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DANTE LABS™ TEST RESULTS

KIT ID: SAMPLE

Metabolic Test

Introduction

The Metabolic Test is based on Whole Genome Sequencing Test. As such, it analyzes all Common and Rare Variants associated with Metabolic Diseases instead of a limited set of genes, like old genetic target panels. Metabolic diseases are a group of diseases that cause disrupted energy metabolism, including Gaucher disease, Maple syrup urine disease, Niemann-Pick, Tay-Sachs disease, and Wilson's disease. Along with environmental factors, Genetics plays a key role in the regulation of Metabolic Diseases.

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

- Legius syndrome
- Hyperglycinuria
- Prostate cancer
- Inflammatory bowel disease 1
- Encephalopathy
- Leanness
- Prekallikrein deficiency
- Autosomal dominant nocturnal frontal lobe epilepsy
- Familial hypercholesterolemia
- Phenylketonuria
- Carcinoma of colon
- APOLIPOPROTEIN A-IV POLYMORPHISM
- Acute myeloid leukemia with maturation
- Congenital heart disease
- Unknown
- Familial Mediterranean fever
- Cancer progression and tumor cell motility
- Diabetes mellitus
- Fetal hemoglobin quantitative trait locus 2
- Preeclampsia/eclampsia 4

Genes/Locations included in report:

FH (2)	PC (0)	SI (0)	ADA (0)	ADK (0)	AGA (0)	AGK (0)	AGL (0)
AMN (1)	AMT (0)	ASL (0)	AUH (0)	BTD (0)	CA2 (0)	CBS (0)	CTH (0)
DBT (3)	DLD (0)	DYM (0)	EBP (0)	EGF (1)	FAH (0)	GAA (0)	GBA (0)
GCK (0)	GIF (0)	GLA (0)	GNE (0)	GNS (0)	HFE (0)	HGD (0)	HPD (0)
IDS (0)	IVD (0)	LCT (0)	LEP (0)	MPI (0)	MTR (1)	MUT (0)	OAT (1)
OTC (0)	PAH (1)	PNP (0)	PTS (0)	REN (0)	TAT (0)	TAZ (1)	TK2 (0)
VDR (2)	XDH (0)	ACY1 (0)	ADAR (1)	ADSL (0)	AGPS (0)	AGXT (6)	AHCY (0)
AKT2 (0)	ALAD (0)	ALG1 (0)	ALG2 (0)	ALG3 (0)	ALG6 (0)	ALG8 (0)	ALG9 (2)
ALPL (0)	ANO5 (2)	APRT (0)	APTX (0)	ARG1 (0)	ARL6 (0)	ARSA (1)	ARSB (0)
ASPA (0)	ASS1 (0)	ATIC (1)	BBS1 (0)	BBS2 (0)	BBS4 (0)	BBS5 (0)	BBS7 (0)
BBS9 (0)	BSND (0)	CASR (0)	CAV1 (0)	CAV3 (0)	CLN3 (0)	CLN5 (0)	CLN6 (1)
CLN8 (0)	CLPB (0)	COG1 (0)	COG4 (0)	COG5 (0)	COG6 (0)	COG7 (1)	COG8 (0)

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COQ2 (1)	COQ4 (0)	COQ5 (0)	COQ6 (0)	COQ7 (0)	COQ9 (0)	CPOX (0)	CPS1 (0)
CPT2 (1)	CTNS (2)	CTSA (1)	CTSC (0)	CTSD (0)	CTSK (1)	CUBN (0)	DOLK (0)
DPM1 (0)	DPM2 (1)	DPM3 (0)	DPYD (0)	DPYS (0)	DYSF (1)	ENO3 (0)	ETFA (0)
ETFB (0)	FBP1 (0)	FECH (1)	FKRP (0)	FKTN (1)	FLNA (0)	FLNB (0)	FMO3 (0)
G6PC (1)	GALC (2)	GALE (0)	GALT (1)	GAMT (0)	GATM (1)	GBE1 (0)	GCDH (0)
GCH1 (0)	GCSH (0)	GFM1 (0)	GLB1 (0)	GLDC (0)	GLUL (1)	GM2A (0)	GNAS (0)
GNMT (0)	GPC3 (0)	GPHN (0)	GUSB (0)	GYG1 (0)	GYS1 (0)	GYS2 (0)	HADH (0)
HAMP (0)	HEXA (0)	HEXB (0)	HFE2 (0)	HLCS (0)	HMBS (0)	HRAS (0)	IDH2 (0)
IDUA (0)	INSR (1)	ISCU (0)	KSR2 (0)	LDB3 (0)	LDHA (0)	LEPR (0)	LIAS (0)
LIPA (0)	LIPE (0)	LMNA (0)	MC3R (0)	MC4R (2)	MCEE (0)	MFN2 (0)	MKKS (0)
MKS1 (0)	MMAA (0)	MMAB (7)	MOGS (0)	MTRR (0)	MYH3 (0)	MYOT (0)	NAGA (1)
NAGS (0)	NBAS (0)	NEU1 (0)	NFU1 (0)	NPC1 (1)	NPC2 (0)	OCRL (0)	OPA1 (0)
OPA3 (1)	PCCA (0)	PCCB (0)	PCK1 (0)	PDHB (0)	PDHX (0)	PDX1 (0)	PEPD (0)

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PEX1 (2)	PEX2 (0)	PEX3 (0)	PEX5 (0)	PEX6 (0)	PEX7 (0)	PFKM (0)	PGK1 (0)
PGM1 (0)	PHF6 (0)	PHKB (0)	PHYH (1)	PMM2 (0)	POLG (0)	POMC (0)	PPOX (0)
PPT1 (0)	PSAP (0)	PTRF (0)	PYGL (0)	PYGM (0)	QDPR (0)	RAI1 (0)	RFT1 (0)
RYR1 (0)	SGSH (0)	SIM1 (0)	SPG7 (0)	SSR4 (0)	SUOX (0)	TCF4 (1)	TCN2 (0)
TFR2 (0)	TPMT (0)	TPP1 (0)	TTC8 (0)	TYMP (0)	UCP2 (0)	UCP3 (0)	UMOD (0)
UMPS (1)	UPB1 (0)	UROD (0)	UROS (0)	WFS1 (1)	ABCC8 (1)	ABCD1 (0)	ABCD3 (0)
ABCD4 (0)	ACAD8 (0)	ACAD9 (0)	ACADL (0)	ACADM (0)	ACADS (1)	ACAT1 (0)	ACOX1 (0)
ACSF3 (0)	ADCK3 (0)	ADCY3 (0)	ALAS2 (0)	ALDOA (0)	ALDOB (0)	ALG11 (1)	ALG12 (0)
ALG13 (0)	ALMS1 (4)	AMACR (0)	AMPD1 (1)	ANO10 (0)	ASAH1 (1)	ATP7B (1)	BBS10 (0)
BBS12 (0)	BCS1L (0)	BOLA3 (0)	BSCL2 (0)	CD320 (0)	CLCN1 (0)	CLCN5 (0)	CNNM2 (0)
CNNM4 (0)	CPT1A (0)	CUL4B (0)	DDOST (2)	DGUOK (0)	DHCR7 (0)	DHDDS (0)	DHODH (0)
DNM1L (0)	ECHS1 (0)	EPM2A (0)	ETFDH (0)	FBXL4 (0)	FLAD1 (0)	FOLR1 (0)	FUCA1 (0)
FXYD2 (0)	GALK1 (0)	GALNS (0)	GLRX5 (0)	GLUD1 (0)	GMPPA (0)	GNA11 (0)	GNPAT (0)

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GNPTG (0)	GRHPR (2)	HADHA (0)	HADHB (0)	HCFC1 (0)	HIBCH (0)	HMGCL (0)	HNF1A (0)
HNF1B (0)	HNF4A (1)	HOGA1 (4)	HPRT1 (0)	HYAL1 (0)	IFIH1 (0)	KCNA1 (0)	KCNJ1 (0)
KCNJ2 (1)	LAMA2 (1)	LAMP2 (0)	LIPT1 (0)	LPIN1 (0)	MAGT1 (0)	MANBA (0)	MCCC1 (0)
MCCC2 (0)	MFSD8 (0)	MGAT2 (0)	MLYCD (0)	MOCOS (0)	MOCS1 (0)	MOCS2 (0)	MPDU1 (0)
MPV17 (0)	MTHFR (1)	NAGLU (0)	NGLY1 (0)	NIPA2 (0)	NR0B2 (0)	NTRK2 (0)	OXCT1 (0)
PCBD1 (0)	PCSK1 (0)	PDHA1 (0)	PDSS1 (0)	PDSS2 (0)	PEX10 (0)	PEX12 (0)	PEX13 (0)
PEX14 (0)	PEX16 (0)	PEX19 (0)	PEX26 (0)	PGAM2 (0)	PHKA1 (0)	PHKA2 (0)	PHKG2 (0)
PLIN1 (0)	POLG2 (0)	PPARG (0)	PRODH (1)	PRPS1 (0)	PTF1A (0)	RBCK1 (0)	RRM2B (0)
SARS2 (0)	SCN4A (0)	SMPD1 (1)	STT3A (0)	STT3B (0)	SUGCT (0)	SUMF1 (0)	TREX1 (0)
TRPM6 (1)	TUSC3 (0)	WDPCP (0)	ACADSB (2)	ACADVL (0)	ADCY10 (0)	AGPAT2 (0)	ANTXR2 (0)
B3GLCT (0)	BCKDHA (0)	BCKDHB (0)	CEP290 (1)	CLCNKB (0)	CLDN16 (0)	CLDN19 (0)	COL2A1 (0)
D2HGDH (0)	DPAGT1 (0)	DYRK1B (0)	FAM20A (0)	GNPTAB (0)	HGSNAT (0)	HMGCS2 (0)	KCNJ10 (0)
KCNJ11 (1)	L2HGDH (0)	LMBRD1 (0)	MAGEL2 (0)	MAN1B1 (0)	MAN2B1 (0)	MCOLN1 (0)	MMACHC (0)

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MMADHC (0)	NDUFS1 (1)	NHLRC1 (1)	NT5C3A (0)	PEX11B (0)	PNPLA2 (0)	PRKAG2 (1)	PRKAG3 (0)
SAMHD1 (0)	SEC23B (0)	SERAC1 (0)	SLC2A1 (0)	SLC2A2 (0)	SLC2A9 (1)	SLC3A1 (0)	SLC4A1 (0)
SLC5A1 (0)	SLC6A8 (0)	SLC6A9 (0)	SLC7A7 (0)	SLC7A9 (0)	SRD5A3 (1)	SUCLA2 (0)	SUCLG1 (0)
TANGO2 (0)	TBC1D4 (0)	TIMM8A (0)	TMEM70 (0)	TRIM32 (0)	TRIM37 (0)	VPS13B (0)	ALDH5A1 (0)
ALDH7A1 (1)	ATP13A2 (0)	B4GALT1 (3)	C10ORF2 (0)	CACNA1S (0)	COL11A2 (0)	CYP24A1 (0)	FAM111A (0)
FOXRED1 (0)	HSD17B4 (0)	NDUFAF2 (0)	SDCCAG8 (0)	SLC12A1 (0)	SLC12A3 (0)	SLC16A1 (1)	SLC17A5 (1)
SLC22A5 (0)	SLC25A1 (0)	SLC25A3 (0)	SLC25A4 (0)	SLC26A1 (0)	SLC34A1 (0)	SLC34A3 (0)	SLC35A1 (1)
SLC35A2 (0)	SLC35C1 (0)	SLC37A4 (0)	SLC39A4 (0)	SLC40A1 (0)	SLC46A1 (0)	SLC6A19 (0)	TMEM165 (0)
ADAMTSL2 (0)	ATP6V0A2 (0)	ATP6V0A4 (0)	ATP6V1B1 (0)	C12ORF65 (0)	HSD17B10 (0)	RNASEH2A (0)	RNASEH2B (0)
RNASEH2C (0)	SERPINA1 (0)	SLC22A12 (0)	SLC25A13 (0)	SLC25A15 (0)	SLC25A20 (0)	SLC25A26 (0)	SLC30A10 (0)
SLC9A3R1 (0)	TMEM126A (0)	ZMPSTE24 (0)					

Variants Found:

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
WFS1	chr4:6295693	rs6446482	Diabetes mellitus	HOM	C>G	0.72125	pathogenic	
PAH	chr12:103310787		Phenylketonuria	HET	G>A	0.36362	likely pathogenic	
MC4R	chr18:57882787	rs489693	amisulpride response - Toxicity/ADR	HET	C>A	0.35124	drug response	★★★
MC4R	chr18:57851097	rs17782313	antipsychotics response - Toxicity/ADR	HET	T>C	0.24002	drug response	★★★
COQ2	chr4:84192168	rs4693075	atorvastatin response - Toxicity/ADR	HET	G>C	0.66014	drug response	★★★
EGF	chr4:110834110	rs4444903	cetuximab response - Efficacy	HET	A>G	0.60523	drug response	★★★
ABCC8	chr11:17409572	rs5219	glibenclamide response - Efficacy	HET	T>C	0.73702	drug response	★★★
KCNJ11	chr11:17409572	rs5219	glibenclamide response - Efficacy	HET	T>C	0.73702	drug response	★★★
GATM	chr15:45673029	rs1346268	hmg coa reductase inhibitors response - Toxicity/ADR	HOM	T>C	0.45088	drug response	★★★
ATIC	chr2:216212339	rs4673993	methotrexate response - Efficacy	HET	T>C	0.28554	drug response	★★★
OPA3	19:46052048	rs58537694	3-Methylglutaconic aciduria type 3	HET	C>CTTATTTAT		uncertain significance	★
ALMS1	2:73613031	rs55889738	Alstrom syndrome	HET	TGGAGGA>T		uncertain significance	★★
KCNJ2	17:68175205	rs35656864	Andersen Tawil syndrome	HOM	A>AT		uncertain significance	★
CPT2 Rare	chr1:53676395		Carnitine palmitoyltransferase II deficiency	HET	G>A	0.00001	uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
ALG9	11:111654647	rs886047666	Congenital disorder of glycosylation	HOM	T>TA		uncertain significance	★
ALG9	chr11:111655273	rs45620134	Congenital disorder of glycosylation	HET	C>T	0.01657	uncertain significance	★
B4GALT1	9:33111274	rs754771244	Congenital disorder of glycosylation	HOM	AAAC>A		uncertain significance	★
B4GALT1	9:33111274	rs886063864	Congenital disorder of glycosylation	HOM	AAAC>A		uncertain significance	★
B4GALT1	9:33111274	rs7041909	Congenital disorder of glycosylation	HOM	AAAC>A		uncertain significance	★
COG7	16:23457290	rs71379679	Congenital disorder of glycosylation	HET	TA>T		uncertain significance	★
DDOST	1:20978294	rs78039244	Congenital disorder of glycosylation	HET	TTTTA>T		uncertain significance	★
DDOST	1:20978294	rs200882134	Congenital disorder of glycosylation	HET	TTTTA>T	0.02955	uncertain significance	★
DPM2	chr9:130697374	rs544907409	Congenital disorder of glycosylation	HET	G>A		uncertain significance	★
SRD5A3	4:56236598	rs3034886	Congenital disorder of glycosylation	HET	TCACA>T		uncertain significance	★
ACADSB	10:124810704	rs760423996	Deficiency of 2-methylbutyryl-CoA dehydrogenase	HET	TAA>T		uncertain significance	★★
ACADSB	10:124812685	rs11307362	Deficiency of 2-methylbutyryl-CoA dehydrogenase	HOM	AT>A		uncertain significance	★
MTR	1:237060945	rs67705775	Disorders of Intracellular Cobalamin Metabolism	HET	CT>C		uncertain significance	★
FECH	18:55216773	rs886053991	Erythropoietic protoporphyria	HET	TA>T		uncertain significance	★
ASAH1	8:17914865	rs374131883	Farber disease	HET	TA>T		uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
FKTN	chr9:108402586	rs1854124	Fukuyama congenital muscular dystrophy	HET	G>A	0.10923	uncertain significance	★
GALC	14:88417095	rs1555379806	Galactosylceramide beta-galactosidase deficiency	HOM	GA>G		uncertain significance	★
GLUL	1:182351944	rs367629181	Glutamine deficiency	HET	CTT>C		uncertain significance	★
G6PC	17:41064987	rs138968865	Glycogen storage disease	HET	TTTTTAGAA>T		uncertain significance	★
TRPM6 Rare	chr9:77337661	rs192845997	Hypomagnesemia 1	HET	G>A	0.0002	uncertain significance	★
NAGA	22:42454493	rs10713176	Kanzaki disease	HET	GA>G		uncertain significance	★
NHLRC1 Rare	chr6:18121324	rs369668171	Lafora disease	HET	G>A	0.001	uncertain significance	★
NDUFS1	2:207014657	rs568965659	Leigh syndrome	HET	TAA>T		uncertain significance	★
INSR	19:7116711	rs71177157	Leprechaunism syndrome	HET	C>CAAAAAAAA		uncertain significance	★
DBT	1:100654907	rs71709231	Maple syrup urine disease	HOM	TA>T		uncertain significance	★
DBT	1:100655695	rs3081711	Maple syrup urine disease	HET	TAA>T		uncertain significance	★
HNF4A	20:43060984	rs11450239	Maturity onset diabetes mellitus in young	HET	C>CT		uncertain significance	★
AMN	14:103396993	rs36040113	Megaloblastic anemia due to inborn errors of metabolism	HET	C>CGCCGGG		uncertain significance	
ARSA	22:51062326	rs6010033	Metachromatic leukodystrophy	HET	CAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA>C		uncertain significance	★
MMAB	12:109993254	rs34507867	Methylmalonic acidemia	HOM	AT>A		uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
MMAB	12:109993254	rs34507867	Methylmalonic acidemia	HOM	AT>A		uncertain significance	★
MMAB	12:109993254	rs34507867	Methylmalonic acidemia	HOM	AT>A		uncertain significance	★
MMAB	12:109994451	rs67024670	Methylmalonic acidemia	HET	TCTCACACA>T		uncertain significance	★
MMAB	12:109994451	rs67024670	Methylmalonic acidemia	HET	TCTCACACA>T		uncertain significance	★
MMAB	12:109994451	rs67024670	Methylmalonic acidemia	HET	TCTCACACA>T		uncertain significance	★
MMAB	12:109994451	rs886048924	Methylmalonic acidemia	HET	TCTCACACA>T		uncertain significance	★
ANO5	11:22301410	rs5790246	Miyoshi myopathy	HOM	CTT>C		uncertain significance	★
ANO5	chr11:22301865	rs117180492	Miyoshi myopathy	HET	C>T	0.01757	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	★
AMPD1	chr1:115236057	rs17602729	Muscle AMP deaminase deficiency	HET	G>A	0.03814	uncertain significance	★★
CTNS	17:3565605	rs397856854	Nephropathic cystinosis	HET	CA>C		uncertain significance	★
CTNS Rare	chr17:3565790	rs72835828	Nephropathic cystinosis	HET	G>A	0.00639	uncertain significance	★
MTHFR	1:11846659	rs55780505	Neural tube defects	HOM	ATTTT>A		uncertain significance	★
CLN6	15:68500317	rs3837692	Neuronal Ceroid-Lipofuscinosis	HET	GACAC>G		uncertain significance	★
OAT Rare	chr10:126107434	rs552799531	Ornithine aminotransferase deficiency	HET	G>A	0.0012	uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
UMPS	3:124465602	rs58981387	Orotic aciduria	HET	T>TTGTGTG		uncertain significance	★
TCF4	18:52891395	rs66807288	Pitt-Hopkins syndrome	HET	CT>C		uncertain significance	★
AGXT	2:241808825	rs180177209	Primary hyperoxaluria	HET	AGGCCTCCCT>A		uncertain significance	
AGXT	chr2:241810957	rs10196315	Primary hyperoxaluria	HET	C>T	0.23982	uncertain significance	
AGXT	chr2:241815307	rs12478859	Primary hyperoxaluria	HET	C>T	0.23982	uncertain significance	
AGXT	chr2:241815308	rs12464426	Primary hyperoxaluria	HOM	A>G	0.78135	uncertain significance	
AGXT	chr2:241815473	rs12695032	Primary hyperoxaluria	HET	G>A	0.34325	uncertain significance	
AGXT	chr2:241817322	rs10199038	Primary hyperoxaluria	HET	C>T	0.2522	uncertain significance	
GRHPR	9:37422880	rs35891798	Primary hyperoxaluria	HET	CG>C		uncertain significance	
GRHPR	chr9:37429661	rs309459	Primary hyperoxaluria	HOM	A>G	0.85204	uncertain significance	
HOGA1	chr10:99358511	rs11817730	Primary hyperoxaluria	HET	A>G	0.17332	uncertain significance	
HOGA1	chr10:99359406	rs75929214	Primary hyperoxaluria	HET	C>T	0.07268	uncertain significance	
HOGA1	chr10:99359412	rs7078003	Primary hyperoxaluria	HET	C>T	0.09085	uncertain significance	
HOGA1	10:99371766	rs5787248	Primary hyperoxaluria	HET	A>AT		uncertain significance	★
CTSK Rare	chr1:150772129	rs41271965	Pyknodysostosis	HET	T>C	0.0014	uncertain significance	★
ALDH7A1	5:125879656	rs60217601	Pyridoxine-dependent epilepsy	HET	C>CTTT		uncertain significance	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
SLC17A5 Rare	chr6:74331606	rs142553916	Sialic acid storage disease	HET	G>A	0.0006	uncertain significance	★★
ADAR	1:154554951	rs113414804	Symmetrical dyschromatosis of extremities	HOM	A>AGGGGCATG		uncertain significance	★
CTSA	20:44520237	rs1555832204	Unknown	HET	CCTG>C		uncertain significance	
NPC1	18:21123536	rs11299077	Unknown	HOM	TA>T		uncertain significance	★
PRODH	chr22:18900750	rs372055	Unknown	HET	G>A	0.76338	uncertain significance	
SMPD1	11:6411935	rs71467507	Unknown	HOM	TGCTGGC>T		uncertain significance	★
VDR	12:48236406	rs17878969	Vitamin D-Dependent Rickets	HET	ATTTTTT>A		uncertain significance	★
VDR	12:48237279	rs11574130	Vitamin D-Dependent Rickets	HET	A>AGCTGG		uncertain significance	★
PRKAG2	7:151253246	rs56898021	Wolff-Parkinson-White syndrome	HOM	G>GA		uncertain significance	★
SLC35A1	6:88218600	rs10638303	CONGENITAL DISORDER OF GLYCOSYLATION	HET	C>CCACT		risk factor	
SLC2A9	chr4:9994215	rs6449213	Uric acid concentration	HOM	C>T	0.85763	association	
TAZ	chrX:153640406	rs62617809	3-Methylglutaconic aciduria type 2	HOM	C>T	0.0649	conflicting interpretations of pathogenicity	★
GALC	14:88417095	rs11300320	Abnormality of brain morphology	HOM	GA>G		conflicting interpretations of pathogenicity	★
ALMS1	2:73613031	rs55889738	Alstrom syndrome	HET	TGGAGGA>T		conflicting interpretations of pathogenicity	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
ALMS1	2:73613031	rs55889738	Alstrom syndrome	HET	TGGAGGA>T		conflicting interpretations of pathogenicity	★
ALMS1	2:73613031	rs55889738	Alstrom syndrome	HET	TGGAGGA>T		conflicting interpretations of pathogenicity	★
ACADS	chr12:121176083	rs1799958	Deficiency of butyryl-CoA dehydrogenase	HET	G>A	0.18231	conflicting interpretations of pathogenicity	★
DYSF Rare	chr2:71886100	rs62145939	Dysferlinopathy	HET	G>A	0.00739	conflicting interpretations of pathogenicity	★
GALT	chr9:34649442	rs2070074	GALT POLYMORPHISM (DUARTE	HET	A>G	0.07288	conflicting interpretations of pathogenicity	★
LAMA2 Rare	chr6:129513837	rs141363186	Laminin alpha 2-related dystrophy	HET	A>G	0.0004	conflicting interpretations of pathogenicity	★
DBT	1:100661987	rs752915898	Maple syrup urine disease	HOM	GAAAAA>G		conflicting interpretations of pathogenicity	★
CEP290 Rare	chr12:88533296	rs373913704	Nephronophthisis	HET	C>T	0.00058	conflicting interpretations of pathogenicity	★
PHYH Rare	chr10:13325784	rs62619919	Nonsyndromic cleft lip palate	HET	C>T	0.00539	conflicting interpretations of pathogenicity	★
PEX1	7:92129161	rs5885806	Peroxisome biogenesis disorder 1A (Zellweger)	HET	CA>C		conflicting interpretations of pathogenicity	★

Gene/Loc	Chr: Pos	RSID	Phenotype Name	Zygosity	Variant	Allele Frequency	Significance	Review Status
PEX1	7:92129161	rs5885806	Peroxisome biogenesis disorder 1A (Zellweger)	HET	CA>C		conflicting interpretations of pathogenicity	★
ATP7B	13:52585591	rs148013251	Wilson disease	HET	T>TCGGCG		conflicting interpretations of pathogenicity	★
ALG11	13:52585591	rs148013251	Wilson disease	HET	T>TCGGCG		conflicting interpretations of pathogenicity	★
SLC16A1	1:113460676	rs149491709	not specified	HOM	CAATA>C		conflicting interpretations of pathogenicity	★

Individual Variant Interpretations:

rs5110 - NM_000482.4(APOA4):c.1140G>T (p.Gln380His)

Lohse et al. (1990) demonstrated that the genetic polymorphism of plasma apolipoprotein A-IV, detected by isoelectric focusing followed by immunoblotting, results from a single nucleotide change. Specifically, the difference between APOA4*1 and APOA4*2 is a G-to-T substitution leading to a conversion of glutamine-360 to histidine in the mature protein. The allelic change is predicted to cause the loss of 2 restriction enzyme sites in the formation of a new restriction site for a third enzyme. In Caucasian populations, the APOA4*1 and APOA4*2 alleles have a frequency of about 0.9 and 0.08, respectively; 3 rare alleles, APOA4*0 (107690.0002), APOA4*3 (107690.0003), and APOA4*4, have been described. In a study of various polymorphisms of APOA4, von Eckardstein et al. (1992) could not confirm the previously reported association of elevated HDL cholesterol concentrations with the his360 allele; from other associations, the authors concluded that the APOA4 gene locus has an important role in the metabolism of apolipoprotein B and, to a lesser extent, apolipoprotein A-I-containing lipoproteins.

PubMed PMID: 1349197
PubMed PMID: 2351649

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

rs886041062 - NM_144772.3(NAXE):c.804_807delinsA (p.Lys270del)

In a male infant, born of unrelated German parents (family 3), with early-onset progressive encephalopathy with brain edema and/or leukoencephalopathy (PEBEL; 617186), Kremer et al. (2016) identified a homozygous c.804_807del/insA mutation in exon 6 of the NAXE gene, resulting in an in-frame deletion of conserved residue Lys270 (Lys270del). The mutation, which was found by exome sequencing and confirmed by Sanger sequencing, segregated with the disorder in the family and was not found in public databases, including ExAC (March 2015). Western blot analysis of patient fibroblasts showed reduced levels of the NAXE protein.

PubMed PMID: 27616477

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

rs5743289 - NM_022162.3(NOD2):c.2798+158C>T

Inflammatory Bowel Disease 1 (Crohn Disease), Susceptibility to

In 112 Ashkenazi Jewish patients with Crohn disease (IBD1; 266600), Sugimura et al. (2003) found a novel disease-predisposing variant in the NOD2 gene, IVS8+158, which is a C-to-T mutation in the palindrome sequence in the intron 8 splicing region. The IVS8+158 variant, which the authors designated 'JW1,' occurred on a specific haplotype with a 268S variant, and this combination exhibited a further increased risk (odds ratio = 5.75, p = 0.0005) and the highest population-attributable risk (15.1%) for Crohn disease (CD) among reported disease-predisposing mutations in Jews. However, no association was found between the 268S-JW1 haplotype and disease in 166 non-Jewish white CD patients. Sugimura et al. (2003) concluded that in Ashkenazi Jews, unrecognized population-specific predisposing factor(s) for CD exist on the 268S-JW1 haplotype at the IBD1 locus.

In a study of 193 Jewish Israeli CD patients, Karban and Eliakim (2004) failed to replicate the association of the S268P variant or S268P-IVS+158 combination with Crohn disease.

Tukel et al. (2004) assessed the haplotypes and allele frequencies of the common NOD2 mutations and variants in 219 members of 50 Ashkenazi Jewish and 53 members of 10 Sephardi/Oriental Jewish multiplex families with CD, in 36 Ashkenazi Jewish patients with sporadic CD, and in 246 Ashkenazi and 82 Sephardi/Oriental Jewish controls, and found no evidence for increased risk associated with the IVS8+158 variant.

Blau Syndrome

In a 9-month-old Caucasian boy with Blau syndrome (BLAUS; 186580), Borzutzky et al. (2010) identified heterozygosity for the IVS8+158 variant in the NOD2 gene. Borzutzky et al. (2010) stated that this was the first reported case of gastrointestinal granulomas in a patient with early-onset sarcoidosis.

Yao Syndrome, Susceptibility to

In 7 unrelated patients with multisystem autoinflammatory disease (YAOS; 617321), Yao et al. (2011) identified heterozygosity for the IVS8+158 variant in the NOD2 gene. Four of the patients also carried the R702W mutation in NOD2 (605956.0003). Yao et al. (2011) stated that the clinical relevance of these gene mutations remained to be determined, and that this disease might be genetically complex rather than mendelian.

In 22 patients with autoinflammatory disease, including the 7 patients previously studied by Yao et al. (2011), Yao et al. (2013) screened the NOD2 gene and found that all carried at least 1 variant: 21 had the IVS8+158 variant, and 8 had the R702W variant. Yao et al. (2013) noted that the allele frequency of the IVS8+158 variant in the healthy white population had been estimated to be approximately 15% by Sugimura et al. (2003), whereas in an aggregated cohort of 41 patients tested by Yao et al. (2013) for IVS8+158, the variant was detected in approximately 55% of patients (p less than 0.001), all of whom were non-Jewish.

Yao et al. (2015) genotyped 143 patients with symptoms suggestive of Yao syndrome for NOD2 variants and identified 54 patients who fulfilled criteria for the disorder, including the presence of NOD2 variants. The IVS8+158 variant was detected in 46 of the 54 patients, including 30 who carried only IVS8+158 and 18 who also carried other known variants, including R702W, 3020insC (605956.0001), and G908R (605956.0002). In addition, 9 other rare NOD2 variants were detected in 13 of the patients. Yao et al. (2015) noted that it remained unclear whether these variants were causative or served as markers indirectly associated with the disease.

PubMed PMID: 12577202
PubMed PMID: 14765395
PubMed PMID: 15024686
PubMed PMID: 19467619
PubMed PMID: 21914217
PubMed PMID: 23102769
PubMed PMID: 26070941

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

rs3733402 - NM_000892.5(KLKB1):c.428G>A (p.Ser143Asn)

For discussion of the asn124-to-ser (N124S) mutation in the KLKB1 gene that was found in compound heterozygous state in patients with plasma prekallikrein deficiency (612423) by Katsuda et al. (2007), see 229000.0004.

Prekallikrein deficiency is a blood condition that usually causes no health problems. In people with this condition, blood tests show a prolonged activated partial thromboplastin time (PTT), a result that is typically associated with bleeding problems; however, bleeding problems generally do not occur in prekallikrein deficiency. The condition is usually discovered when blood tests are done for other reasons.A few people with prekallikrein deficiency have experienced health problems related to blood clotting such as heart attack, stroke, a clot in the deep veins of the arms or legs (deep vein thrombosis), nosebleeds, or excessive bleeding after surgery. However, these are common problems in the general population, and most affected individuals have other risk factors for developing them, so it is unclear whether their occurrence is related to prekallikrein deficiency.

PubMed PMID: 17598838

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

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

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

PubMed PMID: 18264098

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

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

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

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

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

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

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

rs1861972 - NM_001427.4(EN2):c.686-1073G>A

This variant, formerly titled AUTISM, ASSOCIATION WITH, 10, has been reclassified as a variant of unknown significance because its contribution to autism (611016) has not been confirmed.

In a study of 138 families in which at least 2 individuals had a strict diagnosis of autism, Gharani et al. (2004) demonstrated that a haplotype consisting of 2 intronic SNPs of the EN2 gene, the A allele of rs1861972 and the C allele of rs1861973 (131310.0002), showed significant association with autism (p = 0.000005). Less significant association (p = 0.0024) was observed for a larger group of 157 families with a broader phenotype including autism spectrum disorders. Benayed et al. (2005) replicated these association results in an additional 222 Autism Genetic Resource Exchange (AGRE) families and in 129 NIMH families.

PubMed PMID: 15024396
PubMed PMID: 16252243

rs1861973 - NM_001427.4(EN2):c.686-921T>C

This variant, formerly titled AUTISM, ASSOCIATION WITH, 10, has been reclassified as a variant of unknown significance because its contribution to autism (611016) has not been confirmed.

See 131310.0001, Gharani et al. (2004), and Benayed et al. (2005).

PubMed PMID: 15024396
PubMed PMID: 16252243

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

rs10946398 - NM_017774.3(CDKAL1):c.371+11426A>C

This variant, formerly titled DIABETES MELLITUS, NONINSULIN-DEPENDENT, SUSCEPTIBILITY TO, has been reclassified because this SNP has not been shown to be the causal variant accounting for association.

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) identified association of the C allele of a SNP in intron 5 of the CDKAL1 gene, rs10946398, or of its proxy, rs7754840, with type 2 diabetes. Across these studies, all groups cited evidence for association at this marker of P approximately equal to 4.1 x 10(-11).

Zhou et al. (2014) found that expression of CDKAL1v1, but not full-length CDKAL1, was significantly reduced in individuals homozygous for the C allele of rs10946398. Human embryonic fibroblast cell lines homozygous for both the C allele of rs10946398 and the G allele of rs7756992 (611259.0002) showed decreased expression of CDKAL1v1, but not CDKAL1. Zhou et al. (2014) hypothesized that the risk alleles of rs10946398 and rs7756992 influence alternative splicing of the CDKAL1 gene.

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
PubMed PMID: 24760768

rs7756992 - NM_017774.3(CDKAL1):c.371+30101A>G

Steinthorsdottir et al. (2007) identified a variant in intron 5 of the CDKAL1 gene, rs7756992, that was associated with type 2 diabetes (125853) in individuals of European ancestry (allele-specific OR, 1.20; P = 7.7 x 10(-9)) and individuals from Hong Kong of Han Chinese ancestry (OR, 1.25; P = 0.00018). The ORs for homozygotes were 1.50 and 1.55 in the European and Hong Kong groups, respectively. The insulin response for homozygotes was approximately 20% lower than for heterozygotes or noncarriers (P = 2.5 x 10(-8)), suggesting that this variant confers risk of type 2 diabetes through reduced insulin secretion.

This variant, formerly titled DIABETES MELLITUS, NONINSULIN-DEPENDENT, SUSCEPTIBILITY TO, has been reclassified because this SNP has not been shown to be the causal variant accounting for association.

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PubMed PMID: 17460697
PubMed PMID: 24760768

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

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

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

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

PubMed PMID: 23883829
PubMed PMID: 17436250

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

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

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

PubMed PMID: 18204447

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).

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

rs20541 - NM_002188.3(IL13):c.431A>G (p.Gln144Arg)

Heinzmann et al. (2000) determined that R130Q variant of IL13, which they referred to as R110Q, associated with asthma in case-control populations from Britain and Japan (peak odds ratio (OR) = 2.31, 95% confidence interval, 1.33 - 4.00); the variant also predicted asthma and higher serum IL13 levels in a general, Japanese pediatric population. Chen et al. (2004) noted that R110Q numbering does not include a 20-amino acid signal sequence and that the R110Q variant has been referred to as R130Q. Immunohistochemistry demonstrated that both subunits of IL13R are prominently expressed in bronchial epithelium and smooth muscle from asthmatic subjects. Detailed molecular modeling analyses indicated that residue 110 of IL13 is important in the internal constitution of the ligand and crucial in ligand-receptor interaction.

In Chinese adult patients with allergic rhinitis (607154), Wang et al. (2003) found a significant association of the IL13 arg130-to-gln (R130Q) SNP, but not of the IL13 promoter -1112C-T SNP (147683.0001), with serum total IgE levels. Patients with a gln/gln genotype showed much higher serum total IgE than those with an arg/arg genotype.

Hiromatsu et al. (2005) noted that the R130Q amino acid substitution arises from a G-to-A transition at nucleotide 2044 (G2044A) in exon 4 of the IL13 gene.

Vladich et al. (2005) examined the impact of the IL13 R130Q variant on the functional properties of IL13 by comparing the activity of the variant to wildtype IL13 on primary effector cells of human allergic inflammation. IL13 R130Q was significantly more active than wildtype IL13 in multiple effector assays and was neutralized less effectively by an IL13R-alpha-2 decoy. Vladich et al. (2005) suggested that natural variation in the coding region of IL13 may be an important genetic determinant of susceptibility to allergy.

PMID: 10699178
PMID: 15356556
PMID: 12928861
PMID: 15483090
PMID: 15711639

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.

PMID: 16051700
PMID: 19405049

rs34079299 - NM_000619.2(IFNG):c.115-484_115-457CA[12]

TSC2 Renal Angiomyolipoma Modifier

Because interferon-gamma is a useful mediator of tumor regression in animal models of kidney tumors, and because allele 2 of the IFNG gene is known to be highly expressed in humans, Dabora et al. (2002) examined the influence of this IFNG genotype on the severity of renal disease in patients with tuberous sclerosis-2 (613254) who had mutations in the TSC2 gene (191092). The frequency of allele 2, with 12 CA repeats, was significantly higher in the patients without kidney angiomyolipomas than in those with kidney angiomyolipomas.

Susceptibility to Aplastic Anemia

Dufour et al. (2004) studied the distribution of the VNDR 1349 polymorphism of IFNG in 67 Caucasian aplastic anemia (609135) patients and in normal controls. Homozygosity for allele 2 (12 repeats on each chromosome) or the 12 repeats on only 1 chromosome were significantly more frequent (p = 0.005 and 0.004, respectively) in patients versus controls. The polymorphism was equally distributed in aplastic anemia patients regardless of their response to immunosuppression. Dufour et al. (2004) concluded that homozygosity for 12 CA repeats at position 1349 of the IFNG gene is strongly associated with the risk of aplastic anemia in Caucasian subjects.

PMID: 12192641
PMID: 15327519

NM_016511.4(CLEC1A):c.77G>C (p.Gly26Ala)

Stappers et al. (2018) identified a single-nucleotide polymorphism (SNP) in CLEC1A, rs2306894 (gly26 to ala, global minor allele frequency 0.3295) that negatively affects myeloid inflammatory responses. They found that the risk allele of the SNP was significantly associated with susceptibility to aspergillosis in stem-cell transplant recipients (614079) when the variant was carried by the donor, not the recipient (p = 0.003), in a comparison of the incidence of invasive aspergillosis after transplantation according to donor (238 wildtype, 72 risk allele-carrying individuals) or recipient (228 wildtype, 80 risk allele-carrying individuals) genotype at rs2306894. Stappers et al. (2018) found that macrophages from individuals carrying this SNP produced significantly less IL1-beta (147720) and IL8 (146930) after in vitro stimulation with A. fumigatus conidia compared to controls, whereas there was no difference in response upon stimulation with lipopolysaccharide. Stappers et al. (2018) concluded that in humans, the protective functions of MelLec are primarily mediated by myeloid cells.

Aspergillus species are ubiquitous in nature and cause a wide spectrum of diseases, including saprophytic colonization of existing cavities (aspergilloma), allergic asthma, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, and disseminated disease associated with high mortality rates in patients with hematologic malignancies and recipients of solid organs and stem cell transplantations. Immunocompetent and nonatopic individuals are relatively resistant to infection, and disease occurs in the setting of host damage. Association of persistent inflammation with intractable infection is common in nonneutropenic patients after hematopoietic stem cell transplantation, as well as in allergic fungal diseases. The pathophysiology underlying Aspergillus infection highlights the bipolar nature of the inflammatory process in infection, in which early inflammation prevents or limits infection, but an uncontrolled response may oppose disease eradication (summary by Cunha et al., 2010). For information on familial occurrence of allergic bronchopulmonary aspergillosis, see 103920.

PubMed PMID: 29489751

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

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

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

PubMed PMID: 18403759

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

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

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

PubMed PMID: 18179894

rs180195 - NM_003235.4(TG):c.-1623A>G

Stefan et al. (2011) identified a -1623A-G SNP (rs180195) in the promoter region of the TG gene that modified a binding site for IRF1 (147575) and predisposed to autoimmune thyroid disease (AITD; 608175). By genotyping 271 Caucasian patients with AITD (201 with Graves disease and 70 with Hashimoto thyroiditis) and 165 matched controls, they found a significant increase in the frequency of the G allele (p = 0.006) and the GG genotype (p = 0.03; odds ratio = 1.6) in AITD patients compared with controls. Stefan et al. (2011) confirmed the association in a cohort of 102 multiplex families. Database analysis revealed that rs180195 lies within a putative binding motif for IRF1 or ETS1 (164720), and that the AITD-associated G allele is conserved in vertebrates, whereas the protective A allele is unique to humans. Cell culture and in vitro assays revealed that IRF1 bound the TG promoter with the G allele at the rs180195 site and activated transcription of a reporter gene. Binding of IRF1 correlated with histone markers of active chromatin. IRF1 did not activate transcription from the A allele. Stefan et al. (2011) concluded that the disease-associated variant of TG defines an active enhancer element.

PubMed PMID: 21757724

rs10638303 - NM_006416.5(SLC35A1):c.752-157_752-156insCTCA

Martinez-Duncker et al. (2005) identified a 4-bp insertion in intron 6 of the SLC35A1 gene that was found to be a common polymorphism with a frequency of 0.32 (34 of 106 controls). The insertion creates a new U2 snRNA site that is in competition with the putative normal U2 snRNA site. Studies of clones derived from a control with the 4-bp insertion showed 5 different transcript variants: wildtype gene (47%), partial skipping of exon 6 (29%), full skipping of exon 6 (14%), full skipping of exons 5 and 6 (9%), and partial skipping of exon 6 plus full skipping of exon 3 (1%). The authors referred to this polymorphism as 'leaky,' allowing for the expression of enough wildtype transcripts even in homozygous individuals to avoid the disease.

In a patient with congenital disorder of glycosylation type IIf (CDG2F; 603585) who died at age 37 months, Martinez-Duncker et al. (2005) identified compound heterozygosity for the 4-bp insertion inherited from the mother and another mutation (605634.0002) inherited from the father. A clone of the allele inherited from the mother showed a 130-bp deletion, corresponding to the partial skipping of exon 6. The authors noted that when combined with a clearly pathogenic mutation, as in this patient, the leaky mutation can result in disease. Both alleles derived from the patient failed to complement Slc35a1-deficient CHO Lec2 cells, indicating that they were both inactive in this patient. The authors used RNA derived from a buffy coat containing neutrophils from the patient to synthesize cDNA and perform direct sequence analysis.

PubMed PMID: 15576474

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

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

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

PubMed PMID: 16470599

rs11196205 - NM_001146274.2(TCF7L2):c.552+7162G>C

Ng et al. (2007) examined 22 SNPs spanning the TCF7L2 gene for association with type 2 diabetes in Hong Kong Chinese. In a case-control study, they replicated an association with the at-risk C allele of rs11196205 (OR, 2.11; 95% CI, 1.04-4.26), previously identified in a Japanese population (see Hayashi et al., 2007).

Miyake et al. (2008) analyzed 5 SNPs in the TCF7L2 gene in 2,214 Japanese individuals with type 2 diabetes and 1,873 controls and confirmed significant association with the minor allele of rs11196205 (OR, 1.39; p = 4.6 x 10(-4)). The association remained significant after adjustment for age, sex, and BMI (adjusted p = 0.0053).

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: 17340123
PubMed PMID: 17609304
PubMed PMID: 18097733

rs12255372 - NM_001146274.2(TCF7L2):c.552+9017G>T

In an Icelandic population, Grant et al. (2006) found strong linkage disequilibrium between a SNP in intron 4 of the TCF7L2 gene, rs12255372, and a microsatellite marker in intron 3, DG10S478, associated with type 2 diabetes (125853) (p = 2.1 x 10(-9)).

Using a logistic regression model incorporating individual ancestry, sex, age, body mass index, and education in 286 Mexican patients with type 2 diabetes mellitus and 275 controls, Parra et al. (2007) analyzed the DG10S478 microsatellite in intron 3 and rs12255372 in intron 4 of the TCF7L2 gene. All 3 markers were in tight disequilibrium in the Mexican sample. Parra et al. (2007) observed a significant association between rs12255372 and DG10S478 and type 2 diabetes mellitus (OR = 1.78, p = 0.017, and OR = 1.62, p = 0.041, respectively).

Mayans et al. (2007) genotyped 4 SNPs in the TCF7L2 gene in 872 Swedish patients with type 2 diabetes and 857 age-, sex-, and geographically-matched controls and replicated the previously identified association between rs12255372 and disease (p = 0.000004).

Miyake et al. (2008) analyzed 5 SNPs in the TCF7L2 gene in 2,214 Japanese individuals with type 2 diabetes and 1,873 controls and confirmed significant association with the minor allele of rs12255372 (OR, 1.70; p = 9.8 x 10(-5)). The association remained significant after adjustment for age, sex, and BMI (adjusted p = 7.0 x 10(-4)).

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: 16415884
PubMed PMID: 17470138
PubMed PMID: 17245407
PubMed PMID: 18097733

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

rs3842570 - NM_023083.4(CAPN10):c.997+136_998-148dup

See 605286.0001. Horikawa et al. (2000) referred to this 2-allele polymorphism consisting of 2 or 3 copies of 32-bp sequence at nucleotide g.7917 (relative to the initiation start site) as SNP19 (rs3842570).

In view of the role of beta-adrenoceptors (see 109630) in thermogenesis, Hoffstedt et al. (2002) investigated the relationship between beta-1-, beta-2-, and beta-3-adrenoceptor-stimulated lipolysis in abdominal subcutaneous fat cells and 3 different SNPs in the CAPN10 gene (SNP19; SNP43, 605286.0001; and SNP63, 605286.0003). The study sample comprised 240 healthy subjects. A strong association between lipolytic beta-3-receptor (109691) function in adipocytes and SNP19, which is a deletion/insertion (1/2), was observed in overweight subjects (BMI greater than 25 kg/m2), but not in lean ones. No association was found between any of the polymorphisms and lipolytic function of either beta-1- or beta-2- (109690) receptors. Carriers of 1/1 in SNP19 had 30-fold decreased lipolytic sensitivity of beta-3-adrenoceptors in comparison to 1/2 or 2/2 carriers (p = 0.0019, by ANOVA). This was found in both genders and was not influenced by SNP43 or SNP63 in the CAPN10 gene or by the W64R polymorphism in the beta-3-adrenoceptor gene (109691.0001).

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: 11017071
PubMed PMID: 12107250

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

rs2165241 - NM_005576.4(LOXL1):c.1102+1976T>C

Lemmela et al. (2009) analyzed the SNP rs2165241, a C-T change in intron 1 of the LOXL1 gene, as well as 2 other LOXL1 SNPS, rs1048661 (153456.0001) and rs3825942 (153456.0002), 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 (T) allele of rs2165241 (p = 2.62 x 10(-13) and p less than 0.0001, 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: 19343041

rs1143627 - NM_000576.2(IL1B):c.-118C>T

A C-T SNP at position -31 from the transcription start site (rs1143627) involves the TATA sequence in the IL1B promoter. Using electrophoretic mobility shift analysis to assess DNA binding in vitro, El-Omar et al. (2000) found that the IL1B -31T allele was associated with a 5-fold increase in DNA binding after lipopolysaccharide stimulation. Individuals carrying the IL1B -31T allele were at higher risk of hypochlorhydria and of gastric cancer (137215) after H. pylori infection.

Hamajima et al. (2001) observed the near complete linkage of the -31C/-511T and -31T/-511C IL1B alleles in 241 Japanese non-cancer outpatients participating in an H. pylori eradication program. They determined that the C-to-T transition at position -31, creating a TATA box, is associated with vulnerability to persistent H. pylori infection, and that the susceptibility is modified by smoking. They noted that this linkage was opposite to that reported in Caucasian subjects (El-Omar et al., 2000). Prompted by the report of Hamajima et al. (2001), El-Omar et al. (2000) reviewed and corrected their own data. In an erratum, El-Omar et al. (2000) stated that consistent with the observation of Hamajima et al. (2001), -511T/-31C is the correct linkage in Caucasians.

Among 310 individuals from eastern India, Chakravorty et al. (2006) found that the frequency of the IL1B -31TT genotype was 0.071 compared to 0.37 as reported in Caucasians. Among the Indian population, they observed a significantly higher frequency of the IL1B -511TT genotype (OR of 4.22) and -31CC genotype (OR of 2.16) in H. pylori-infected persons with duodenal ulcer compared to infected persons with normal mucosa. The -511T/-31C haplotype was present at a higher frequency in H. pylori-infected duodenal ulcer patients than in infected controls (OR of 2.47). Carriers of the -31CC genotype had significantly lower IL1B mRNA levels in gastric mucosa compared to other genotypes, and IL1B promoter assay showed that the -31T promoter had a 10-fold increase in activity compared to -31C. Chakravorty et al. (2006) suggested that H. pylori-infected individuals with the -31CC genotype secrete less IL1B and are susceptible to duodenal ulcers.

---Possible Association with Tuberculosis Susceptibility

Zhang et al. (2014) examined the genotype distribution of 4 IL1B SNPs with potential regulatory effects in 2 independent Chinese populations with tuberculosis (TB; see 607948) and 2 independent sets of healthy controls (1,799 total TB cases and 1,707 total controls). They found that only the frequency of the T allele of the -31C-T SNP in the IL1B promoter was significantly higher in patients with active TB, both pulmonary and extrapulmonary. High-resolution computer-assisted tomography analysis indicated that the -31T allele was associated with more severe pulmonary TB than the -31C allele. Stimulation of monocytes with Mycobacterium tuberculosis (Mtb) antigens resulted in higher amounts of IL1B protein and mRNA, but not of IL1R antagonist (IL1RN; 147679), in healthy controls carrying -31TT or -31TC compared with those carrying -31CC. Stimulation of PBMCs with Mtb antigens resulted in no significant differences in IFNG (147570) or IL17 (603149) production in controls; however, stimulation was associated with higher IFNG production in TB patients carrying -31TT. Analysis of bronchoalveolar lavage fluid from patients with active TB showed that higher IL1B production was associated with higher neutrophil recruitment. EMSA supershift analysis detected higher binding of CEBPA (116897) and PU.1 (SPI1; 165170) to the -31T oligonucleotide compared with the -31C oligonucleotide. Zhang et al. (2014) concluded that the higher IL1B production and neutrophil recruitment associated with -31T lead to increased tuberculosis susceptibility, tissue-damaging inflammatory responses, and accelerated disease progression.

PubMed PMID: 10746728
PubMed PMID: 11346459
PubMed PMID: 16550552
PubMed PMID: 25329476

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

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

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

PubMed PMID: 12724780
PubMed PMID: 15199380

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

rs3737787 - NM_007122.5(USF1):c.*187C>T

Pajukanta et al. (2004) identified 2 SNPs of the USF1 gene, usf1s1 (rs3737787) and usf1s2 (191523.0002), that were associated with familial combined hyperlipidemia mapping to a locus on 1q21-q23 (FCHL1; 602491). The usf1s1 SNP is located in the 3-prime untranslated region (Naukkarinen et al., 2005). The common alleles (1-1) of the 2 SNPs define an at-risk haplotype. Allelic associations of the at-risk haplotype were found with triglycerides, apoB (107730), total cholesterol, and LDL peak particle size, supporting the concept that USF1 affects the complex lipid phenotype of FCHL and not only 1 lipid trait.

PubMed PMID: 14991056
PubMed PMID: 16076849

rs2073658 - NM_007122.5(USF1):c.561-100G>A

The usf1s2 SNP (rs2073658), which was associated with susceptibility to familial combined hyperlipidemia (FCHL1; 602491) by Pajukanta et al. (2004), is located in intron 7; see 191523.0001.

Naukkarinen et al. (2005) identified a 20-bp DNA sequence in intron 7 of the USF1 gene, containing rs2073658, that bound nuclear proteins and likely represented a transcriptional regulatory element. This functional role was further supported by the differential expression of USF1-regulated genes in fat biopsy between individuals carrying different allelic variants of USF1. Apolipoprotein E (APOE; 107741) was the most downregulated gene in the at-risk individuals, linking the potential risk alleles of USF1 with the impaired APOE-dependent catabolism of atherogenic lipoprotein particles.

PubMed PMID: 14991056
PubMed PMID: 16076849

rs2266788 - NM_001166598.2(APOA5):c.*158C>T

The APOA5*2 haplotype includes the rare C allele of the SNP c.*158C-T (rs2266788, also referred to as c.1891T-C, c.1259T-C, or SNP1), located in the 3-prime untranslated region (UTR), in strong linkage disequilibrium with 3 other SNPs (g.4430C-T, rs662799, also referred to g.-1131T-C or SNP3; c.-3A-G, rs651821; and c.162-43A-G, rs2072560, also referred to as IVS3+476G-A or SNP2). The APOA5*2 haplotype was associated with a 20 to 30% elevation in plasma triglyceride levels (145750) in 500 unrelated Caucasian men and women, and was more than 3 times as common in individuals who had plasma triglyceride concentrations greater than the 90th percentile than in those with plasma triglyceride concentrations below the 10th percentile for age and sex (Pennacchio et al., 2001; summary by Pennacchio et al., 2002). Individuals with APOA5*2 display reduced APOA5 expression at the posttranscriptional level. Caussy et al. (2014) hypothesized that the hypertriglyceridemic effects of APOA5*2 could involve miRNA regulation in the APOA5 3-prime UTR. Bioinformatic studies identified the creation of a potential miRNA binding site for liver-expressed MIR485 (615385)-5p in the mutant APOA5 3-prime UTR with the c.*158C allele. In HEK293T cells cotransfected with an APOA5 3-prime UTR luciferase reporter vector and a MIR485-5p precursor, c.*158C allele expression was significantly decreased. Moreover, in Huh-7 cells endogenously expressing MIR485-5p, Caussy et al. (2014) observed that luciferase activity was significantly lower in the presence of the c.*158C allele than in the presence of the c.*158T allele, which was completely reversed by a MIR485-5p inhibitor. Caussy et al. (2014) suggested that the well-documented hypertriglyceridemic effect of APOA5*2 involves an APOA5 posttranscriptional downregulation mediated by MIR485-5p. Caussy et al. (2014) cited a frequency of APOA5*2 of approximately 7% in populations of European descent.

PubMed PMID: 12417524
PubMed PMID: 11588264
PubMed PMID: 24387992

rs28493229 - NM_025194.3(ITPKC):c.1155+9G>C

Onouchi et al. (2008) found a significant association between susceptibility to Kawasaki disease (611775) and a functional SNP, which the authors designated itpkc_3 (rs28493229), in the ITPKC gene. It was associated also with increase in coronary artery lesions in both Japanese and U.S. children. Among 78 affected Japanese sib pairs, 40 pairs shared more than one allele near itpkc_3; in this subset, the itpkc_3 allele was overrepresented compared to controls (OR = 2.46, 95% CI 1.63-3.73). The C allele of rs28493229 was associated with the increased risk.

In an association study involving 385 unrelated Taiwanese children with Kawasaki disease, 140 with coronary artery lesions, and 1,158 ethnically matched healthy controls, Chi et al. (2010) did not find a statistically significant association between the ITPKC gene SNP rs28493229 and Kawasaki disease or coronary artery lesions in Taiwanese children.

PubMed PMID: 18084290
PubMed PMID: 20045869

rs3793784 - NM_001277059.1(ERCC6):c.-76C>G

In a cohort of 460 ARMD cases and 269 age-matched controls and 57 archived ARMD cases and 18 age-matched non-ARMD controls, Tuo et al. (2006) found that a -6530C-G SNP (rs3793784) in the 5-prime flanking region of the ERCC6 gene was associated with ARMD5 susceptibility (613761), both independently and through interaction with an intronic G-C SNP in the CFH gene (rs380390; 134370.0008) previously reported to be highly associated with ARMD. A disease odds ratio of 23 was conferred by homozygosity for risk alleles at both ERCC6 and CFH (G allele and C allele, respectively) compared to homozygosity for nonrisk alleles. Tuo et al. (2006) suggested that the strong ARMD predisposition conferred by the ERCC6 and CFH SNPs may result from biologic epistasis. In functional studies on the -6530C-G SNP, Tuo et al. (2006) found that the SNP conferred a distinct change in regulation of gene expression in vitro and in vivo, with enhanced expression associated with the G allele.

Lin et al. (2008) found that the -6530C allele has about 2-fold decreased transcriptional activity as well as decreased binding affinity of nuclear proteins compared to the G allele. In a case-control study of 1,000 Chinese patients with various types of lung cancer (see 211980) and 1,000 Chinese controls, those with the CC genotype had a 1.76-fold increased risk of disease compared to those with the CG or GG genotypes (p = 10(-9)). The C allele also interacted with smoking to intensify lung cancer risk, yielding an odds ratio of 9.0 for developing cancer among heavy smokers.

PubMed PMID: 16754848
PubMed PMID: 17854076

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

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

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

PubMed PMID: 18455130

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

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

PubMed PMID: 11978667

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

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

PubMed PMID: 18458324

rs1048990 - NM_002791.3(PSMA6):c.-8C>G

Ozaki et al. (2006) found a significant association of susceptibility to myocardial infarction (608446) in the Japanese population with a -8C-G SNP (rs1048990) in the 5-prime UTR of exon 1 of the PSMA6 gene. The SNP enhanced the transcription of PSMA6.

Hinohara et al. (2009) analyzed the -8C-G polymorphism in a total of 1,330 patients with coronary artery disease (CAD) and 2,554 controls from Japanese and Korean populations but found no evidence for association. However, metaanalysis of data from this study and earlier studies yielded an odds ratio of 1.08 for the G allele (p = 0.0057), suggesting that the contribution of PSMA6 to CAD is not large enough to be readily replicated. Hinohara et al. (2009) concluded that further studies are required to establish the contribution of this variant in susceptibility to CAD.

PubMed PMID: 16845397
PubMed PMID: 19282875

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

rs3127334 - NM_003181.3(TBXT):c.1034+79C>T

Morrison et al. (1996) identified a T-to-C transition polymorphism in the T gene located 79 bp downstream from the 5-prime end of intron 7. They referred to this variant as 'TIVS7-2.' They observed a bias in transmission of the C allele from heterozygous parents to offspring with neural tube defects (NTD; 182940) in Dutch and U.K. families.

Shields et al. (2000) also found an association between the TIVS7-2 allele and neural tube defects. However, Trembath et al. (1999) and Speer et al. (2002) found no association.

Jensen et al. (2004) developed a genotyping assay for the TIVS7 T/C polymorphism and used it to genotype spina bifida case-parent trios. Analyses of the data demonstrated that heterozygous parents transmitted the C allele to their offspring with spina bifida significantly more frequently than expected under the assumption of mendelian inheritance. Moreover, the analyses suggested that the C allele acts in a dominant fashion, such that individuals carrying 1 or more copies of this allele have a 1.6-fold increased risk of spina bifida compared with individuals with 0 copies.

PubMed PMID: 8733136
PubMed PMID: 10332959
PubMed PMID: 10817656
PubMed PMID: 12116228
PubMed PMID: 15449172

rs1421085 - NM_001080432.3(FTO):c.46-43098T>C

Dina et al. (2007) identified 2 potentially functional SNPs in intron 1 of the FTO gene that were consistently strongly associated with early-onset and severe obesity (BMIQ14; 612460) in 2,900 affected individuals and 5,100 controls (p = 1.67 x 10 (-26) for the C allele of rs1421085 and p = 1.07 x 10 (-24) for the G allele of rs17817449). The at-risk haplotype yielded a proportion of attributable risk of 22% for common obesity.

Meyre et al. (2009) analyzed genomewide association data from 1,380 Europeans with early-onset and morbid adult obesity and 1,416 age-matched normal-weight controls and found the strongest association signal in the first intron of the FTO gene for the imputed SNP rs1421085 (p = 3 x 10(-12)). Subsequent analysis confirmed the association in an additional 14,186 European individuals (combined p = 1.2 x 10(-28)).

In a study examining the contribution of a risk haplotype for obesity involving 3 SNPs in introns 1 and 2 of the FTO gene (rs1421085, rs9930506, and rs1558902), Claussnitzer et al. (2015) obtained the highest phylogenetic module complexity analysis (PMCA) score for rs1421085, which they noted is in perfect linkage disequilibrium with the most significant reported SNP, rs1558902. Analysis of the rs1421085 T-C alteration revealed that it disrupts a conserved motif for the regulatory gene ARID5B (608538), causing derepression of a potent preadipocyte enhancer and doubling of IRX3 (612985) and IRX5 (606195) expression during early adipocyte differentiation. This results in a cell-autonomous developmental shift from energy-dissipating beige (brite) adipocytes to energy-storing white adipocytes, with a 5-fold reduction in mitochondrial thermogenesis and an increase in lipid storage. Inhibition of Irx3 in adipose tissue in mice reduced body weight and increased energy dissipation without a change in physical activity or appetite. Knockdown of IRX3 or IRX5 in primary adipocytes from homozygous carriers of risk alleles at rs1421085, rs9930506, and rs1558902 restored thermogenesis, increasing it by a factor of 7, whereas overexpression of these genes had the opposite effect in adipocytes from carriers homozygous for the nonrisk variant of these 3 SNPs. Repair of the ARID5B motif in primary adipocytes from a patient with the risk alleles restored IRX3 and IRX5 repression, activated browning expression programs, and restored thermogenesis, increasing it by a factor of 7. Claussnitzer et al. (2015) concluded that the FTO SNP rs1421085 represents the causal variant that disrupts a pathway for adipocyte thermogenesis involving ARID5B, IRX3, and IRX5, providing a mechanistic basis for the genetic association between FTO and obesity.

PubMed PMID: 17496892
PubMed PMID: 19151714
PubMed PMID: 26287746

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

rs2975760 - NM_023083.4(CAPN10):c.471-187T>C

Horikawa et al. (2000) referred to a polymorphism consisting of a g.4841T-C transition (relative to the initiator codon) in intron 3 of the CAPN10 gene as SNP44.

Using family-based and case-control studies, Evans et al. (2001) examined the contribution of CAPN10 to the development of type II diabetes (125853) in white subjects of English/Irish ancestry. While they did not confirm the previously described 3-SNP haplotype associated with type II diabetes in Mexican Americans and in 2 northern European populations (Horikawa et al., 2000), they observed significantly increased (p = .033) transmission of the less common C allele at SNP44 to affected offspring in parents-offspring trios (odds ratio 1.6). An independent UK case-control study and a small discordant-sib study did not show significant association individually. In a combined analysis of all U.K. studies (p = .015) and in combination with a Mexican American study (p = .004), the C allele at SNP44 was associated with type II diabetes.

Gonzalez et al. (2002) investigated whether polymorphisms in the CAPN10 gene are associated with polycystic ovary syndrome (PCOS; 184700), which is characterized by chronic anovulation infertility, hyperandrogenemia, and frequently, insulin resistance. The allelic frequencies and genotypes of CAPN10 polymorphisms SNP44, SNP43, SNP19, and SNP63 were determined in 55 women with polycystic ovaries and 93 unrelated healthy controls, using spectrofluorimetric analyses and RT-PCR. The data indicated that the CAPN10 SNP44 allele is associated with PCOS in the Spanish population (p = 0.01) and the results supported a role of the CAPN10 gene in PCOS susceptibility in humans.

Weedon et al. (2003) confirmed a role for calpain-10 variation in type II diabetes susceptibility, by a metaanalysis and a large association study. The results confirmed that the SNP44 variant, located in intron 3, predisposes to type II diabetes. They noted that in several studies SNP44 was in perfect linkage disequilibrium with a missense mutation and 2 SNPs in the 5-prime UTR and therefore may not be the causal variant.

In an extension analysis of 148 patients, Gonzalez et al. (2003) confirmed the association of the SNP44 allele of CAPN10 with PCOS in Spanish women.

PubMed PMID: 11017071
PubMed PMID: 11481585
PubMed PMID: 12161543
PubMed PMID: 14574648
PubMed PMID: 14602801

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

rs3766379 - NM_016382.4(CD244):c.834+526A>G

In an analysis of a 1.1-Mb linkage disequilibrium segment associated with susceptibility to rheumatoid arthritis (180300) involving 2 independent rheumatoid arthritis cohorts from Japan, Suzuki et al. (2008) observed the most significant association at rs3766379 (P = 3.23 x 10(-8), odds ratio = 1.31, confidence interval 1.19-1.44) in intron 5 of the CD244 gene. The SNP rs3766379 is located in a heat-shock transcription factor-1 (HSF1)/HSF2/early growth response-2 (EGR2) binding site and an upstream transcription factor-1 (USF1) binding site. The susceptibility allele increased the expression of CD244 in luciferase and allele-specific transcript quantification assays.

PubMed PMID: 18794858

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

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

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

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

PubMed PMID: 17189288
PubMed PMID: 18063667

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

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

PubMed PMID: 17377159

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

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

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

PubMed PMID: 17236130
PubMed PMID: 18252221

rs414171 - NM_001243926.1(MAPKAPK3):c.-436A>T

In a case-control study testing for association between CISH polymorphisms and susceptibility to major infectious diseases involving 8,402 individuals from Gambia, Hong Kong, Keyna, Malawi, and Vietnam, Khor et al. (2010) found that rs414171 at the -292 position relative to the CISH gene results in increased susceptibility to tuberculosis (607948), malaria (611162), and invasive bacterial disease (BACTS2; 614383) (p = 4.58 x -10(-7)). In addition, peripheral blood mononuclear cells obtained from adult subjects carrying the -292 variant, as compared with wildtype cells, showed a muted response to the stimulation of interleukin-2 (IL2; 147680), i.e., 25 to 40% less CISH expression.

PubMed PMID: 20484391

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

rs326 - NM_000237.3(LPL):c.1323-187A>G

In an association study of 7 HDL metabolism genes in participants in the Dallas Heart Study and in 849 African American men and women from Maywood, Illinois, Spirin et al. (2007) identified a SNP of the LPL gene, rs326, that was associated with incremental changes in HDL cholesterol levels in 3 independent samples (see HDLCQ11, 238600). This SNP achieved a P value of 3.49 x 10(-8) in analysis of covariance in the entire sample in a model that included race, sex, age, and body mass index (BMI). The A allele was associated with lowering of HDL cholesterol.

Richardson et al. (2013) showed that rs326 is in linkage disequilibrium with rs13702 (609708.0043), which is the functional variant in this LD region.

PubMed PMID: 17952847
PubMed PMID: 23246289

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

rs2124437 - NM_170672.3(RASGRP3):c.-261+9727G>T

The frequency of the homozygous SNP genotype AA in cases was 31% from a total of 500 patients analysed and the frequency in the control group comprising of long term tobacco chewers (minimum of 10 years tobacco chewing habit) was 25% of the total 500 subjects. The p-value calculated was <0.01 and the OR was 1.34 (1.01-1.76) indicating a 34% increased risk of oral cancer in tobacco habitues to oral cancer.

rs1957358 - NM_001161576.2(SAMD4A):c.912+4220T>C

A significant association of rs1957358 (SAMD4A) TT (odds ratio [OR] 1.44; 95% confidence interval [CI] 1.10-1.90) indicated increased risk to oral cancer. While, the rs1957358 (SAMD4A) TC (OR 0.67; 95% CI 0.53-0.87) indicated decreased risk to oral cancer.

rs2306058 - NM_032217.5(ANKRD17):c.7731G>A (p.Thr2577=)

A significant association of rs2306058 (ANKRD17) CT (odds ratio [OR] 0.72; 95% confidence interval [CI] 0.56-0.93) indicated decreased risk to oral cancer.

rs1335022 - NM_021956.4(GRIK2):c.2086-16819C>T

The homozygous SNP genotype TT demonstrated a higher frequency in the cases (0.528) than in controls (0.414). A significant association was observed with an OR of 1.58 (1.23-2.03) while the heterozygous genotype CT decreased risk of oral cancer with OR 0.68 (0.53-0.87). The SNP allele was associated with increased risk and WT allele with decreased risk of oral cancer.

rs12654264 - NM_000859.3(HMGCR):c.1368+1176A>T

Kathiresan et al. (2008) replicated the association of rs12654264 (300A-T) of the HMGCR gene with LDL cholesterol levels in 5,414 subjects from the cardiovascular cohort of the Malmo Diet and Cancer Study (p = 4 x 10(-4)).

PubMed PMID: 18354102

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

rs973851559|2004640|1432329681 - NM_001098629.3(IRF5):c.-12+198=

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

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

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

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

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

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

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

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

PubMed PMID: 18327256
PubMed PMID: 18327257

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.

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PubMed PMID: 17718394
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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

rs3834129 - NM_001228.4(CASP8):c.-937_-932del

Sun et al. (2007) identified a 6-nucleotide insertion/deletion polymorphism in the CASP8 promoter, -652 AGTAAG ins/del (rs3834129), the deletion variant of which was associated with decreased risk of developing lung cancer (211980) in a population of Han Chinese subjects. The -652 6N deletion was also associated with decreased risk of cancer of various other forms including esophageal, gastric, colorectal, cervical, and breast, acting in an allele dose-dependent manner. The frequency of the -652 6N deletion was significantly lower in individuals with lung cancer (P = 4.1 x 10(-5)).

Haiman et al. (2008) did not find an association between this SNP and breast (114480), colorectal (114500), or prostate (176807) cancer among 2,098, 1,139, and 2,825 patients, respectively. The study included patients in Hawaii and California of various ethnic groups.

PubMed PMID: 17450141
PubMed PMID: 18305469

List of Conditions:

- Legius syndrome
- Hyperglycinuria
- Prostate cancer
- Inflammatory bowel disease 1
- Encephalopathy
- Leanness
- Prekallikrein deficiency
- Autosomal dominant nocturnal frontal lobe epilepsy
- Familial hypercholesterolemia
- Phenylketonuria
- Carcinoma of colon
- APOLIPOPROTEIN A-IV POLYMORPHISM
- Acute myeloid leukemia with maturation
- Congenital heart disease
- Unknown
- Familial Mediterranean fever
- Cancer progression and tumor cell motility
- Diabetes mellitus
- Fetal hemoglobin quantitative trait locus 2
- Preeclampsia/eclampsia 4

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.