Cardiometabolic Disorders Panel

Kit ID: KITSAMPLE

Report Description

The Cardiometabolic test is based on Germline DNA mutation analysis. As such, it analyzes all Common and Rare Variants associated with Cardiometabolic disorders instead of a limited set of genes. "Cardiometabolic Disorders" is an umbrella term that encompasses several medical conditions, most of which are preventable, that affect heart health and metabolic homeostasis. These are common diseases such as insulin resistance and impaired glucose tolerance, hypertension and dyslipidemias which, in recent years, have undergone a rapid increase in incidence, becoming the leading cause of death in the world. These conditions, in fact, represent universally recognized risk factors for cardiovascular accidents such as heart attack and stroke and for serious metabolic complications such as type 2 diabetes. Cardiometabolic Disorders fully symbolize the changes in lifestyles of recent decades in which excess food (especially processed food), associated with a sedentary lifestyle and alcohol / smoking habit, contributes to altering the physiological energy balance, especially in particularly predisposed subjects. Central adiposity, i.e. the accumulation of fat in the abdominal area, represents the major cardiometabolic risk factor and is the mirror of the imbalance between calories consumed and calories consumed. The etiopathogenesis of Cardiometabolic Disorders is multifactorial and has an important genetic component, although they are not strictly "transmissible" pathologies. In fact, there are genes and predisposing conditions (such as familiarity) on which environmental and individual factors (linked to lifestyles) act which, acting in synergy, favor its onset. Cardiometabolic Disorders well represent the interconnections existing between the different systems of the body (in particular the excretory and cardiovascular one) and our energy metabolism, highlighting how serious and prolonged alterations in the latter can have long-term repercussions on the well-being of the whole organism. Along with environmental factors, Genetics plays a key role in the regulation of Cardiometabolic Disorders. - more than 500 genes analyzed - 100% of genomic regions covered - Intragenic and intergenic regions analyzed - All variants reported."

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

- Hereditary fructosuria

Variants analyzed

PC 1	DBT 1	DMD 1	DSP 1	GHR 1	INS 1	LEP 1	LPL 1	TTN 1
ANK2 1	APOB 1	CHD7 1	JAG1 1	LDHA 1	LDLR 1	MC4R 2	PCK1 1	PLEC 1
PLTP 1	RYR2 1	SGCD 1	SOS1 1	ABCC8 1	ALDOB 1	APOA5 2	GATA4 4	KCNJ5 1
MED12 1	PCSK9 3	POMT2 1	SCN1A 1	TNNI3 2	TNNT1 1	ACVR2B 1	BMPR1B 1	COL5A2 1
KCNJ11 2	PNPLA2 1	TMEM43 1	CYP27A1 1	LDLRAP1 1	SELENON 1	TOR1AIP1 1		

Summary Table

Pathogenic/Likely pathogenic variant(s) detected.

Gene	Coordinates	Nucleotide Change	rsID	Clinvar class.	Zygosity	Disease
ALDOB	9: 104189856	NM_000035.4(ALDOB):c.448G>C	rs1800546	Pathogenic	HET	Hereditary fructosuria, Fructose intolerance

Clinical Variants Found

ALDOB [PATHOGENIC] [RARE] [HGMD]

9 104189856 C>G

rs1800546 - NM_000035.4(ALDOB):c.448G>C (p.Ala150Pro)

Phenotypes

Hereditary fructosuria, Fructose intolerance

ZYG	HET
MAF	0.0018
ACMG	Likely pathogenic
CLIN. SIG	Pathogenic [★★]
HGMD Rankscore	0.41
HGMD Variant Class	DM

ALDOB Description

Cross et al. (1988) reported the first identification of a molecular lesion in the ALDOB gene in hereditary fructose intolerance (HFI; 229600). A G-to-C transversion in exon 5 of the ALDOB gene created a new recognition site for the restriction enzyme AhaII and resulted in an ala149-to-pro (A149P) substitution within a region critical for substrate binding. Utilizing this novel restriction site and the polymerase chain reaction (PCR), Cross et al. (1988) showed that the patient was homozygous. Three other patients with hereditary fructose intolerance unrelated to the original patient were found to have the same mutation; 2 were homozygous and 1 was compound heterozygous with another mutation in the ALDOB gene.

PubMed 3383242

Cross and Cox (1989) used allele-specific oligonucleotide probes to detect the A149P mutation in other pedigrees. They found the same mutation in all 12 British patients examined. Diagnosis of both homozygotes and heterozygotes could be achieved by specific amplification of DNA derived from mouthwash samples followed by hybridization to allele-specific oligonucleotides.

PubMed 2623136

In a study of patients with fructose intolerance drawn widely from Europe and the U.S., Cross et al. (1990) found the A149P mutation in 67% of alleles tested. The mutation was significantly more common in patients from northern than from southern Europe.

PubMed 1967768

Brooks and Tolan (1993) studied the possible origin of the A149P mutation, which accounts for 57% of fructose intolerance chromosomes. In 15 homozygotes they found absolute linkage disequilibrium between the A149P mutation and a particular 2-site RFLP, suggesting a single origin and founder effect.

PubMed 8096362

Dursun et al. (2001) screened 13 Turkish patients with hereditary fructose intolerance for 3 common mutations. Nine of the patients were homozygous for the A149P mutation, which corresponded to a frequency of about 55%.

PubMed 11757579

Davit-Spraul et al. (2008) identified the A149P mutation, which they referred to as ALA150PRO (A150P), in 64% of mutant alleles from 162 patients from 92 families with hereditary fructose intolerance. Most of the patients were French.

PubMed 18541450

APOB [CONFLICTING] [HGMD]

2 21231592 G>A

rs6413458 - NM_000384.3(APOB):c.8148C>T (p.Ile2716=)

Phenotypes

Familial hypercholesterolemia, Familial hypercholesterolemia 1, Familial hypercholesterolemia 2, Hypobetalipoproteinemia, familial, 1, Hypercholesterolaemia

ZYG	HET
MAF	0.01438
ACMG	Benign
CLIN. SIG	Conflicting interpretations of pathogenicity [★]
HGMD Variant Class	DM?

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PROGENICS
CORD BLOOD CRYOBANK

COL5A2 CONFLICTING RARE

2 189907963 C>T

rs199802059 - NM_000393.5(COL5A2):c.3385G>A (p.Asp1129Asn)

Phenotypes

Connective tissue disease, Ehlers-Danlos syndrome, classic type

ZYG HET
MAF 0.00008
ACMG Uncertain significance
CLIN. SIG Conflicting interpretations of pathogenicity [★]

CYP27A1 CONFLICTING RARE HGMD

2 219678877 C>T

rs41272687 - NM_000784.4(CYP27A1):c.1151C>T (p.Pro384Leu)

Phenotypes

Cholestanol storage disease, Cerebrotendinous xanthomatosis

ZYG HET
MAF 0.00859
ACMG Uncertain significance
CLIN. SIG Conflicting interpretations of pathogenicity [★]
HGMD Rankscore 0.13
HGMD Variant Class DM?

DMD CONFLICTING RARE

X 33192450 G>A

rs182597890 - NM_004006.3(DMD):c.31+36949C>T

ZYG HOM
MAF 0.00291
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity [★]

DSP CONFLICTING RARE

6 7584173 T>A

rs149070106 - NM_004415.4(DSP):c.6678T>A (p.Gly2226=)

Phenotypes

Cardiomyopathy, Dilated cardiomyopathy with woolly hair and keratoderma, Arrhythmogenic right ventricular dysplasia 8, Skin fragility-woolly hair-palmoplantar keratoderma syndrome, Lethal acantholytic epidermolysis bullosa, Cardiovascular phenotype

ZYG HET
MAF 0.0004
ACMG Benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]

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GATA4   CONFLICTING

8 11606312 T>C

rs3735819 - NM_001308093.3(GATA4):c.617-113T>C

Phenotype

Congenital heart disease

ZYG HOM
MAF 0.87161
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity

GATA4   CONFLICTING   HGMD

8 11612698 C>A

rs804280 - NM_001308093.3(GATA4):c.1000+56C>A

Phenotypes

Congenital heart disease, Tetralogy of Fallot: association with

ZYG HOM
MAF 0.73443
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity
HGMD Variant Class DP

GATA4   CONFLICTING

8 11617240 A>T

rs12458 - NM_001308093.3(GATA4):c.*1256A>T

Phenotype

Congenital heart disease

ZYG HET
MAF 0.39996
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity

INS   CONFLICTING   RARE

11 2181080 G>A

rs200306755 - NM_000207.3(INS):c.*2C>T

Phenotypes

Maturity-onset diabetes of the young, type 10, Transient Neonatal Diabetes, Dominant/Recessive

ZYG HET
MAF 0.00013
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity [★]

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JAG1 CONFLICTING RARE

20 10621899 C>T

rs201573066 - NM_000214.3(JAG1):c.2917-7G>A

Phenotype

Isolated Nonsyndromic Congenital Heart Disease

ZYG HET
MAF 0.0006
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity [★]

KCNJ11 CONFLICTING RARE

11 17408496 C>T

rs8175351 - NM_000525.4(KCNJ11):c.1143G>A (p.Lys381=)

Phenotypes

Islet cell hyperplasia, Transient neonatal diabetes mellitus 3, Maturity-onset diabetes of the young, type 13, Permanent neonatal diabetes mellitus

ZYG HET
MAF 0.00439
ACMG Likely benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]

LDLR CONFLICTING

19 11221454 T>C

NM_000527.5(LDLR):c.1060+7=

Phenotype

Familial hypercholesterolemia 1

ZYG HOM
MAF -
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity [★]

LDLRAP1 CONFLICTING HGMD

1 25890247 C>T

rs41291058 - NM_015627.3(LDLRAP1):c.712C>T (p.Arg238Trp)

Phenotypes

Familial hypercholesterolemia, Familial hypercholesterolemia 4, Hypercholesterolaemia: autosomal recessive

ZYG HET
MAF 0.01597
ACMG Benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]
HGMD Rankscore 0.11
HGMD Variant Class R

MED12 `CONFLICTING` `RARE`

X 70342211 T>C

rs187377817 – NM_005120.3(MED12):c.1248+15T>C

ZYG HOM
MAF 0.00079
ACMG –
CLIN. SIG Conflicting interpretations of pathogenicity [★]

PC `CONFLICTING` `RARE`

11 66638540 C>A

rs147945506 – NM_001040716.2(PC):c.616G>T (p.Val206Leu)

Phenotype

Pyruvate carboxylase deficiency

ZYG HET
MAF 0.00399
ACMG Likely benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]

PCSK9 `CONFLICTING`

1 55518093 G>A

rs11800243 – NM_174936.4(PCSK9):c.657+9G>A

Phenotypes

Familial hypercholesterolemia 1, Familial hypercholesterolemia 3, Hypobetalipoproteinemia

ZYG HET
MAF 0.03914
ACMG –
CLIN. SIG Conflicting interpretations of pathogenicity [★]

PCSK9 `CONFLICTING` `HGMD`

1 55523033 A>G

rs509504 – NM_174936.4(PCSK9):c.1026A>G (p.Gln342_Asp343=)

Phenotypes

Familial hypercholesterolemia 1, Familial hypercholesterolemia 3, Hypobetalipoproteinemia, Hypercholesterolaemia

ZYG HOM
MAF 0.98183
ACMG Benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]
HGMD Variant Class DM?

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PLEC CONFLICTING RARE

8 144999499 C>T

rs201430180 - NM_201384.3(PLEC):c.4598G>A (p.Arg1533Gln)

Phenotypes

Epidermolysis bullosa simplex, Ogna type, Epidermolysis bullosa simplex with
muscular dystrophy, Epidermolysis bullosa simplex with pyloric atresia, Limb-
girdle muscular dystrophy, type 2Q, Epidermolysis bullosa simplex with nail
dystrophy

ZYG HET
MAF 0.0024
ACMG Likely benign
CLIN. SIG Conflicting
interpretations of pathogenicity
[★]

PNPLA2 CONFLICTING RARE

11 824042 C>T

rs137866968 - NM_020376.4(PNPLA2):c.964C>T (p.Leu322Phe)

Phenotype

Neutral lipid storage myopathy

ZYG HET
MAF 0.0006
ACMG Likely benign
CLIN. SIG Conflicting
interpretations of pathogenicity
[★]

RYR2 CONFLICTING RARE

1 237664060 T>G

rs762905211 - NM_001035.3(RYR2):c.2253T>G (p.Thr751=)

Phenotypes

Cardiomyopathy, Arrhythmogenic right ventricular dysplasia, familial, 2,
Catecholaminergic polymorphic ventricular tachycardia type 1,
Catecholaminergic polymorphic ventricular tachycardia

ZYG HET
MAF 0.00015
ACMG Likely benign
CLIN. SIG Conflicting
interpretations of pathogenicity
[★]

SELENON CONFLICTING

1 26126680 T>C

rs12121707 - NM_020451.2(SELENON):c.-42T>C

Phenotype

SEPN1-Related Disorders

ZYG HOM
MAF -
ACMG -
CLIN. SIG Conflicting
interpretations of pathogenicity
[★]

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SGCD `CONFLICTING` `RARE`

5 156193318 C>T

rs549743616 - NM_000337.6(SGCD):c.*6917C>T

Phenotypes

Qualitative or quantitative defects of delta-sarcoglycan, Limb-Girdle Muscular Dystrophy, Recessive

ZYG HET
MAF 0.0016
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity [★]

TNNI3 `CONFLICTING`

19 55665410 C>T

rs3729841 - NM_000363.5(TNNI3):c.537G>A (p.Glu179=)

Phenotypes

Cardiomyopathy, Hypertrophic cardiomyopathy, Primary ciliary dyskinesia, Familial restrictive cardiomyopathy 1, Dilated cardiomyopathy 2A, Familial hypertrophic cardiomyopathy 7, Cardiovascular phenotype, Familial Hypertrophic Cardiomyopathy with Wolff-Parkinson-White Syndrome

ZYG HET
MAF 0.04772
ACMG Benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]

TNNI3 `CONFLICTING`

19 55665584 A>C

rs7252610 - NM_000363.5(TNNI3):c.373-10=

Phenotypes

Cardiomyopathy, Hypertrophic cardiomyopathy, Primary ciliary dyskinesia, Familial restrictive cardiomyopathy 1, Dilated cardiomyopathy 2A, Familial hypertrophic cardiomyopathy 7, Primary familial hypertrophic cardiomyopathy, Familial Hypertrophic Cardiomyopathy with Wolff-Parkinson-White Syndrome, Nemaline Myopathy, Recessive

ZYG HOM
MAF -
ACMG -
CLIN. SIG Conflicting interpretations of pathogenicity [★]

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TNNT1 CONFLICTING

19 55665584 A>C

rs7252610 - NM_000363.5(TNNI3):c.373-10=

Phenotypes

Cardiomyopathy, Hypertrophic cardiomyopathy, Primary ciliary dyskinesia, Familial restrictive cardiomyopathy 1, Dilated cardiomyopathy 2A, Familial hypertrophic cardiomyopathy 7, Primary familial hypertrophic cardiomyopathy, Familial Hypertrophic Cardiomyopathy with Wolff-Parkinson-White Syndrome, Nemaline Myopathy, Recessive

ZYG HOM

MAF -

ACMG -

CLIN. SIG Conflicting interpretations of pathogenicity [★]

TOR1AIP1 CONFLICTING

1 179858444 G>A

rs2245425 - NM_015602.4(TOR1AIP1):c.554-4G>A

Phenotypes

Muscular dystrophy, limb-girdle, type 2y

ZYG HET

MAF 0.63538

ACMG -

CLIN. SIG Conflicting interpretations of pathogenicity [★]

ACVR2B

3 38534296 T>C

NM_001106.4(ACVR2B):c.*9473T>C

Phenotypes

Heterotaxy, visceral, 4, autosomal

ZYG HET

MAF -

ACMG -

CLIN. SIG Uncertain significance [★]

ANK2 RARE

4 114303583 C>G

rs143635798 - NM_001148.6(ANK2):c.*956C>G

Phenotypes

Cardiac arrhythmia, ankyrin B-related

ZYG HET

MAF 0.0008

ACMG -

CLIN. SIG Uncertain significance [★]

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BMPR1B

4 96076652 T>G

NM_001203.3(BMPR1B):c.*828T>G

Phenotype
Brachydactyly

ZYG HET
MAF –
ACMG –
CLIN. SIG Uncertain significance [★]

CHD7 HGMD

8 61690321 A>G

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

Phenotypes
Scoliosis, idiopathic 3, Scoliosis: idiopathic: association with

ZYG HOM
MAF 0.86062
ACMG –
CLIN. SIG Uncertain significance
HGMD Variant Class DP

CHD7 Description

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

PubMed 23883829

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).

PubMed 17436250

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 23883829 | 17436250

DBT

1 100654909 A>T

NM_001918.5(DBT):c.*6902T>A

Phenotype
Maple syrup urine disease

ZYG HOM
MAF –
ACMG –
CLIN. SIG Uncertain significance [★]

GATA4

8 11616338 A>C

rs867858 – NM_001308093.3(GATA4):c.*354A>C

ZYG HET
MAF 0.36142
ACMG –
CLIN. SIG Uncertain significance

GHR `RARE`

5 42721818 A>G

rs35415717 – NM_000163.5(GHR):c.*2292A>G

Phenotype

Laron-type isolated somatotropin defect

ZYG HET
MAF 0.0022
ACMG –
CLIN. SIG Uncertain significance
[★]

KCNJ5

11 128761336 C>G

NM_000890.5(KCNJ5):c.-291C>G

Phenotype

Familial hyperaldosteronism type 3

ZYG HET
MAF –
ACMG –
CLIN. SIG Uncertain significance
[★]

LEP

7 127895182 A>T

rs28954118 – NM_000230.3(LEP):c.*366A>T

Phenotypes

Leptin deficiency or dysfunction, Monogenic Non-Syndromic Obesity

ZYG HET
MAF 0.01837
ACMG –
CLIN. SIG Uncertain significance
[★]

PCK1

20 56141221 G>A

rs878859807 – NM_002591.4(PCK1):c.*361G>A

Phenotypes

Phosphoenolpyruvate carboxykinase deficiency, cytosolic

ZYG HET
MAF –
ACMG –
CLIN. SIG Uncertain significance
[★]

PCSK9

1 55518287 G>A

rs11800265 - NM_174936.4(PCSK9):c.658-36G>A

Phenotype

Familial hypercholesterolemia 1

ZYG HET
MAF 0.03914
ACMG -
CLIN. SIG Uncertain significance [★]

POMT2 `RARE`

14 77741568 T>C

rs45579739 - NM_013382.7(POMT2):c.*2151A>G

Phenotypes

Limb-girdle muscular dystrophy-dystroglycanopathy, type C2

ZYG HET
MAF 0.00359
ACMG -
CLIN. SIG Uncertain significance [★]

SOS1 `RARE` `HGMD`

2 39278394 A>G

rs142094234 - NM_005633.4(SOS1):c.755T>C (p.Ile252Thr)

Phenotype

Noonan syndrome

ZYG HET
MAF 0.0002
ACMG Uncertain significance
CLIN. SIG Uncertain significance [★]
HGMD Rankscore 0.92
HGMD Variant Class DM

TTN `RARE` `HGMD`

2 179590654 G>A

rs751534449 - NM_001267550.2(TTN):c.20395C>T (p.Arg6799Trp)

Phenotypes

Hypertrophic cardiomyopathy, Skeletal myopathy

ZYG HET
MAF 0.00003
ACMG Uncertain significance
CLIN. SIG Uncertain significance [★★]
HGMD Rankscore 0.27
HGMD Variant Class DM

Informational Variants Found

APOA5 `HGMD`

11 116660686 G>A

rs2266788 - NM_001371904.1(APOA5):c.*158C>T

Phenotypes

Hypertriglyceridemia, susceptibility to, Increased plasma triglyceride levels

ZYG	HOM
MAF	0.8742
ACMG	–
CLIN. SIG	Risk factor
HGMD Variant Class	FP

APOA5 Description

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 SNP2; 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 (HYTG1; 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 11588264 | 12417524 | 24387992

APOA5 `HGMD`

11 116663707 G>A

rs662799 - NM_052968.4(APOA5):c.-644C>T

Phenotypes

lovastatin response - Efficacy, atorvastatin response - Efficacy, simvastatin response - Efficacy, Increased plasma triglyceride levels

ZYG	HOM
MAF	0.83706
ACMG	–
CLIN. SIG	Drug response [★★★]
HGMD Variant Class	DFP

KCNJ11 HGMD

11 17409572 T>C

rs5219 – NM_000525.4(KCNJ11):c.67A>G (p.Lys23Glu)

ZYG	HET
MAF	0.73702
ACMG	Benign
CLIN. SIG	Drug response [★★★]
HGMD Rankscore	0.1
HGMD Variant Class	DFP

Phenotypes

Diabetes mellitus type 2, susceptibility to, glibenclamide response –
Efficacy, gliclazide response – Efficacy, glimepiride response – Efficacy,
glipizide response – Efficacy, gliquidone response – Efficacy, Maturity onset
diabetes mellitus in young, Islet cell hyperplasia, Transient neonatal
diabetes mellitus 3, Maturity-onset diabetes of the young, type 13, Permanent
neonatal diabetes mellitus, Exercise stress response, impaired, association
with, sulfonamides, urea derivatives response – Efficacy, Transient Neonatal
Diabetes, Dominant, Hyperinsulinism, Dominant/Recessive, Diabetes mellitus 2:
association with

KCNJ11 Description

Hani et al. (1998) identified a glu23-to-lys (E23K) amino acid substitution in the KCNJ11 gene by molecular screening using SSCP and direct sequencing in 72 French Caucasian families with type II diabetes (125853). They genotyped this variant in French cohorts of 191 unrelated type II diabetic probands and 119 normoglycemic control subjects and performed association studies. Homozygosity for lys23 (KK) was more frequent in type II diabetic than in control subjects (27 vs 14%; p = 0.015). Analyses in a recessive model (KK vs EK/EE) showed a stronger association of the K allele with diabetes. In a metaanalysis of their data for the E23K variant and data obtained from 3 other Caucasian groups, Hani et al. (1998) found the E23K variant to be significantly associated with type II diabetes.

PubMed 9867219

Hansen et al. (2005) investigated the separate and combined effects of the PPARG pro12-to-ala (P12A; 601487.0002) and the KCNJ11 E23K polymorphisms on risk of type II diabetes. The combined analysis involved 1,164 type II diabetic patients and 4,733 middle-aged, glucose-tolerant subjects. In the separate analyses, the K allele of KCNJ11 E23K associated with type II diabetes (odds ratio, 1.19; p = 0.0002), whereas PPARG P12A showed no significant association with type 2 diabetes. The combined analysis indicated that the 2 polymorphisms acted in an additive manner to increase the risk of type II diabetes, and the authors found no evidence for a synergistic interaction between them. Together, the 2 polymorphisms conferred a population-attributable risk for type II diabetes of 28%. The authors concluded that their results showed no evidence of a synergistic interaction between the KCNJ11 E23K and PPARG P12A polymorphisms, but indicated that they may act in an additive manner to increase the risk of type II diabetes.

PubMed 15797964

Laukkanen et al. (2004) found an additive effect of a high risk ABCC8 (600509) haplotype, composed of a silent polymorphism (AGG-AGA; arg1273 to arg) and 3 promoter polymorphisms, and the 23K allele of the KCNJ11 gene.

PubMed 15579791

In genomewide association studies of type 2 diabetes involving genotype data from a variety of international consortia, 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) confirmed association of the E23K polymorphism (rs5219) with diabetes susceptibility. Although this association was not strongly observed in any single scan, all-data metaanalyses resulted in genomewide significant association (OR = 1.14, p = 6.7 x 10(-11)).

PubMed 17463246 | 17463249 | 17463248

Association with Impaired Exercise Stress Response

Reyes et al. (2009) found that the E23K polymorphism was overrepresented in 115 individuals with dilated cardiomyopathy (see 115200) and congestive heart failure (CHF) compared to 2,031 community-based controls (p less than 0.001). In addition, the KK genotype, which was present in 18% of the CHF patients, was associated with abnormal cardiopulmonary exercise stress testing: despite similar baseline heart rates among genotype subgroups, individuals with the KK genotype had a significantly reduced heart rate increase at matched workload, at 75% of maximum oxygen consumption, and at peak VO(2), compared to those with the EE or EK genotypes. Noting that the glu23 residue is located within the functionally relevant intracellular slide helix region, Reyes et al. (2009) suggested that E23K might represent a biomarker for impaired stress performance.

PubMed 19685080

ABCC8 `HGMD`

11 17409572 T>C

rs5219 - NM_000525.4(KCNJ11):c.67A>G (p.Lys23Glu)

Phenotypes

Diabetes mellitus type 2, susceptibility to, glibenclamide response -
Efficacy, gliclazide response - Efficacy, glimepiride response - Efficacy,
glipizide response - Efficacy, gliquidone response - Efficacy, Maturity onset
diabetes mellitus in young, Islet cell hyperplasia, Transient neonatal
diabetes mellitus 3, Maturity-onset diabetes of the young, type 13, Permanent
neonatal diabetes mellitus, Exercise stress response, impaired, association
with, sulfonamides, urea derivatives response - Efficacy, Transient Neonatal
Diabetes, Dominant, Hyperinsulinism, Dominant/Recessive, Diabetes mellitus 2:
association with

ZYG	HET
MAF	0.73702
ACMG	Benign
CLIN. SIG	Drug response [★★★]
HGMD Rankscore	0.1
HGMD Variant Class	DFP

ABCC8 Description

Hani et al. (1998) identified a glu23-to-lys (E23K) amino acid substitution in the KCNJ11 gene by molecular screening using SSCP and direct sequencing in 72 French Caucasian families with type II diabetes (125853). They genotyped this variant in French cohorts of 191 unrelated type II diabetic probands and 119 normoglycemic control subjects and performed association studies. Homozygosity for lys23 (KK) was more frequent in type II diabetic than in control subjects (27 vs 14%; p = 0.015). Analyses in a recessive model (KK vs EK/EE) showed a stronger association of the K allele with diabetes. In a metaanalysis of their data for the E23K variant and data obtained from 3 other Caucasian groups, Hani et al. (1998) found the E23K variant to be significantly associated with type II diabetes.

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Publ**M**ed 19685080

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MC4R

18 57851097 T>C

rs17782313 – NC_000018.9:g.57851097T>C

ZYG	HET
MAF	0.24002
ACMG	–
CLIN. SIG	Drug response [★★★]

Phenotype

antipsychotics response - Toxicity/ADR

MC4R

18 57882787 C>A

rs489693 – NC_000018.9:g.57882787C>A

ZYG	HET
MAF	0.35124
ACMG	–
CLIN. SIG	Drug response [★★★]

Phenotypes

amisulpride response - Toxicity/ADR, aripiprazole response - Toxicity/ADR,
clozapine response - Toxicity/ADR, haloperidol response - Toxicity/ADR,
olanzapine response - Toxicity/ADR, paliperidone response - Toxicity/ADR,
quetiapine response - Toxicity/ADR, risperidone response - Toxicity/ADR,
ziprasidone response - Toxicity/ADR

SCN1A `HGMD`

2 166909544 C>T

rs3812718 – NM_001165963.4(SCN1A):c.603-91G>A

ZYG	HET
MAF	0.49341
ACMG	–
CLIN. SIG	Drug response [★★★]
HGMD Variant Class	DFP

Phenotypes

Febrile seizures, familial, 3a, carbamazepine response - Dosage, phenytoin
response - Dosage, antiepileptics response - Efficacy, carbamazepine response
- Efficacy, Febrile seizures: association with

SCN1A Description

In a 2-stage case-control study including a total of 234 patients with febrile seizures (FEB3A; see 604403), Schlachter et al. (2009) found a significant association between the major A allele of rs3812718 and febrile seizures (first stage p value of 0.000017; replication p value of 0.00069). The data suggested that homozygosity for the A allele confers a 3-fold increased relative risk of febrile seizures and may account for a population attributable risk factor of up to 50%. The data were consistent with the hypothesis that low-risk variants with a high population frequency contribute to the risk of common and genetically complex diseases such as epilepsy.

PubMed 19289736

The SCN1A IVS5N+5G-A polymorphism, formerly SCN1A IVS5-91G-A (rs3812718), was shown by Tate et al. (2005) to affect the alternative

splicing of exon 5. The major allele, A, disrupts the consensus sequence of fetal exon 5N, resulting in decreased expression of the fetal SCN1A isoform compared to the adult isoform. Among a total of 706 patients with epilepsy, Tate et al. (2005) found maximum required antiepileptic drug dose to be lowest in patients with a GG genotype, intermediate in those with the GA genotype, and highest in those with the AA genotype. Tate et al. (2005) emphasized that their findings required replication. In a separate study by Tate et al. (2006) that involved patients of Chinese ancestry, an association was found between SCN1A IVS5N+5G-A and phenytoin serum concentrations at maintenance dose; presence of the A allele was associated with higher doses.

PubMed 15805193 | 17001291

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Heinzen et al. (2007) found that in human brain tissue, the SCN1A IVS5N+5G-A polymorphism has a substantial effect on the percentage of transcripts containing exon 5N (neonatal form) of SCN1A. Individuals with the AA genotype had a mean of 0.7% of SCN1A transcripts in the neonatal form, whereas subjects with the GG genotype had 41% of transcripts containing exon 5N. The G allele elicited a dominant effect, with those with the AG genotype having 28% of transcripts in the neonatal form. Heinzen et al. (2007) noted that individuals with the AA genotype require increased doses of antiepileptic drugs compared to those with the GG genotype, suggesting that patients with the AA genotype have a more severe form of epilepsy. Alternatively, the different splice forms may cause alterations in pharmacology, since the drugs act on the SCN1A gene. The authors noted that future work was required to elucidate the functional differences between the transcripts containing exons 5A and 5N. The findings emphasized an emerging role of genetic polymorphisms in modulation of drug effect, and illustrated the importance of considering the activity of compounds at alternative splice forms of drug targets.

PubMed 17436242

Petrovski et al. (2009) was unable to replicate the association between rs3812718 and febrile seizures in a study of 558 Australian patients with seizures, including 76 (14%) with febrile seizures and 482 (86%) without febrile seizures. Only 10 (2%) had isolated febrile seizures. The association was also not replicated in a second cohort of 1,589 European patients with focal epilepsy, consisting of 232 with febrile seizures and 1,357 without febrile seizures.

PubMed 19949041

TMEM43 HGMD

3 14187449 G>T

rs2228001 - NM_004628.5(XPC):c.2815C>A (p.Gln939Lys)

Phenotypes

Xeroderma pigmentosum, group C, Arrhythmogenic right ventricular cardiomyopathy, Xeroderma pigmentosum, cisplatin response - Toxicity/ADR, DNA repair rate: association with

ZYG	HET
MAF	0.6847
ACMG	Benign
CLIN. SIG	Drug response [★★★]
HGMD Rankscore	0.1
HGMD Variant Class	DFP

LDHA

11 18325146 C>T

rs2403254 - NM_181507.2(HPS5):c.896+1823G>A

Phenotype

decreased blood alpha-hydroxyisovalerate levels

ZYG	HET
MAF	0.41873
ACMG	-
CLIN. SIG	Association

LPL

8 19819439 A>G

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

Phenotype

High density lipoprotein cholesterol level quantitative trait locus 11

ZYG	HET
MAF	0.34944
ACMG	-
CLIN. SIG	Association

LPL Description

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.

PubMed 17952847

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 23246289

PLTP

20 44548193 C>T

rs3843763 - NC_000020.10:g.44548193C>T

ZYG	HET
MAF	0.3143
ACMG	-
CLIN. SIG	Association

Phenotype

High density lipoprotein cholesterol level quantitative trait locus 9

PLTP Description

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, IL, Spirin et al. (2007) identified a SNP of the PLTP gene, rs3843763, that was associated with incremental changes in HDL cholesterol levels in 3 independent samples. This SNP achieved a P value of 1.19 x 10(-4) in analysis of covariance in the entire sample in a model that included race, sex, age, and body mass index (BMI). The minor allele, T, was associated with lowering of HDL cholesterol.

PubMed 17952847

Related Conditions:

- Hereditary fructosuria

Genes Analyzed

This report analyzed the following genes:

PTH1R, MPI, GNAS, ACADVL, ENO3, CHKB, LAMA2, PLN, SDHA, TGFB3, GBE1, SOS1, RAI1, GCK, IFT27, ISPD, GALNT2, BLK, IFT172, TBX19, LIPC, LEFTY2, CACNA2D1, SLC40A1, CYP7B1, KCNQ3, JPH2, ETFA, KLF11, HNRNPDL, GCM2, CSRP3, NF1, SH2B1, ELAC2, ARL6, ACTC1, APOA4, HNF1A, KCNE5, GJA1, KRAS, MYLK, BBS4, GNA11, POMGNT2, SUN2, BBS5, DPM2, KCNQ2, LCAT, ZIC3, DSG2, MAP2K1, MTO1, NR0B1, PFKM, CNTN1, RBM20, NNT, ALG6, PHKA2, MKKS, B4GAT1, LIPA, NEB, HADHA, NEXN, BBS1, DSP, NKX2-2, RPS6KA3, SCARB1, HADHB, FKTN, POMT1, HNF4A, CYP24A1, COG7, GLUD1, MYOZ2, PLOD1, ACADS, CACNA1C, FOXE3, APOB, APPL1, CALM2, SLC2A1, OXCT1, LIPG, NRAS, COL12A1, FBN2, GDF2, DYRK1B, MKS1, CHST14, CFL2, NKX2-5, SLC22A5, MAGEL2, ADCY3, NOTCH1, BMPR2, CHRM2, GYS2, APOC2, SLC34A1, SMAD4, CPT2, ABCA1, KCNJ2, COL1A2, TBX5, GDF1, MLYCD, ENG, MYBPC3, LRRC10, SHOC2, DEPDC5, CYP27A1, GPC3, PRRT2, STIM1, BAG3, CASQ2, PYGL, CHD7, DBT, COL5A2, ETFB, MYOM1, ALDOA, ABCG8, DNAJB6, PPARG, SGCG, EP300, BDNF, SYNE2, GPR101, BCKDHB, FKBP14, CAV1, LIMS2, KCNE1, KCND3, DLD, ADK, LDLR, BBS2, COL1A1, GATA3, CAV3, DSC2, KSR2, CRTAP, BRAF, MTM1, MYH6, SDCCAG8, KCNE2, CASR, EYA4, NEUROD1, LEP, MYLIP, ACVR2B, MPV17, BBS9, SPRED1, CACNB2, FHL1, ACAD9, TCAP, ALDOB, MYH7, GPD1, BCKDHA, MYH11, IER3IP1, CUL4B, KMT2D, FKRP, PRKG1, SCN9A, HADH, LEPR, PGAM2, TFR2, ANKRD1, CRELD1, KCNA5, MYPN, GLIS3, DPM1, CPT1A, TRPM4, COL6A2, CREB3L3, ANGPTL3, PHGDH, ZFP57, GPIHBP1, TBX1, LARGE1, CTF1, G6PC, POMT2, RYR2, NR0B2, SKI, GNE, FOXP3, NEUROG3, COL6A1, SLC52A2, SCN10A, LDLRAP1, SOS2, CRYAB, SCN8A, SETD2, ALG3, GALE, PCK2, GYG1, BIN1, DGUOK, GPD1L, MAT2A, TTC8, DBH, SQSTM1, ABCG5, GATA6, SNTA1, TTR, RBCK1, HAND1, ALMS1, MYL3, PRKAG2, MYF6, BBS10, CEP290, PCSK1, TRMT10A, KCNJ8, SCN1B, PKP2, NSD1, MRAP2, DPM3, BBS7, ELN, SLC37A4, VCL, P3H1, ABCC9, CEP19, NKX2- 6, RAF1, PDE4D, SYNE1, CTNNA3, NODAL, HK1, GLA, GHR, SCLT1, WDPCP, KCNK3, UCP2, AIRE, LIPI, POMK, NLGN2, PRMT7, ACAT1, CPE, RRAS, MC4R, OPLAH, HMGCS2, ABCC8, KIDINS220, KBTBD13, PC, INS, KCNJ11, OTX2, PCDH19, MYOT, RASA1, BBIP1, APOA5, TRAPPC9, ANO5, FLNA, SLMAP, MYLK2, TRDN, TXNRD2, PYGM, SOX2, AKAP9, LDB3, IFT74, GALT, LDHA, C8ORF37, PAX4, B3GALNT2, LAMA4, TNNC1, KCNJ5, VPS13B, HFE, ACTA2, ABCD1, PCSK9, LMNA, APOC3, PDLIM3, AKT2, PHKG2, SCN4B, MEIS2, SELENON, SLC52A1, PTH, GAA, RIT1, ATP2A1, ILK, ACADSB, TGFBR1, DTNA, SGCB, PNPLA2, SGCA, KDM6A, HMGCL, ACSF3, TMEM43, INSR, BCOR, PTF1A, HAMP, LMOD3, RYR1, GYS1, TAZ, PHF6, ATP7A, EMD, AFF4, MNX1, PLEC, AGL, CETP, VCP, GCKR, GATAD1,

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STAC3, NTRK2, KLHL40, SOX3, SIM1, STX16, SUN1, SLC39A13, RANGRF, FBN1, JUP, ANK2, KCNH2, TTN, CALM3, KLHL41, NR2F2, WFS1, CBS, KCNE3, UCP3, DAG1, PRDM16, PDX1, CYP7A1, PROP1, SLC16A1, SMAD3, RXYLT1, MEGF8, FAM111A, DMXL2, DOLK, FLAD1, CA5A, SLC2A2, RAB23, COL3A1, SMAD6, DYSF, FLNC, ADAMTS2, CDKN1C, DES, JAG1, GATA4, FAH, PMM2, ITGA7, HCN4, RFX6, TBCE, TPM3, LRP6, LZTFL1, PHKA1, MYL2, MYL4, CALR3, PHKB, DMD, A2ML1, DNM2, NPY, CREBBP, SCN3B, TNPO3, ACTA1, PCK1, MEGF10, GMPPB, KCNQ1, HESX1, SGCD, TGFB2, TMPO, SLC2A10, MC3R, ACTN2, GH1, FHL2, BMPR1B, COL5A1, PTPN11, SLC25A32, SLC52A3, MED12, MED13L, SERAC1, TNNT1, TRIM32, BBS12, CACNA1D, HJV, EIF2AK3, CALM1, TPM1, TPM2, HNF1B, TRAPPC3, NEBL, DDC, NADK2, KCNA1, SEMA3E, AAAS, PGM1, LMF1, CCDC78, NPPA, LAMP2, GJA5, ZHX3, SCN1A, SCN5A, SLC19A2, HSD3B7, SCN2B, POMGNT1, FBP1, EFEMP2, CBL, MAP2K2, TMEM70, DNAJC19, FBN3, NR3C1, TGFBR2, SAR1B, PLTP, KCNT1, CAPN3, PLEKHM2, TRAPPC11, MTTP, ZFPM2, ETFDH, APOA1, TIA1, TNNT2, GALK1, CEP164, LHX3, HRAS, MATR3, SLC25A20, POMC, KIF7, TNNI3, COL6A3, SMAD9, ACVRL1, TOR1AIP1, ACADM, FOXH1, LPL

Terminology

Name	Symbol	Description
Zygosity	ZYG	Zygosity describes whether you inherited one copy of this variant from one of your parents (heterozygous), or you inherited two copies from both of your partents (homozygous). Typically for pathogenic variants homozygosity cause a more severe form of the condition. In many cases, heterozygous variants do not lead to the condition becoming apparent in the patient (also known as a recessive condition) but do mean that the next generation is at risk of inheriting the condition (or themselves becoming a carrier).
American College of Medical Genetics	ACMG	The American College of Medical Genetics is an organisation dedicated to the practice of medical genetics. Using a series of factors related to the variant and its context, they have identified the likelihood of a specific variant being causative for a disease. This score is based on a few factors, including allelic frequency (AF) an transcription consequence.
Allelic frequency	AF	Allelic frequency defines how often this variant has been observed in the general population. A very low allelic frequency could potentially be denovo (i.e. it wasn't inherited from either of your parents). Low allelic frequency variants are often considered more likely to be the cause of a negative phenotype or disease.
Autosomal dominant	AD	One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. In some cases, an affected person inherits the condition from an affected parent. In others, the condition may result from a new mutation in the gene and occur in people with no history of the disorder in their family.
Autosomal recessive	AR	In autosomal recessive inheritance, both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Autosomal recessive disorders are typically not seen in every generation of an affected family.
X-linked	X-linked dominant	Dominant X-linked dominant disorders are caused by mutations in genes on the X chromosome, one of the two sex chromosomes in each cell. In one of the two sex chromosomes in each cell. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).
Y-linked		A condition is considered Y-linked if the mutated gene that causes the disorder is located on the Y chromosome, one of the two sex chromosomes in each of a male's cells. Because only males have a Y chromosome, in Y-linked inheritance, a mutation can only be passed from father to son.
Mitochondrial		Mitochondrial inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial mutations to their children. Conditions resulting from mutations in mitochondrial DNA can appear in every generation of a family and can affect both males and females, but fathers do not pass these disorders to their daughters or sons.
Pathogenic		This variant directly contributes to the development of disease. Some pathogenic variants may not be fully penetrant. In the case of recessive or X-linked conditions, a single pathogenic variant may not be sufficient to cause disease on its own. Additional evidence is not expected to alter the classification of this variant.
Likely Pathogenic		There is a high likelihood (greater than 90% certainty) that this variant is disease-causing. Additional evidence is expected to confirm this assertion of pathogenicity, but there is a small chance that new evidence may demonstrate that this variant does not have clinical significance.
Variant Uncertain significance	VUS	There is not enough information at this time to support a more definitive classification of this variant.
Phenotype Name		Phenotype represents the observable characteristics or traits of an organism that are produced by the interaction of the genotype and the environment : the physical expression of one or more genes. Multiple phenotypes can be associated with a single variant.

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Name	Symbol	Description
Significance		Significance refers to the standard term used by ClinVar, the internationally recognized database on which this report is based, to classify the types of variants. As the database is a clinical database, the information is clinical and based on an authoritative source when available. The Significance section includes the following standard terms to classify the variants: • **Pathogenic**: A Pathogenic is classified as such if this variant directly contributes to the development of disease. Some pathogenic variants may not be fully penetrant. In the case of recessive or X-linked conditions, a single pathogenic variant may not be sufficient to cause disease on its own. Additional evidence is not expected to alter the classification of this variant. • **Likely Pathogenic**: A Likely Pathogenic variant is classified as such if there is a high likelihood (greater than 90% certainty) that this variant is disease-causing. Additional evidence is expected to confirm this assertion of pathogenicity, but there is a small chance that new evidence may demonstrate that this variant does not have clinical significance. • **Conflicting Interpretations of Pathogenicity**: A Conflicting Interpretations of Pathogenecity variant is classified as such if it is submitted from a scientific consortium, where groups within the consortium have conflicting interpretations of a variant but provide a single submission to ClinVar. • **Variant of Unknown Significance**: A Variant of Unknown Significance is classified as such if it is there is not enough information at this time to support a more definitive classification of this variant. • **Drug response**: A Drug response variant is classified as such if it represents a complex phenotype that emerges from the interplay of drug-specific genetics, human body, and environmental factors. • **Association**: An association variant is classified as such if there are one or more genotypes within a population co-occur with a phenotypic trait more often than would be expected by chance occurrence.
Review Status		ClinVar reports the level of review supporting the assertion of clinical significance for the variation as review status. Stars provide a graphical representation of the aggregate review status on web pages. Table 1 provides definitions of each review status and the corresponding number of stars. Review status is reported in text format in ClinVar's products available by FTP. A higher number of gold stars corresponds to higher review status. If you wish to get more information about that, please visit ClinVar at the following link: https://www.ncbi.nlm.nih.gov/clinvar/docs/review_status/
HGMD Rankscore		The HGMD computed rankscore is a probability of pathogenicity between 0 and 1, with 1 being most likely disease-causing compared to other HGMD entries. The score is computed using a machine learning approach, and is based upon multiple lines of evidence, including HGMD literature support for pathogenicity, evolutionary conservation (100 way vertebrate alignment), variant allele frequency and in-silico pathogenicity prediction.
HGMD Variant Class		**DM:** Pathological mutation reported to be disease-causing in the corresponding literature report (majority of HGMD data). **DM?:** Likely pathological mutation reported to be disease-causing in the corresponding report, but where the author has indicated that there may be some degree of doubt, or subsequent evidence has come to light in the literature, calling the deleterious nature of the variant into question. **DF:** A polymorphism reported to be in significant association with a disease/phenotype (p<0.05) that is assumed to be functional (e.g. as a consequence of location, evolutionary conservation, replication studies etc.), although there may as yet be no direct evidence (e.g. from an expression study) of a functional effect. **DFP:** A polymorphism reported to be in significant association with disease (p<0.05) that has evidence of being of direct functional importance (e.g. as a consequence of altered gene expression, mRNA studies etc). **FP:** A polymorphism reported to affect the structure, function or expression of the gene (or gene product), but with no disease association reported as yet. **R:** A variant entry retired from HGMD due to being found to have been erroneously included ab initio, or variant that has been subjected to correction in the literature resulting in the record becoming obsolete, merged or otherwise invalid.

Methods

Versions

VCF Version: 2vDw1xGaHcQfSiSF4KEOwG.55GTCWvkN
Clinvar Database Version: FgUM_0StTQ4PCkHW_E7OkqqE0l.5KRql

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

This report is based on SNP VCF data.

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.

Doctor's Signature

Signature

Date

Report: Cardiometabolic Disorders Panel [v1.0.2, v5.3.4]
Powered by Progenics
Run: 1

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Kit ID: KITSAMPLE
Lot: 11:47:50
Batch: 2023-01-17