SOX2 (0)	SOX9 (1)
SPEN (0)	SPOP (0)	SUFU (0)	TAF1 (0)	TBX3 (0)	TERC (0)	TERT (2)

TET2 (0)	TOP1 (0)	TP53 (1)	TSC1 (0)	TSC2 (0)	TSHR (0)	XPO1 (0)
AMER1 (0)	ARID2 (0)	ASXL1 (0)	AURKA (0)	AURKB (0)	AXIN1 (0)	AXIN2 (0)
BARD1 (1)	BRCA1 (2)	BRCA2 (1)	BRIP1 (1)	BUB1B (0)	CCND1 (0)	CCND2 (0)
CCND3 (0)	CCNE1 (0)	CD274 (0)	CD798 (0)	CD79A (0)	CDC73 (0)	CDK12 (0)
CEBPA (0)	CEP57 (0)	CRLF2 (0)	CSF1R (0)	DDX41 (0)	DOT1L (0)	ELANE (0)
EP300 (4)	EPCAM (0)	EPHA3 (0)	EPHA7 (0)	EPHA5 (0)	EPHB1 (0)	ERBB2 (0)
ERBB3 (0)	ERBB4 (0)	ERCC1 (1)	ERCC2 (0)	ERCC3 (0)	ERCC4 (0)	ERCC5 (0)
FANCA (1)	FANCB (0)	FANCC (0)	FANCE (0)	FANCF (1)	FANCG (0)	FANCI (0)
FANCL (0)	FANCM (0)	FBXW7 (0)	FGF10 (0)	FGF14 (0)	FGF19 (0)	FGF23 (2)
FGFR1 (0)	FGFR2 (0)	FGFR3 (0)	FGFR4 (1)	GATA1 (0)	GATA2 (0)	GATA3 (2)
GATA4 (4)	GATA6 (0)	GNA11 (0)	GNA13 (0)	GREM1 (0)	GSK3B (0)	H3F3A (0)

HNF1A (0)	IGF1R (2)	IKBKE (0)	IKZF1 (0)	INHBA (0)	KDM6A (0)	KDMSC (0)
KEAP1 (0)	KITLG (0)	KLHL6 (0)	KMT2A (0)	KMT2C (0)	KMT2D (0)	LRP18 (0)
LZTR1 (0)	MAGI2 (0)	MED12 (0)	MEF2B (0)	MUTYH (0)	MYCL1 (0)	MYD88 (0)
MYST3 (0)	NSUN2 (0)	NTHL1 (0)	NTRK1 (0)	NTRK2 (0)	NTRK3 (0)	NUP93 (0)
PALB2 (0)	PARK2 (0)	PBRM1 (0)	PLCG2 (0)	POLD1 (0)	PPM1D (0)	PRDM1 (0)
PREX2 (0)	PRKCI (0)	PRKDC (0)	PRSS8 (0)	PTCH1 (0)	RAD50 (0)	RADS1 (0)
RASA2 (0)	RNF43 (0)	RPTOR (0)	RUNX1 (0)	SETD2 (0)	SF381 (0)	SHOC2 (0)
SLIT2 (0)	SMAD2 (0)	SMAD3 (0)	SMAD4 (0)	SOCS1 (0)	SOX10 (0)	SPTA1 (5)
SRP72 (0)	STAG2 (0)	STAT3 (0)	STAT4 (0)	STK11 (0)	TINF2 (0)	TOP2A (0)
U2AF1 (0)	VEGFA (1)	WISP3 (0)	ACVR1B (0)	ARFRP1 (0)	ARID18 (0)	ARID1A (0)
BCL2L1 (0)	BCL2L2 (0)	BCORL1 (0)	BMPR1A (0)	CARD11 (0)	CDKN18 (0)	CDKN1A (0)

CDKN1B (0)	CDKN1C (0)	CDKN28 (0)	CDKN2A (0)	CDKN2C (0)	CTNNA1 (0)	CTNNB1 (0)
DICER1 (1)	DIS3L2 (0)	DNMT3A (0)	ERRFI1 (0)	FAM46C (0)	FANCD2 (0)	GPR124 (0)
GRIN2A (1)	HOXB13 (0)	HSO381 (0)	INPP48 (0)	MAP2K1 (0)	MAP2K2 (0)	MAP2K4 (0)
MAP3K1 (1)	NFE2L2 (0)	NFKBIA (0)	NKX2-1 (1)	NOTCH1 (1)	NOTCH2 (0)	NOTCH3 (0)
PDGFRA (0)	PDGFRB (0)	PHOX2B (0)	PIK3CA (0)	PIK3CB (0)	PIK3CG (0)	PIK3R1 (0)
PIK3R2 (0)	PTPN11 (0)	RAD51C (0)	RAD51D (0)	RANBP2 (3)	RHBDF2 (0)	RICTOR (0)
SAMD9L (0)	SDHAF2 (0)	SNCAIP (0)	SPRED1 (2)	TGFBR2 (0)	ANKRD26 (0)	PIK3C2B (0)
PPP2R1A (0)	PRKAR1A (0)	RUNX1T1 (0)	SMARCA4 (0)	SMARCB1 (0)	TMEM127 (0)	TMPRSS2 (0)
TNFAIP3 (0)	HSP90AA1 (0)	PDCD1LG2 (0)	TNFRSF14 (0)			

Variants Found:

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
FGFR4	chr5:176520243	rs351855	Cancer progression and tumor cell motility	HET	G>A	0.29952	pathogenic	
GATA4	chr8:11606312	rs3735819	Congenital heart disease	HOM	T>C	0.87161	pathogenic	
GATA4	chr8:11617240	rs12458	Congenital heart disease	HET	A>T	0.39996	pathogenic	
SPRED1	chr15:38643574	rs1566876929	Legius syndrome	HOM	T>C		pathogenic	★
BRCA2	chr13:32906729	rs1555281742	Unknown	HET	A>C		pathogenic	★
ERCC1	chr19:45912736	rs3212986	cisplatin response - Toxicity/ADR	HET	C>A	0.29513	drug response	★★★
MAP3K1	5:56177848	rs5868032	46	HOM	TCAA>T		uncertain significance	★
NOTCH1 Rare	chr9:139405133	rs369645726	Adams-Oliver syndrome 5	HET	G>A	0.00016	uncertain significance	★
AR	X:66766356	rs746853821	Androgen resistance syndrome	HET	TGGCGGC>T		uncertain significance	★
AR	X:66766356	rs746853821	Androgen resistance syndrome	HET	TGGCGGC>T		uncertain significance	★
GATA3	10:8096706	rs60098638	Barakat syndrome	HET	T>TAA		uncertain significance	★
GATA3	10:8116241	rs3839918	Barakat syndrome	HOM	G>GA		uncertain significance	★
NKX2-1	14:36986022	rs5807883	Benign hereditary chorea	HOM	C>CA		uncertain significance	★
BLM Rare	chr15:91352442	rs760554566	Bloom syndrome	HET	C>A	0.00001	uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
BRCA1 Rare	17:41256089	rs45489593	Breast-ovarian cancer	HET	AAAAAAAAAGAAAAG>A	0.00024	uncertain significance	
BRCA1	17:41256089	rs45569832	Breast-ovarian cancer	HET	AAAAAAAAAGAAAAG>A		uncertain significance	
JAK2	9:5128080	rs139964957	Budd-Chiari syndrome	HOM	TTGTGTG>T		uncertain significance	★
JAK2	9:5128080	rs139964957	Budd-Chiari syndrome	HOM	TTGTGTG>T		uncertain significance	★
JAK2	9:5128080	rs139964957	Budd-Chiari syndrome	HOM	TTGTGTG>T		uncertain significance	★
SOX9	17:70122505	rs11448561	Camptomelic dysplasia	HOM	CT>C		uncertain significance	★
ESR1	6:152442903	rs71660056	Cerebellar ataxia	HET	CT>C		uncertain significance	★
CYLD	16:50832525	rs74757288	Cylindromatosis	HET	GA>G		uncertain significance	★
SPTA1	1:158580921	rs55832242	Elliptocytosis	HET	G>GCACACACA		uncertain significance	★
SPTA1	1:158637865	rs3039789	Elliptocytosis	HOM	GA>G		uncertain significance	★
SPTA1	1:158637865	rs3039789	Elliptocytosis	HOM	GA>G		uncertain significance	★
SPTA1	1:158637865	rs3039789	Elliptocytosis	HOM	GA>G		uncertain significance	★
SPTA1 Rare	chr1:158648205	rs36058424	Elliptocytosis	HET	T>C	0.0014	uncertain significance	★
GRIN2A	16:9854231	rs35189803	Epilepsy	HET	A>ATTTT		uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
FANCF	11:22644893	rs45554234	Fanconi anemia	HOM	A>AT		uncertain significance	★
IGF1R	15:99501929	rs397772788	Insulin-like growth factor 1 resistance to	HET	GA>G		uncertain significance	★
SPRED1	15:38644442	rs147547509	Legius syndrome	HOM	G>GATAT		uncertain significance	★
TP53	17:7572154	rs200757381	Li-Fraumeni syndrome	HET	GA>G		uncertain significance	★
AR Rare	X:66765158	rs200185441	Malignant tumor of prostate	HOM	TGCAGCA>T	0	uncertain significance	★★
FH	1:241663902	rs144131869	Multiple cutaneous leiomyomas	HET	TGA>T		uncertain significance	★
FH	1:241663902	rs144131869	Multiple cutaneous leiomyomas	HET	TGA>T		uncertain significance	★
BRIP1	17:59757841	rs1555571892	Neoplasm of the breast	HET	C>CTTTCTT		uncertain significance	★★
NF2	22:30092055	rs886057354	Neurofibromatosis	HET	C>CT		uncertain significance	★
BRAF	7:140434597	rs60814637	Noonan syndrome	HOM	G>GA		uncertain significance	★
PTEN	10:89726659	rs5786797	PTEN hamartoma tumor syndrome	HET	GTT>G		uncertain significance	★
PTEN	10:89726659	rs5786797	PTEN hamartoma tumor syndrome	HET	GTT>G		uncertain significance	★
PTEN	10:89726659	rs5786797	PTEN hamartoma tumor syndrome	HET	GTT>G		uncertain significance	★
DICER1	14:95556508	rs35649919	Pleuropulmonary blastoma	HOM	CA>C		uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
EP300	22:41545024	rs747710183	Rubinstein-Taybi syndrome 1	HET	GT>G		uncertain significance	★
EP300	22:41575537	rs60283061	Rubinstein-Taybi syndrome 1	HET	T>TA		uncertain significance	★
EP300	22:41575884	rs59721178	Rubinstein-Taybi syndrome 1	HOM	TCACACACACACACA>T		uncertain significance	★
EP300	22:41575884	rs59721178	Rubinstein-Taybi syndrome 1	HOM	TCACACACACACACA>T		uncertain significance	★
DDR2	1:162750210	rs5778295	Spondyloepimetaphyseal dysplasia	HOM	CTT>C		uncertain significance	★
FLCN	17:17115789	rs397932764	Spontaneous pneumothorax	HET	T>TA		uncertain significance	★
FGF23	12:4479136	rs58735464	Tumoral calcinosis	HOM	CTTTTTT>C		uncertain significance	★
FGF23	12:4479136	rs58735464	Tumoral calcinosis	HOM	CTTTTTT>C		uncertain significance	★
GATA4	chr8:11616338	rs867858	Unknown	HET	A>C	0.36142	uncertain significance	
RANBP2	chr2:109522720	rs260639	Unknown	HOM	G>A	0.67432	uncertain significance	
RANBP2	chr2:109527087	rs260631	Unknown	HOM	G>A	0.66554	uncertain significance	
RANBP2	chr2:109527373	rs260630	Unknown	HOM	A>G	0.92752	uncertain significance	
VHL	3:10193744	rs757106274	Von Hippel-Lindau syndrome	HOM	CA>C		uncertain significance	★
FANCA	16:89883148	rs11275235	not specified	HET	A>AGGCCTTGCGTCGT		uncertain significance	★
MDM2	chr12:69202580	rs2279744	Accelerated tumor formation	HET	T>G	0.36661	risk factor	

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
FAS	chr10:90749256	rs2234767	LUNG CANCER	HET	G>A	0.18411	risk factor	
VEGFA	chr6:43738350	rs2010963	Microvascular complications of diabetes 1	HOM	C>G	0.67392	risk factor	
CDH1	chr16:68771034	rs16260	Prostate cancer	HET	C>A	0.23562	risk factor	
TERT	chr5:1286516	rs2736100	Chronic osteomyelitis	HOM	C>A	0.51538	association	
TERT	chr5:1296486	rs2735940	Chronic osteomyelitis	HOM	A>G	0.47264	association	
GATA4	chr8:11612698	rs804280	Congenital heart disease	HOM	C>A	0.73443	conflicting interpretations of pathogenicity	
IGF1R	15:99503083	rs398028512	Insulin-like growth factor 1 resistance to	HOM	TA>T		conflicting interpretations of pathogenicity	★
BARD1	2:215657182	rs56130510	Neoplasm of the breast	HET	TA>T		conflicting interpretations of pathogenicity	★
SDHA	5:256434	rs372662724	Pheochromocytoma	HET	ACT>A		conflicting interpretations of pathogenicity	★

Individual Variant Interpretations:

rs351855 - NM_213647.3(FGFR4):c.1162G>A (p.Gly388Arg)

Bange et al. (2002) found a relationship between the gly388-to-arg substitution in FGFR4 and cancer progression and tumor cell motility. The arg388 allele was associated with metastasis and poor prognosis in breast cancer and in colon cancer. In a control group of 123 subjects, the frequencies of the gly/gly, gly/arg, and arg/arg genotypes were 45%, 49%, and 6%, respectively.

Ulaganathan et al. (2015) noted that the FGFR4 SNP rs351855 (c.1162G-A, G388R), associated with cancer progression and poor prognosis, was found in the 1000 Genomes Project database at a minor allele frequency of 0.30 and was found in approximately 50% of patients with cancer (Bange et al., 2002). Ulaganathan et al. (2015) showed that substitution of the conserved glycine-388 residue to a charged arginine residue alters the transmembrane-spanning segment and exposes a membrane-proximal cytoplasmic STAT3 (102582)-binding site Y(390)-(P)XXQ(393). Ulaganathan et al. (2015) demonstrated that such membrane-proximal STAT3-binding motifs in the germline of type I membrane receptors enhance STAT3 tyrosine phosphorylation by recruiting STAT3 proteins to the inner cell membrane. Remarkably, such germline variants frequently colocalize with somatic mutations in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. Using Fgfr4 G385R (mouse homolog of human G388R) knockin mice and transgenic mouse models for breast and lung cancers, the authors validated the enhanced STAT3 signaling induced by the FGFR4 G388R variant in vivo. Ulaganathan et al. (2015) concluded that their findings elucidated the molecular mechanism behind the genetic association of rs351855 with accelerated cancer progression and suggested that germline variants of cell surface molecules that recruit STAT3 to the inner cell membrane confer a significant risk for cancer prognosis and disease progression.

PubMed PMID: 11830541
PubMed PMID: 26675719

rs1566734 - NM_002843.4(PTPRJ):c.827A>C (p.Gln276Pro)

In a colon cancer (see 114500), Ruivenkamp et al. (2002) found a gln276-to-pro (Q276P) mutation in exon 5 of the PTPRJ gene. The change was predicted to result in torsional stress.

Lynch syndrome is characterized by an increased risk for colorectal cancer (CRC) and cancers of the endometrium, stomach, ovary, small bowel, hepatobiliary tract, urinary tract, brain, and skin. In individuals with Lynch syndrome the following lifetime risks for cancer are seen: CRC: 52%-82% (mean age at diagnosis 44-61 years). Endometrial cancer in females: 25%-60% (mean age at diagnosis 48-62 years). Gastric cancer: 6%-13% (mean age at diagnosis 56 years). Ovarian cancer: 4%-12% (mean age at diagnosis 42.5 years; ~30% are diagnosed < age 40 years). The risk for other Lynch syndrome-related cancers is lower, though substantially increased over general population rates.

PubMed PMID: 12089527

rs77010315 - NM_181776.3(SLC36A2):c.260G>T (p.Gly87Val)

In 5 families with iminoglycinuria (IG; 242600) or hyperglycinuria (HG; 138500) and 2 with HG only, Broer et al. (2008) screened 5 known imino acid and glycine transporter candidates and identified homozygosity or heterozygosity for a 260G-T transversion in the SLC36A2 gene, resulting in a gly87-to-val (G87V) substitution at a highly conserved residue in the second transmembrane helix in 5 of the pedigrees. Studies in Xenopus oocytes demonstrated that the G87V mutation was partially inactivating, with about 50% of the transport activity of wildtype for both proline and glycine at physiologic concentrations. The reduced transport activity was due to shift of the substrate concentration dependence, resulting in an increased K(m) value; however, maximum transport velocity and surface expression were preserved. Broer et al. (2008) stated that the partial inactivation of SLC36A2 by G87V explained why IG was only observed when homozygosity for G87V was accompanied by haploinsufficiency of the imino acid transporter SLC6A20 (see 605616.0001) or deficiency of the neutral amino acid transporter SLC6A19 (see 608893.0005). Affected individuals homozygous or heterozygous for G87V who were wildtype for SLC6A20 had only HG. Noting that most of these affected individuals also carried mono- or biallelic variants of the putative glycine transporter gene SLC6A18 (610300), Broer et al. (2008) suggested that these variants might also contribute to the phenotype.

PubMed PMID: 19033659

rs5030980 - NM_001138.1(AGRP):c.199G>A (p.Ala67Thr)

Brown et al. (2001) reported a polymorphism in the third exon of the AGRP gene, 199G-A, that resulted in a nonconservative ala67-to-thr (A67T) substitution. Argyropoulos et al. (2002) examined the association of this polymorphism with body mass index, adiposity, and abdominal fat in members of the HERITAGE (HEalth, RIsk factors, exercise Training, And GEnetics) Family Study cohort. Computational analysis of the protein showed significant differences in the coils of the 2 polymorphic isoforms of the protein. Human studies showed no genotype effects in individuals with a mean age of 25 years. However, the G/G genotype was significantly associated with fatness and abdominal adiposity in the parental population with a mean age of 53 years. The authors concluded that the 199G-A polymorphism in AGRP could, therefore, play a role in the development of human obesity (601665) in an age-dependent fashion.

Haploinsufficiency of the type 4 melanocortin receptor (155541) is associated with early-onset obesity, implying that this receptor provides an important tonic inhibition of weight gain. AGRP is an endogenous antagonist of melanocortin signaling. Therefore, Marks et al. (2004) reasoned that loss of AGRP function could lead to the expression of a lean phenotype. They investigated the potential role of AGRP in human weight regulation by examining the association between the A67T AGRP polymorphism and indices of body composition phenotype in 874 subjects of the Quebec family study. In this group they found 8 individuals who were homozygous for the thr67 allele. These 8 had lower weight, body mass index (BMI), fat free mass, fat mass, and leptin (164160) when compared to those carrying at least 1 ala67 allele. Individuals homozygous for the thr67 allele had a BMI that was either at or slightly below an ideal range for their age. Thus, the A67T AGRP polymorphism is associated with lower body weight in humans, with the largest effect being observed on body fat mass. The authors did not observe any difference in the stability or cellular distribution of the mutant protein in a heterologous expression system; thus, the mechanism of this effect required further investigation. It is noteworthy that no homozygotes for thr67 were found in the individuals registered in the San Antonio Family Heart Study (SAFHS).

PubMed PMID: 11602360
PubMed PMID: 12213871
PubMed PMID: 15054840

rs10509305 - NM_152709.5(STOX1):c.1824A>C (p.Glu608Asp)

In 2 preeclamptic Dutch sib pairs (609404), van Dijk et al. (2005) identified a glu608-to-asp (E608D) substitution in exon 3 of the STOX1 gene. The mutation was also found in their mothers, who had a history of pregnancy-induced hypertension (see 189800). One sib pair also carried the Y153H mutation (609397.0001): 1 third-generation daughter carried both mutations and was born of a preeclamptic pregnancy; the other carried neither and was born of a normal pregnancy.

Preeclampsia is a complication of pregnancy in which affected women develop high blood pressure (hypertension); they can also have abnormally high levels of protein in their urine (proteinuria). This condition usually occurs in the last few months of pregnancy and often requires early delivery of the infant. However, this condition can also appear shortly after giving birth (postpartum preeclampsia).Many women with mild preeclampsia do not feel ill, and the condition is often first detected through blood pressure and urine testing in their doctor's office. In addition to hypertension and proteinuria, signs and symptoms of preeclampsia can include excessive swelling (edema) of the face or hands and a weight gain of more than 3 to 5 pounds in a week due to fluid retention. Affected women may also experience headaches, dizziness, irritability, shortness of breath, a decrease in urination, upper abdominal pain, and nausea or vomiting. Vision changes may develop, including flashing lights or spots, increased sensitivity to light (photophobia), blurry vision, or temporary blindness.In many cases, symptoms of preeclampsia go away within a few days after the baby is born. In severe cases, however, preeclampsia can damage the mother's organs, such as the heart, liver, and kidneys, and can lead to life-threatening complications. Extremely high blood pressure in the mother can cause bleeding in the brain (hemorrhagic stroke). The effects of high blood pressure on the brain (hypertensive encephalopathy) may also result in seizures. If seizures occur, the condition is considered to have worsened to eclampsia, which can result in coma. About 1 in 200 women with untreated preeclampsia develop eclampsia. Eclampsia can also develop without any obvious signs of preeclampsia.Between 10 and 20 percent of women with severe preeclampsia develop another potentially life-threatening complication called HELLP syndrome. HELLP stands for hemolysis (premature red blood cell breakdown), elevated liver enzyme levels, and low platelets (cell fragments involved in blood clotting), which are the key features of this condition.Severe preeclampsia can also affect the fetus, with impairment of blood and oxygen flow leading to growth problems or stillbirth. Infants delivered early due to preeclampsia may have complications associated with prematurity, such as breathing problems caused by underdeveloped lungs.Women who have had preeclampsia have approximately twice the lifetime risk of heart disease and stroke than do women in the general population. Researchers suggest that preeclampsia, heart disease, and stroke may share common risk factors. Women who have health conditions such as obesity, hypertension, heart disease, diabetes, or kidney disease before they become pregnant have an increased risk of developing preeclampsia. Preeclampsia is most likely to occur in a woman's first pregnancy, although it can occur in subsequent pregnancies, particularly in women with other health conditions.

PubMed PMID: 15806103

rs10246939 - NM_176817.5(TAS2R38):c.886A>G (p.Ile296Val)

Kim et al. (2003) identified an 886A-G transition in the PTC gene, resulting in an ile296-to-val (I296V) substitution (rs10246939). This polymorphism, in conjunction with other SNPs in the gene, give rise to the ability to taste or not taste phenylthiocarbamide (see 171200).

PubMed PMID: 12595690

rs713598 - NM_176817.5(TAS2R38):c.145G>C (p.Ala49Pro)

Within the PTC gene, Kim et al. (2003) found 3 common polymorphisms that influence the ability to taste phenylthiocarbamide (see 171200). One was a 145G-C transversion, resulting in an ala49-to-pro (A49P) substitution (rs713598).

PubMed PMID: 12595690

rs4879809 - NM_005866.4(SIGMAR1):c.*31A>G

This variant is classified as a variant of unknown significance because its contribution to amyotrophic lateral sclerosis-16 (ALS16; 614373) has not been confirmed.

In 2 sibs, born of consanguineous Pakistani parents, with amyotrophic lateral sclerosis, Ullah et al. (2015) identified a homozygous A-to-G transition in the 3-prime UTR of the SIGMAR1 gene (rs4879809) The variant was not found in 100 healthy ethnically matched controls. Functional studies of the variant were not performed, but the variant was predicted to disturb miRNA binding, which could affect regulation of gene expression. The patients had no signs of dementia. Linkage analysis excluded a pathogenic expanded hexanucleotide repeat in the C9ORF72 gene (614260) in this family.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease involving both upper motor neurons (UMN) and lower motor neurons (LMN). UMN signs include hyperreflexia, extensor plantar response, increased muscle tone, and weakness in a topographic representation. LMN signs include weakness, muscle wasting, hyporeflexia, muscle cramps, and fasciculations. Initial presentation varies. Affected individuals typically present with either asymmetric focal weakness of the extremities (stumbling or poor handgrip) or bulbar findings (dysarthria, dysphagia). Other findings may include muscle fasciculations, muscle cramps, and labile affect, but not necessarily mood. Regardless of initial symptoms, atrophy and weakness eventually affect other muscles. The mean age of onset is 56 years in individuals with no known family history and 46 years in individuals with more than one affected family member (familial ALS or FALS). Average disease duration is about three years, but it can vary significantly. Death usually results from compromise of the respiratory muscles.

PubMed PMID: 26205306

rs4746 - NM_006708.3(GLO1):c.332A>C (p.Glu111Ala)

This variant, formerly titled AUTISM, SUSCEPTIBILITY TO, has been reclassified based on the findings of Rehnstrom et al. (2008) and Wu et al. (2008).

Using a proteomics method to identify abnormal proteins in autopsied brains of patients with autism (209850), Junaid et al. (2004) found an increase in polarity of glyoxalase I by 2-dimensional gel electrophoresis; direct sequencing of the GLO1 gene identified a 419C-A transversion in the gene, resulting in an ala111-to-glu (A111E) substitution. The glu111 enzyme is more acidic than the ala111 enzyme and has reduced functional activity. Four brains were homozygous for A/A (glu111), 3 were heterozygous for A/C (ala111/glu111), and 1 was homozygous for C/C (ala111). Of 9 controls, which included 1 patient with Down syndrome and 3 patients with mental retardation, 2 were A/A, 3 were A/C, and 4 were C/C. In a larger sample of autism patients and controls, the frequency of the 419A allele was 0.6 in autism and 0.4 in controls. Junaid et al. (2004) suggested that a reduction in GLO1 enzyme activity could result in the accumulation of methylglyoxal, which may be toxic to the developing brain. The data suggested that homozygosity for the glu111 allele is a predisposing factor in the development of autism.

Rehnstrom et al. (2008) genotyped 6 polymorphisms in the GLO1 gene, including A111E, in Finnish families with more than 230 individuals with autism spectrum disorders and carried out both linkage and association analyses. They observed no significant linkage or association between any SNP and ASD.

Wu et al. (2008) performed mutation screening of all exons of the GLO1 gene in 272 Han Chinese patients with autism and 310 healthy controls. They found no significant differences in the frequency distributions of A111E between the autism and control groups. Moreover, they did not identify any other mutations associated with autism in the exon regions.

PubMed PMID: 17722011
PubMed PMID: 18721844
PubMed PMID: 15386471

rs11544238 - NM_032496.4(ARHGAP9):c.1108T>G (p.Ser370Ala)

This variant, formerly titled CORONARY ARTERY SPASM 3, SUSCEPTIBILITY TO, has been reclassified because its contribution to the phenotype has not been confirmed.

Takefuji et al. (2010) analyzed 67 missense SNPs in Rho-family GTPases and their regulators in 103 unrelated Japanese individuals with acetylcholine-induced coronary artery spasm and 102 Japanese controls without acetylcholine-induced coronary artery spasm. They found a significant association between coronary artery spasm and a C-A transversion (rs11544238) in the ARHGAP9 gene, resulting in an ala370-to-ser (A370S) substitution in the PH domain (odds ratio, 2.67). Boyden chamber assay demonstrated that the ser370 mutant had a weaker inhibitory effect on cell migration, spreading, and adhesion than wildtype protein. Takefuji et al. (2010) suggested that ARHGAP9 variation has a critical function in the infiltration of hematopoietic cells into the endothelium and inflammation leading to endothelial dysfunction.

PubMed PMID: 19911011

rs6688832 - NM_004285.4(H6PD):c.1358G>A (p.Arg453Gln)

This variant, formerly titled CORTISONE REDUCTASE DEFICIENCY, has been reclassified based on the findings of White (2005), Draper et al. (2006), Smit et al. (2007), and Lavery et al. (2008).

In 2 subjects with cortisone reductase deficiency (see 604931), Draper et al. (2003) found heterozygosity for a double intronic mutation in HSD11B1 (600713.0001) and homozygosity for an arg453-to-gln (R453Q) mutation in H6PD. One of the subjects was an Indo-Asian female who presented with longstanding hirsutism at 44 years of age. The other was a 6-year-old male of Polish descent, who presented with gonadotropin-independent precocious puberty and hyperandrogenism.

Because the phenotype of cortisone reductase deficiency resembles that of polycystic ovary syndrome (PCOS; see 184700), San Millan et al. (2005) investigated the R453Q variant of H6PD and the 83557insA variant of HSD11B1 (see 600713.0001) in 116 patients with PCOS and 76 nonhyperandrogenic controls. Four controls and 5 patients presented 3 of 4 mutant alleles in H6PD R453Q and HSD11B1 83557insA, which is the genotype observed in some subjects with cortisone reductase deficiency. Estimates of 11-beta-HSD oxoreductase activity were measured in 6 of these 9 women, ruling out cortisone reductase deficiency. Patients homozygous for the R453 allele, which was more frequent in PCOS patients, presented with increased cortisol and 17-hydroxyprogesterone levels compared with carriers of Q453 alleles; these differences were not observed in controls. HSD11B1 83557insA genotypes were not associated with PCOS and did not influence any phenotypic variable. San Millan et al. (2005) concluded that digenic triallelic genotypes of the H6PD R453Q variant and HSD11B1 83557insA mutation do not always cause CRD. They also suggested that the H6PD R453Q variant is associated with PCOS and might influence its phenotype by influencing adrenal activity.

In a population-based association study, White (2005) genotyped 3,551 individuals for the 83597T-G polymorphism in intron 3 of the HSD11B1 gene (see 600713.0001) and the R453Q polymorphism in the H6PD gene. Both polymorphisms occurred more frequently than had been reported, with the so-called 'apparent CRD (ACRD) genotypes' (at least 3 of 4 minor alleles present) occurring in 7% of subjects. There were no associations between genotype and body mass index; waist/hip ratio; visceral adiposity; measures of insulin sensitivity; levels of testosterone, FSH, or LH (in females); or risk of PCOS. In addition, there was no genotype effect on urinary free cortisol/cortisone or corticosteroid metabolite ratios, which were measured in 10 subjects, each carrying 0, 3, or 4 minor alleles. White (2005) concluded that previously reported associations of ACRD with HSD11B1 and H6PD alleles represented ascertainment bias, but noted that rare severe mutations in these genes could not be ruled out.

In a case-control study involving 256 nuclear families ascertained from PCOS offspring, 213 singleton cases, and 549 controls, Draper et al. (2006) analyzed CRD-related variants in the HSD11B1 (83597T-G; rs12086634) and H6PD (R453Q; rs6688832) genes but found no differences in genotype distribution between PCOS cases and controls. Draper et al. (2006) concluded that the variants do not influence susceptibility to PCOS.

Smit et al. (2007) analyzed the 83557insA polymorphism in the HSD11B1 gene and the R453Q polymorphism in H6PD in 6,452 elderly Caucasian individuals from 2 population-based cohorts and found no association between genotype distribution or combined genotypes on body mass index, adrenal androgen production, waist-to-hip ratio, systolic and diastolic blood pressure, fasting glucose levels, glucose tolerance test, or incidence of dementia (see 600274). Given the high frequency of the 2 polymorphisms in these 2 Caucasian populations, with 3.8% and 4.0% carrying at least 3 affected alleles, respectively, Smit et al. (2007) concluded that it was very unlikely that these SNPs interact to cause CRD.

Lavery et al. (2008) could not demonstrate an effect of the R453Q variant on enzyme activity, in contrast to the findings of Draper et al. (2003), and noted that reasons for the discrepancy remained to be fully elucidated.

PubMed PMID: 18628520
PubMed PMID: 16091483
PubMed PMID: 16817821
PubMed PMID: 17062770
PubMed PMID: 12858176
PubMed PMID: 15827106

rs1131454 - NM_016816.4(OAS1):c.484G>A (p.Gly162Ser)

This variant, formerly titled DIABETES MELLITUS, TYPE 1, SUSCEPTIBILITY TO, has been reclassified based on a review of the gnomAD database by Hamosh (2018).

Tessier et al. (2006) confirmed the association of type 1 diabetes (222100) with a splicing alteration in OAS1 (164350.0001) but concluded that the closely linked ser162-to-gly (S162G; rs3741981) mutation is more likely responsible for the association. Tessier et al. (2006) described this variant as a C-to-T substitution and gave the frequency of the minor allele (C) as 0.373.

Hamosh (2018) found this variant (GLY162SER) in 155,412 of 275,902 alleles and in 46,108 homozygotes in the combined populations of the gnomAD database, for an allele frequency of 0.5633 (July 3, 2018).

PubMed PMID: 16014697

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

rs2279744 - NM_002392.5(MDM2):c.14+309T>G

By screening 50 healthy volunteers, Bond et al. (2004) identified a SNP in the MDM2 promoter, -410T-G, which they called SNP309 (rs2279744) because of its position at the 309th nucleotide of intron 1. SNP309 was present at a relatively high frequency in both the heterozygous state (T/G, 40%) and the homozygous state (G/G, 12%). Bond et al. (2004) showed that SNP309 increased the affinity of the transcriptional activator Sp1 (189906), resulting in higher levels of MDM2 RNA and protein and the subsequent attenuation of the p53 (191170) pathway. They demonstrated that SNP309 was associated with accelerated tumor formation (614401) in both hereditary and sporadic cancers in humans. Bond et al. (2004) studied 88 individuals who were members of Li-Fraumeni syndrome (LFS1; 151623) families and had germline mutations in 1 allele of p53. The frequency of SNP309 in these individuals was similar to that found in the 50 normal volunteers. Of the 88 individuals in the Li-Fraumeni cohort, 66 were diagnosed with at least 1 cancer at a median age of 22 years old. Those either heterozygous or homozygous for SNP309 developed tumors on average 7 years earlier than those lacking SNP309. To determine whether SNP309 acted upon sporadic tumors as well as genetically altered individuals with a p53 defect, Bond et al. (2004) studied a group of patients who developed sporadic adult soft tissue sarcomas and had no known hereditary cancer predisposition and no known germline p53 mutation. Individuals homozygous for SNP309 were diagnosed on average 12 years earlier than those without SNP309, and the frequency of the SNP309 G allele was greatly increased in those who developed soft tissue sarcomas at a young age. These data demonstrated that SNP309 does not require the presence of an inactivating germline p53 mutation to associate with earlier soft tissue sarcoma formation.

Bougeard et al. (2006) studied the effect of the SNP309 polymorphism and the arg72-to-pro polymorphism of the p53 gene (191170.0005) on cancer risk in 61 French carriers of the p53 germline mutation. The mean age of tumor onset in MDM2 SNP309 G allele carriers (19.6 years) was significantly different from that observed in patients homozygous for the T allele (29.9 years, p less than 0.05). For the p53 codon 72 polymorphism, the mean age of tumor onset in arg allele carriers (21.8 years) was also different from that of pro/pro patients (34.4 years, p less than 0.05). Bougeard et al. (2006) also observed a cumulative effect of both polymorphisms because the mean ages of tumor onset in carriers of MDM2 G and p53 arg alleles (16.9 years) and those with the MDM2 T/T and p53 pro/pro genotypes (43 years) were clearly different (p less than 0.02). Therefore, the results confirmed the impact of the MDM2 SNP309 G allele on the age of tumor onset in germline p53 mutation carriers, and suggested that this effect may be amplified by the p53 arg72 allele. Polymorphisms affecting p53 degradation therefore represent one of the few examples of modifier genetic factors identified to that time in mendelian predispositions to cancer.

Using 14 different SNPs across the MDM2 gene from Caucasian, African American, and Ashkenazi Jewish population samples, Atwal et al. (2007) characterized the haplotype structure of the MDM2 gene. They found reduced variability of the deleterious SNP309 G allele haplotype and multiple common SNP309 T alleles in all 3 populations. These data suggested that the G allele haplotype underwent recent positive selection.

In 25 Dutch and 11 Finnish p53 mutation carriers, Ruijs et al. (2007) observed a significantly earlier age of tumor onset in SNP309 G allele carriers versus those homozygous for the T allele (mean difference, 16 years earlier; p = 0.005), confirming previously reported results. In 72 Dutch p53-negative LFS and LFS-related patients, no difference was seen in the age of tumor onset, but there was a significantly higher percentage of SNP309 G/G homozygotes than in the general population (p = 0.02). Ruijs et al. (2007) suggested that the MDM2 SNP309 G allele contributes to cancer susceptibility in LFS and LFS-related families.

Smoking-Related Accelerated Decline in Lung Function

In a study of 863 individuals with European grandparents from an unselected New Zealand birth cohort, Hancox et al. (2009) analyzed lung function (FEV1 and FEV1/FVC) between ages 18 and 32 in relation to cumulative history of cigarette smoking and the rs2279244 SNP, and found that the G allele was associated with accelerated smoking-related decline in lung function (608852) (FEV1, p = 0.004).

PMID: 15550242
PMID: 16258005
PMID: 17360557
PMID: 17003841
PMID: 19521721

rs8042919 - NM_017672.6(TRPM7):c.4445C>T (p.Thr1482Ile)

Hermosura et al. (2005) reported a heterozygous C-to-T transition in the TRPM7 gene, resulting in a thr1482-to-ile (T1482I; rs8042919) substitution, in 5 of 22 patients with ALS-Parkinsonism/dementia complex of Guam (105500). The T1482I variant was not identified in 23 control Chamorro individuals. Threonine-1482 is a highly conserved residue that lies between the channel and kinase domains of the protein and is predicted to be a potential substrate for autophosphorylation. In vitro functional expression studies showed that mutant channels were functional but showed increased susceptibility to inhibition by intracellular magnesium concentrations compared to wildtype channels. Noting that the neurodegenerative disorders on Guam had been related to an environment deficient in calcium and magnesium, Hermosura et al. (2005) suggested that the T1482I variant in the TRPM7 gene may confer susceptibility to disease development.

Hara et al. (2010) did not find an association between the TRPM7 T1482I variant and disease in affected members from a large extended family with ALS-PDC from the Kii peninsula of Japan. The frequency of the T1482I variant in the family was similar to that observed in controls.

PubMed PMID: 16051700
PubMed PMID: 19405049

rs324981 - NM_207172.2(NPSR1):c.320A>T (p.Asn107Ile)

Laitinen et al. (2004) found a coding polymorphism SNP591694 (rs324981) in the GPRA gene in which asparagine-107 in the first exoloop lining the putative ligand-binding pocket is replaced by isoleucine (N107I). This SNP occurs within the 133-kb asthma susceptibility region that spans introns 2 to 5 of GPRA (see 608584).

PubMed PMID: 15073379

rs569108 - NM_000139.5(MS4A2):c.710A>G (p.Glu237Gly)

Hill and Cookson (1996) found this exon 7 E237G polymorphism in 53 of 1004 Australian subjects studied (5.3%). E237G subjects had elevated reactions to a number of common measures of atopy and bronchial hyperresponsiveness. The investigators also found that the relative risk for E237G individuals having asthma compared to those without the allele was 2.3.

Shirakawa et al. (1996) reported that the gly237 form of the IgE Fc receptor was associated with atopic asthma (odds ratio = 3.00, chi-square = 5.10, p less than 0.03) and with elevated serum IgE levels (odds ratio = 8.56) in the Japanese population. This association was particularly noted in childhood asthma (odds ratio = 3.92, chi-square = 8.66, p less than 0.005).

Among 333 Japanese subjects, including 233 with nasal allergy and 100 controls, Nagata et al. (2001) observed a significant relationship between gly237 and elevated levels of serum total IgE and very high IgE. The findings suggested that the glu237-to-gly variant of the FCER1B gene is involved in the development of nasal allergy through the process for the production of both specific and nonspecific IgE antibodies.

PubMed PMID: 8817330
PubMed PMID: 8842731
PubMed PMID: 11702205

rs1801275 - NM_000418.4(IL4R):c.1727A>G (p.Gln576Arg)

Hershey et al. (1997) described a polymorphism of the IL4A gene that occurred with increased frequency in patients with allergic inflammatory disorders. The variant allele consisted of an A-to-G transition at nucleotide 1902, causing a change from glutamine to arginine at codon 576 (Q576R) in the cytoplasmic domain of the interleukin-4 receptor alpha protein. The R576 allele was found in 3 of 3 patients with the hyper-IgE syndrome (147060) and in 4 of 7 patients with severe atopic dermatitis. Among 50 prospectively recruited adults, it was found in 13 of 20 subjects with atopy (147050) and in 5 of 30 without atopy; the relative risk of atopy among those with a mutant allele was 9.3. The R576 allele was associated with higher levels of expression of CD23 (151445) by interleukin-4 than was the wildtype allele. This enhanced signaling was associated with a change in the binding specificity of the adjacent tyrosine residue at position 575 to signal-transducing molecules.

Deichmann et al. (1998) confirmed the association of IL4R alleles with atopy. However, in a subsequent association study of individuals aged 6 to 22 years from 109 nuclear families (Kruse et al., 1999), they found significantly reduced total IgE concentrations in individuals with the minor R576 allele of the Q576R polymorphism in IL4R, a direct contrast to the findings of Hershey et al. (1997). Kruse et al. (1999) also found that Q576R is in direct linkage disequilibrium with another polymorphism, S503P (147781.0003), with 76% of R576 carriers also carrying P503, and 95% of P503 carriers also carrying R576. The P503 allele was also associated with significantly reduced IgE levels, and the most significant result occurred with carriers of both P503 and R576 ($p = 0.0008$). R576 and P503 were not associated with specific sensitization to common inhalant allergens. Functional studies suggested that the S503P and Q576R polymorphisms independently reduce STAT6 (601512) binding and STAT6 phosphorylation, leading to reduced total IgE levels. In addition, the occurrence of both polymorphisms together, but not alone, increases IRS (see 147545) phosphorylation, leading to an even greater reduction in total IgE levels.

Grimbacher et al. (1998) investigated the frequency of Q576R in 25 control subjects and 20 unrelated patients with the hyper-IgE syndrome who were followed at the National Institutes of Health Clinical Center. Only 4 of the 20 patients had the Q576R mutation (allelic frequency, 10%), which was not significantly different from the frequency of 12% (6 of 25) in the control subjects.

Patuzzo et al. (2000) could find no evidence of linkage or association of atopic asthma with this mutation in 851 Italian subjects with atopic asthma.

Tang et al. (2004) screened affected members of a 3-generation family with diffuse cutaneous mastocytosis (MASTC; 154800) due to mutation in the KIT gene (164920) for the Q576R variant in IL4R. Q576R was present in 2 of the 5 affected individuals in this family; however, there was no clear difference in disease severity between those with and those without Q576R, and the only individual with known systemic disease did not carry the polymorphism.

Franjkovic et al. (2005) found that transfection of mouse B-cell lines with human IL4R containing both the I75V (147781.0002) and Q576R variants did not result in enhanced IL4-induced CD23 expression compared with cell lines expressing wildtype IL4R. Analysis of 6 common IL4R coding SNPs, including I75V, Q576R, and S503P, and common haplotypes in 300 blood donors failed to show a significant association with elevated serum IgE level. Moreover, analysis of the 3 most informative coding SNPs and related 2- and 3-point haplotypes in a second group of 689 blood donors failed to detect a significant association with elevated serum IgE. Franjkovic et al. (2005) concluded that common coding SNPs in IL4R are unlikely to contribute significantly to elevated IgE levels.

PubMed PMID: 9392697
PubMed PMID: 10233717
PubMed PMID: 9515586
PubMed PMID: 9537881
PubMed PMID: 10905893
PubMed PMID: 15173254
PubMed PMID: 15712015

rs861539 - NM_005432.4(XRCC3):c.722C>T (p.Thr241Met)

Winsey et al. (2000) found an association between a T allele at nucleotide 18067 in exon 7 of the XRCC3 gene and susceptibility to cutaneous malignant melanoma (613972). The 18067C-T transition was predicted to cause a thr-to-met substitution in the XRCC3 protein.

PubMed PMID: 11059748

rs4402960 - NM_006548.6(IGF2BP2):c.239+29254C>A

In genomewide association studies of type 2 diabetes (125853), the Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research (2007), Zeggini et al. (2007), and Scott et al. (2007) found that the T allele of rs4402960 confers increased susceptibility to type 2 diabetes. Combined analyses obtained a P value of 8.9 x 10(-16).

Type 2 diabetes is a disorder characterized by abnormally high blood sugar levels. In this form of diabetes, the body stops using and making insulin properly. Insulin is a hormone produced in the pancreas that helps regulate blood sugar levels. Specifically, insulin controls how much glucose (a type of sugar) is passed from the blood into cells, where it is used as an energy source. When blood sugar levels are high (such as after a meal), the pancreas releases insulin to move the excess glucose into cells, which reduces the amount of glucose in the blood.Most people who develop type 2 diabetes first have insulin resistance, a condition in which the body's cells use insulin less efficiently than normal. As insulin resistance develops, more and more insulin is needed to keep blood sugar levels in the normal range. To keep up with the increasing need, insulin-producing cells in the pancreas (called beta cells) make larger amounts of insulin. Over time, the beta cells become less able to respond to blood sugar changes, leading to an insulin shortage that prevents the body from reducing blood sugar levels effectively. Most people have some insulin resistance as they age, but inadequate exercise and excessive weight gain make it worse, greatly increasing the likelihood of developing type 2 diabetes.Type 2 diabetes can occur at any age, but it most commonly begins in middle age or later. Signs and symptoms develop slowly over years. They include frequent urination (polyuria), excessive thirst (polydipsia), fatigue, blurred vision, tingling or loss of feeling in the hands and feet (diabetic neuropathy), sores that do not heal well, and weight loss. If blood sugar levels are not controlled through medication or diet, type 2 diabetes can cause long-lasting (chronic) health problems including heart disease and stroke; nerve damage; and damage to the kidneys, eyes, and other parts of the body.

PubMed PMID: 17463246
PubMed PMID: 17463248
PubMed PMID: 17463249

rs1048661 - NM_005576.4(LOXL1):c.422G>T (p.Arg141Leu)

Thorleifsson et al. (2007) found that a SNP in exon 1 of the LOXL1 gene, rs1048661, which corresponds to an arg-to-leu substitution at codon 141 (R141L), is associated with risk of developing exfoliation syndrome (XFS; 177650), resulting in glaucoma. The risk allele of this SNP, G, showed strong individual association in combined case-control samples from Iceland and Sweden (OR = 2.46, P = 2.3 x 10(-12)). The rs1048661 SNP was in strong linkage disequilibrium with another SNP in exon 1, rs3825942 (153456.0002). In samples of adipose tissue with genotype data for these 2 SNPs, LOXL1 expression was reduced by an estimated 7.7% with each copy carried of the G allele of rs1048661 (P = 8.3 x 10(-7)).

In a Caucasian Australian population-based cohort of 2,508 individuals, 86 (3.4%) of whom were diagnosed with pseudoexfoliation syndrome, Hewitt et al. (2008) confirmed that 2 previously identified nonsynonymous variants in exon 1 of LOXL1, R141L and G153D (153456.0002), were strongly associated with pseudoexfoliation: 2 copies of the high-risk haplotype at these SNPs conferred a risk of 7.20 (95% CI, 3.04 to 20.75) compared to no copies of the high-risk haplotype.

Lemmela et al. (2009) analyzed rs1048661 as well as 2 other LOXL1 SNPS, rs3825942 and rs2165241 (153456.0003), in a case-control study of 59 Finnish patients with XFS and 82 with exfoliation glaucoma (XFG) and a family study of 28 patients with XFS or XFG and 92 unaffected relatives from an extended Finnish family. They found significant association in both studies with the risk (G) allele of rs1048661 (p = 2.65 x 10(-5) and 0.0007, respectively). The corresponding 3-locus haplotype GGT increased the risk of XFS/XFG nearly 15-fold relative to the low-risk GAC haplotype (p = 1.6 x 10(-16)).

PubMed PMID: 17690259
PubMed PMID: 18037624
PubMed PMID: 19343041

rs2229207 - NM_207585.2(IFNAR2):c.23T>C (p.Phe8Ser)

Frodsham et al. (2006) found that SNPs in the IFNAR2 and IL10RB (123889) genes resulting in phe8-to-ser (F8S) and lys47-to-glu (K47E; 123889.0001) changes, respectively, were associated, both independently and as a haplotype, with a higher risk of hepatitis B virus (HBV; see 610424) persistence. In both cases, the more common variant (F8 and K47, respectively) was associated with HBV persistence.

PubMed PMID: 16757563

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

rs2073711 - NM_003613.4(CILP):c.1184T>C (p.Ile395Thr)

Through genotyping 30 sequence variants in 20 candidate genes in 188 individuals with lumbar disc disease (see 603932) and 376 controls, Seki et al. (2005) identified a functional SNP in the CILP gene, 1184T-C, resulting in the amino acid change ile395 to thr (I395T), that was significantly associated with the phenotype. They confirmed the association in an additional 279 cases and 278 controls. The susceptibility-associated 1184C allele showed increased binding and inhibition of TGFB1 (190180).

PubMed PMID: 15864306

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

rs5174 - NM_004631.5(LRP8):c.2855G>A (p.Arg952Gln)

Shen et al. (2007) identified association of an arg952-to-gln (R952Q) missense change in LRP8 with susceptibility to premature coronary artery disease and/or myocardial infarction (MCI1; 608446). Transfection assays showed that the R952Q variant of LRP8 increased activation of p38 mitogen-activated protein kinase (600289) by oxidized low density lipoprotein.

PubMed PMID: 17847002

rs288326 - NM_001463.4(FRZB):c.598C>T (p.Arg200Trp)

By linkage and association studies, Loughlin et al. (2004) identified a haplotype in the FRZB gene, defined by arg200-to-trp (R200W; 605083.0001) and arg324-to-gly (R324G) (rs288326) substitutions, as a strong risk factor for primary osteoarthritis of the hip in females (see OS1, 165720) (OR = 4.1, p = 0.004).

PubMed PMID: 15210948

rs1341667 - NM_152709.5(STOX1):c.457T>C (p.Tyr153His)

In 23 preeclamptic Dutch sib pairs (609404), van Dijk et al. (2005) identified a tyr153-to-his (Y153H) substitution in exon 2 of the STOX1 gene. The substitution arose from a 458T-C transition. The authors traced informative nucleotide variations across 3 generations in 6 of the 23 families and found that the mutation on the maternal allele in the second generation was transmitted to 13 children in the third generation who were born from preeclamptic pregnancies, whereas the 2 children who were born of normal pregnancies did not carry the mutated maternal allele.

Iglesias-Platas et al. (2007) observed a high frequency of the CC genotype of the Y153H variation in uncomplicated pregnancies, which led them to conclude that this allele cannot be considered a mutation predisposing to preeclampsia.

Preeclampsia is a complication of pregnancy in which affected women develop high blood pressure (hypertension); they can also have abnormally high levels of protein in their urine (proteinuria). This condition usually occurs in the last few months of pregnancy and often requires early delivery of the infant. However, this condition can also appear shortly after giving birth (postpartum preeclampsia).Many women with mild preeclampsia do not feel ill, and the condition is often first detected through blood pressure and urine testing in their doctor's office. In addition to hypertension and proteinuria, signs and symptoms of preeclampsia can include excessive swelling (edema) of the face or hands and a weight gain of more than 3 to 5 pounds in a week due to fluid retention. Affected women may also experience headaches, dizziness, irritability, shortness of breath, a decrease in urination, upper abdominal pain, and nausea or vomiting. Vision changes may develop, including flashing lights or spots, increased sensitivity to light (photophobia), blurry vision, or temporary blindness.In many cases, symptoms of preeclampsia go away within a few days after the baby is born. In severe cases, however, preeclampsia can damage the mother's organs, such as the heart, liver, and kidneys, and can lead to life-threatening complications. Extremely high blood pressure in the mother can cause bleeding in the brain (hemorrhagic stroke). The effects of high blood pressure on the brain (hypertensive encephalopathy) may also result in seizures. If seizures occur, the condition is considered to have worsened to eclampsia, which can result in coma. About 1 in 200 women with untreated preeclampsia develop eclampsia. Eclampsia can also develop without any obvious signs of preeclampsia.Between 10 and 20 percent of women with severe preeclampsia develop another potentially life-threatening complication called HELLP syndrome. HELLP stands for hemolysis (premature red blood cell breakdown), elevated liver enzyme levels, and low platelets (cell fragments involved in blood clotting), which are the key features of this condition.Severe preeclampsia can also affect the fetus, with impairment of blood and oxygen flow leading to growth problems or stillbirth. Infants delivered early due to preeclampsia may have complications associated with prematurity, such as breathing problems caused by underdeveloped lungs.Women who have had preeclampsia have approximately twice the lifetime risk of heart disease and stroke than do women in the general population. Researchers suggest that preeclampsia, heart disease, and stroke may share common risk factors. Women who have health conditions such as obesity, hypertension, heart disease, diabetes, or kidney disease before they become pregnant have an increased risk of developing preeclampsia. Preeclampsia is most likely to occur in a woman's first pregnancy, although it can occur in subsequent pregnancies, particularly in women with other health conditions.

PubMed PMID: 15806103
PubMed PMID: 17325670

rs16260 - NM_004360.4(CDH1):c.-124-161C>A

Jonsson et al. (2004) genotyped 1,036 patients with sporadic familial (2 close relatives) or hereditary (3 or more close relatives) prostate cancer (176807) and 669 controls for the -160C/A promoter polymorphism (rs16260). The risk of hereditary prostate cancer was increased among CA carriers (odds ratio = 1.7) and AA carriers (odds ratio = 2.6) compared to controls; genotype frequencies did not differ between sporadic or familial cases and controls. Jonsson et al. (2004) concluded that CDH1 is a low-penetrant prostate cancer susceptibility gene that might explain a proportion of familial and particularly hereditary prostate cancer.

In an independent replication study population consisting of 612 patients with sporadic prostate cancer and 211 patients with at least 2 relatives with prostate cancer in a nuclear family (so-called 'FH+' cases) and 540 controls, Lindstrom et al. (2005) found strong evidence of an association between the -160C-A promoter polymorphism and risk of prostate cancer (p = 0.003) when comparing FH+ cases and controls. In the total study population, CA and AA carriers had an increased risk compared to CC carriers (odds ratio = 1.5 and 2.6, respectively). No significant difference in genotype frequency was observed between sporadic cases and controls.

PubMed PMID: 14961571
PubMed PMID: 16189707

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

rs11276 - NM_021071.4(ART4):c.793G>A (p.Asp265Asn)

To determine if ART4 polymorphisms correlate with Do blood group (616060) antigenicity, Gubin et al. (2000) studied 8 blood donors of defined serology, i.e., 4 Do(a+b-) and 4 Do(a-b+), and sequenced the coding region of ART4. Three SNP sites were identified. While 2 SNPs did not alter the predicted amino acid primary structure, the third predicted a change in the protein sequence, asn265 to asp (N265D). This SNP fell within an RGD adhesion motif of the molecule. All 3 SNP sites were consistent among the 8 donors, with N265 found in the 4 Do(a+b-) samples, and D265 found the 4 Do(a-b+) samples.

PubMed PMID: 11001920

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

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

rs698 - NM_000669.5(ADH1C):c.1048A>G (p.Ile350Val)

The ILE349VAL variant has been designated as I350V based on numbering which includes the translation initiation codon (Edenberg, 2007).

Hoog et al. (1986) found 2 amino acid differences between the gamma-1 and gamma-2 alleles: an arg271-to-gln (R271Q; 103730.0001) substitution in exon 6 and an ile349-to-val (rs698) substitution in exon 8 of the ADH1C gene. They determined that the R272Q substitution was responsible for the differences in enzymatic properties, whereas the I350V substitution had no special importance. The location of R272Q appeared important for total charge and catalytic properties, as well as NADH coenzyme interaction.

The gamma-1 allele, now known as ADH1C*1, was originally defined as a gamma subunit that has arg272 and ile350 (Hoog et al., 1986). In almost all cases, these 2 SNPs are in linkage disequilibrium with one another. The gamma-2 allele, now known as ADH1C*2, has gln272 and val350. Homozygosity for the ADH1C*1 allele has a 70% higher turnover rate than homozygosity for ADH1C*2 allele (Edenberg, 2007).

Xu et al. (1988) used the I350V substitution to distinguish ADH1C*1 from ADH1C*2 by means of allele-specific oligonucleotide probes.

Osier et al. (1999) showed that I350V substitution is in linkage disequilibrium with the ADH1B arg48-to-his (R48H; 103720.0001) substitution, and identified the R48H variant as being responsible for differences in ethanol metabolism and alcoholism (103780) among Taiwanese, with the I350V variant showing association only because of linkage disequilibrium.

Chai et al. (2005) examined ADH1B, ADH1C, and ALDH2 polymorphisms in 72 alcoholic and 38 nonalcoholic healthy Korean men; 48 patients had type I alcoholism, and 24 had type II alcoholism. The frequency of ADH1B*1 (103720.0001) and ADH1C*2 alleles was significantly higher in men with type II alcoholism (103780) than in men with type I alcoholism and in healthy men. The frequency of the ALDH2*1 (100650.0001) allele was significantly higher in men with alcohol dependence than in healthy men. Chai et al. (2005) suggested that the genetic characteristics of alcohol metabolism in type I alcoholism fall between nonalcoholism and type II alcoholism.

Among 9,080 Caucasian Danish men and women using the Michigan Alcohol Screening Test, Tolstrup et al. (2008) found that men heterozygous or homozygous for the slower metabolizing ADH1C*2 allele had a 40 to 70% higher risk for heavy or excessive alcohol intake compared to those homozygous for the fast metabolizing ADH1C*1 allele. Similar results were found for women, but effect sizes were smaller and reached significance only for heavy drinking.

Alcohol use disorder is a diagnosis made when an individual has severe problems related to drinking alcohol. Alcohol use disorder can cause major health, social, and economic problems, and can endanger affected individuals and others through behaviors prompted by impaired decision-making and lowered inhibitions, such as aggression, unprotected sex, or driving while intoxicated.Alcohol use disorder is a broad diagnosis that encompasses several commonly used terms describing problems with drinking. It includes alcoholism, also called alcohol addiction, which is a long-lasting (chronic) condition characterized by a powerful, compulsive urge to drink alcohol and the inability to stop drinking after starting. In addition to alcoholism, alcohol use disorder includes alcohol abuse, which involves problem drinking without addiction.Habitual excessive use of alcohol changes the chemistry of the brain and leads to tolerance, which means that over time the amount of alcohol ingested needs to be increased to achieve the same effect. Long-term excessive use of alcohol may also produce dependence, which means that when people stop drinking, they have physical and psychological symptoms of withdrawal, such as sleep problems, irritability, jumpiness, shakiness, restlessness, headache, nausea, sweating, anxiety, and depression. In severe cases, agitation, fever, seizures, and hallucinations can occur; this pattern of severe withdrawal symptoms is called delirium tremens.The heavy drinking that often occurs in alcohol use disorder, and can also occur in short-term episodes called binge drinking, can lead to a life-threatening overdose known as alcohol poisoning. Alcohol poisoning occurs when a large quantity of alcohol consumed over a short time causes problems with breathing, heart rate, body temperature, and the gag reflex. Signs and symptoms can include vomiting, choking, confusion, slow or irregular breathing, pale or blue-tinged skin, seizures, a low body temperature, a toxic buildup of substances called ketones in the blood (alcoholic ketoacidosis), and passing out (unconsciousness). Coma, brain damage, and death can occur if alcohol poisoning is not treated immediately.Chronic heavy alcohol use can also cause long-term problems affecting many organs and systems of the body. These health problems include irreversible liver disease (cirrhosis), inflammation of the pancreas (pancreatitis), brain dysfunction (encephalopathy), nerve damage (neuropathy), high blood pressure (hypertension), stroke, weakening of the heart muscle (cardiomyopathy), irregular heartbeats (arrhythmia), and immune system problems. Long-term overuse of alcohol also increases the risk of certain cancers, including cancers of the mouth, throat, esophagus, liver, and breast. Alcohol use in pregnant women can cause birth defects and fetal alcohol syndrome, which can lead to lifelong physical and behavioral problems in the affected child.

PMID: 17718394
PMID: 3758060
PMID: 3397059
PMID: 10090900
PMID: 15863807
PMID: 17923853

rs1693482 - NM_000669.5(ADH1C):c.815G>A (p.Arg272Gln)

The ARG271GLN variant has been designated as R272Q based on numbering which includes the translation initiation codon (Edenberg, 2007).

Hoog et al. (1986) found 2 amino acid differences between the gamma-1 and gamma-2 alleles: an arg272-to-gln (rs1693482) substitution in exon 6 and an ile350-to-val (I350V; 103730.0002) substitution in exon 8 of the ADH1C gene. They determined that the R272Q substitution was responsible for the differences in enzymatic properties, whereas the I350V substitution had no special importance. The location of R272Q appeared important for total charge and catalytic properties, as well as NADH coenzyme interaction.

The gamma-1 allele, now known as ADH1C*1, was originally defined as a gamma subunit that has arg272 and ile350 (Hoog et al., 1986). In almost all cases, these 2 SNPs are in linkage disequilibrium with one another. The gamma-2 allele, now known as ADH1C*2, has gln272 and val350. Homozygosity for the ADH1C*1 allele has a 70% higher turnover rate than homozygosity for ADH1C*2 allele (Edenberg, 2007).

Chai et al. (2005) examined ADH1B, ADH1C, and ALDH2 polymorphisms in 72 alcoholic and 38 nonalcoholic healthy Korean men; 48 patients had type I alcoholism, and 24 had type II alcoholism. The frequency of ADH1B*1 (103720.0001) and ADH1C*2 alleles was significantly higher in men with type II alcoholism than in men with type I alcoholism and in healthy men. The frequency of the ALDH2*1 (100650.0001) allele was significantly higher in men with alcohol dependence (103780) than in healthy men. Chai et al. (2005) suggested that the genetic characteristics of alcohol metabolism in type I alcoholism fall between nonalcoholism and type II alcoholism.

Among 9,080 Caucasian Danish men and women using the Michigan Alcohol Screening Test, Tolstrup et al. (2008) found that men heterozygous or homozygous for the slower metabolizing ADH1C*2 allele had a 40 to 70% higher risk for heavy or excessive alcohol intake compared to those homozygous for the fast metabolizing ADH1C*1 allele. Similar results were found for women, but effect sizes were smaller and reached significance only for heavy drinking.

Alcohol use disorder is a diagnosis made when an individual has severe problems related to drinking alcohol. Alcohol use disorder can cause major health, social, and economic problems, and can endanger affected individuals and others through behaviors prompted by impaired decision-making and lowered inhibitions, such as aggression, unprotected sex, or driving while intoxicated.Alcohol use disorder is a broad diagnosis that encompasses several commonly used terms describing problems with drinking. It includes alcoholism, also called alcohol addiction, which is a long-lasting (chronic) condition characterized by a powerful, compulsive urge to drink alcohol and the inability to stop drinking after starting. In addition to alcoholism, alcohol use disorder includes alcohol abuse, which involves problem drinking without addiction.Habitual excessive use of alcohol changes the chemistry of the brain and leads to tolerance, which means that over time the amount of alcohol ingested needs to be increased to achieve the same effect. Long-term excessive use of alcohol may also produce dependence, which means that when people stop drinking, they have physical and psychological symptoms of withdrawal, such as sleep problems, irritability, jumpiness, shakiness, restlessness, headache, nausea, sweating, anxiety, and depression. In severe cases, agitation, fever, seizures, and hallucinations can occur; this pattern of severe withdrawal symptoms is called delirium tremens.The heavy drinking that often occurs in alcohol use disorder, and can also occur in short-term episodes called binge drinking, can lead to a life-threatening overdose known as alcohol poisoning. Alcohol poisoning occurs when a large quantity of alcohol consumed over a short time causes problems with breathing, heart rate, body temperature, and the gag reflex. Signs and symptoms can include vomiting, choking, confusion, slow or irregular breathing, pale or blue-tinged skin, seizures, a low body temperature, a toxic buildup of substances called ketones in the blood (alcoholic ketoacidosis), and passing out (unconsciousness). Coma, brain damage, and death can occur if alcohol poisoning is not treated immediately.Chronic heavy alcohol use can also cause long-term problems affecting many organs and systems of the body. These health problems include irreversible liver disease (cirrhosis), inflammation of the pancreas (pancreatitis), brain dysfunction (encephalopathy), nerve damage (neuropathy), high blood pressure (hypertension), stroke, weakening of the heart muscle (cardiomyopathy), irregular heartbeats (arrhythmia), and immune system problems. Long-term overuse of alcohol also increases the risk of certain cancers, including cancers of the mouth, throat, esophagus, liver, and breast. Alcohol use in pregnant women can cause birth defects and fetal alcohol syndrome, which can lead to lifelong physical and behavioral problems in the affected child.

PubMed PMID: 17718394
PubMed PMID: 3758060
PubMed PMID: 15863807
PubMed PMID: 17923853

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

rs11739136 - NM_004137.4(KCNMB1):c.193G>A (p.Glu65Lys)

By direct sequencing of the exons encoding the KCNMB1 gene in 11 severely hypertensive and 12 strictly normotensive individuals, Fernandez-Fernandez et al. (2004) identified a 352G-A transition in the third exon, resulting in a glu65-to-lys (E65K) substitution. They screened a population sample of 3,876 randomly selected participants for this mutation and found genotype frequencies of 78.4% for EE homozygotes, 20% for EK heterozygotes, and 1.6% for KK homozygotes. The frequency of the E65K mutation (KK + KE) decreased with increasing diastolic blood pressure values, from 21.6% in the normotensive group to 3.2% in the severely hypertensive group, consistent with a protective effect of the K allele against the severity of diastolic hypertension (608622).

In 101 Spanish nuclear families consisting of offspring with ischemic heart disease who were younger than 55 years and both parents, Via et al. (2005) did not detect any association between the E65K polymorphism and ischemic heart disease.

PubMed PMID: 15057310
PubMed PMID: 16155733

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:

- Leanness
- Congenital heart disease
- Preeclampsia/eclampsia 4
- Unknown
- Hyperglycinuria
- Cancer progression and tumor cell motility
- Carcinoma of colon
- Legius syndrome

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.