Stem Cell Therapy-Related Diseases Panel

Kit ID: KITSAMPLE

Report Description

The 'Stem Cell Therapy-Related Diseases' panel is based on DNA germline mutation analysis. As such, it analyses all common and rare variants associated with various diseases treated with stem cells instead of a limited set of genes like the old gene targeting panels. Over the past decades, the in-depth study of stem cell biology has enabled the development of innovative techniques that allow their use in what is now called regenerative medicine. The use of stem cells is aimed at curing or treating various diseases belonging to multiple fields of interest, such as haematology, oncology, immunology and hereditary metabolic disorders.
Genetics play a crucial role in developing many of these stem cell therapy-related diseases, which have been analysed in this panel.
In this Test, we analyse germline mutations such as single nucleotide polymorphisms (SNPs) and INDELs of 150 bp or less in length. We recommend further analysis to detect other disease-related mutations (such as CNV analysis, STR analysis, etc.). - More than 205 genes analysed - 100% of genomic regions covered - Intragenic and intergenic regions analysed - All variants reported

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

- Breast-ovarian cancer, familial 1

Variants analyzed

`ALK 1` `CR2 1` `EPO 1` `ICOS 1` `RAG1 1` `TERT 2` `TP53 1` `BRCA1 1` `FANCA 1`
`FANCC 1` `FANCE 2` `IKZF1 2` `MRE11 1` `RAD51 1`

Summary Table

Pathogenic/Likely pathogenic variant(s) detected.

Gene	Coordinates	Nucleotide Change	rsID	Clinvar class.	Zygosity	Disease
BRCA1	17: 41199722	NM_007294.4(BRCA1):c.5407-2A>G	rs80358002	Pathogenic	HOM	Breast-ovarian cancer, familial 1, Breast and/or ovarian cancer

Clinical Variants Found

BRCA1 PATHOGENIC HGMD

17 41199722 T>C

rs80358002 - NM_007294.4(BRCA1):c.5407-2A>G

Phenotypes

Breast-ovarian cancer, familial 1, Breast and/or ovarian cancer

ZYG HOM
MAF -
ACMG -
CLIN. SIG Pathogenic [★★]
HGMD Rankscore 0.69
HGMD Variant Class DM

FANCA CONFLICTING RARE

16 89865630 G>A

rs752311383 - NM_000135.4(FANCA):c.837C>T (p.Asp279=)

Phenotypes

Fanconi anemia, complementation group A, Fanconi anemia

ZYG HET
MAF 0.00002
ACMG Likely benign
CLIN. SIG Conflicting interpretations of pathogenicity [★]

ALK

2 29446184 C>G

NM_004304.5(ALK):c.3359+24G>C

Phenotype

Squamous cell lung carcinoma

ZYG HET
MAF -
ACMG -
CLIN. SIG Uncertain significance

FANCC

9 98009494 C>T

NM_000136.3(FANCC):c.250+220G>A

ZYG HET
MAF -
ACMG -
CLIN. SIG Uncertain significance

FANCE

6 35420628 A>C

NM_021922.3(FANCE):c.248+58A>C

ZYG HOM
MAF -
ACMG -
CLIN. SIG Uncertain significance

FANCE

6 35424188 A>G

NM_021922.3(FANCE):c.855+58A>G

ZYG HOM
MAF -
ACMG -
CLIN. SIG Uncertain significance

ICOS

2 204825615 T>C

rs528769953 - NM_012092.4(ICOS):c.*1293T>C

Phenotype

Common variable immunodeficiency 1

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

MRE11 RARE

11 94152443 T>C

rs13447750 - NM_005591.4(MRE11):c.*848A>G

Phenotype

Ataxia-telangiectasia-like disorder 1

ZYG HET
MAF 0.0006
ACMG -
CLIN. SIG Uncertain significance [★]

RAG1 RARE

11 36599087 G>A

rs145963034 - NM_000448.3(RAG1):c.*1101G>A

Phenotypes

Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-negative, NK cell-positive, Histiocytic medullary reticulosis

ZYG HET
MAF 0.0012
ACMG -
CLIN. SIG Uncertain significance [★]

Informational Variants Found

EPO HGMD

7 100317298 C>A

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

ZYG HOM
MAF 0.67472
ACMG -
CLIN. SIG Risk factor
HGMD Variant Class DFP

Phenotypes

Microvascular complications of diabetes 2, Diabetic eye and kidney complications: association with

EPO Description

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 18458324

RAD51 HGMD

15 40987528 G>C

rs1801320 - NM_002875.5(RAD51):c.-98G>C

ZYG HET
MAF 0.14317
ACMG -
CLIN. SIG Risk factor
HGMD Variant Class DFP

Phenotypes

Breast cancer, susceptibility to, in BRCA1 and BRCA2 carriers, Breast cancer: increased risk in BRCA2 carriers: association with

RAD51 Description

Wang et al. (1999) presented evidence that a single nucleotide polymorphism (SNP) in the 5-prime untranslated region of RAD51 is associated with increased breast cancer risk in BRCA1 (113705) and BRCA2 (600185) carriers but does not influence breast cancer risk in women who are not BRCA1 or BRCA2 carriers. This SNP, designated 135g/c, is a substitution of C for G at position 135 in the RAD51 cDNA. Levy-Lahad et al. (2001) studied 257 female Ashkenazi Jewish carriers of one of the common BRCA1 (185delAG; 113705.0003, or 5382insC; 113705.0018) or BRCA2 (6174delT; 600185.0009) mutations. They found that the 135 SNP modified cancer risk in BRCA2 carriers but not in BRCA1 carriers. Survival analysis in BRCA2 carriers showed that 135C increased risk of breast and/or ovarian cancer with a hazard ratio (HR) of 4.0. This effect was largely due to increased breast cancer risk with an HR of 3.46 for breast cancer in BRCA2 carriers who were 135C heterozygotes. RAD51 status did not affect ovarian cancer risk.

PubMed 11248061

Antoniou et al. (2007) pooled genotype data for 8,512 female carriers from 19 studies for the RAD51 135G-C SNP. They found evidence of an increased breast cancer risk in CC homozygotes (hazard ratio 1.92; 95% confidence interval 1.25-2.94) but not in heterozygotes. When BRCA1 and BRCA2 mutation carriers were analyzed separately, the increased risk was statistically significant only among BRCA2 mutation carriers, in whom they observed hazard ratios of 1.17 (95% confidence interval 0.91-1.51) among heterozygotes and 3.18 (95% confidence interval 1.39-7.27) among rare homozygotes. In addition, they determined that the 135G-C variant affects RAD51 splicing within the 5-prime untranslated region. Thus, 135G-C may modify the risk of breast cancer in BRCA2 mutation carriers by altering the expression of RAD51. Antoniou et al. (2007) stated that RAD51 was the first gene to be reliably identified as a modifier of risk among BRCA1/2 mutation carriers.

PubMed 17999359

TP53 HGMD

17 7579472 G>C

rs1042522 - NM_000546.6(TP53):c.215C>G (p.Pro72Arg)

ZYG HET

MAF 0.54293

ACMG Benign

CLIN. SIG Drug response [★★★]

HGMD Rankscore 0.1

HGMD Variant Class DFP

Phenotypes

CODON 72 POLYMORPHISM, Li-Fraumeni syndrome 1, Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome, Lip and oral cavity carcinoma, antineoplastic agents response - Efficacy, Toxicity/ADR, cisplatin response - Efficacy, Toxicity/ADR, cyclophosphamide response - Efficacy, Toxicity/ADR, fluorouracil response - Efficacy, Toxicity/ADR, paclitaxel response - Efficacy, Toxicity/ADR, Lung cancer: association with

TP53 Description

Ara et al. (1990) reported that the pro72-to-arg (P72R) change in p53 is caused by polymorphism rather than mutation. Olschwang et al. (1991) assessed the frequency of the pro72-to-arg (P72R) polymorphism and, from its frequency in colon cancer patients and control subjects, concluded that there was no strong association with colon cancer. In both the cancer group and the control group, the frequencies of the pro72 and arg72 alleles were about 31 and 69%, respectively.

PubMed 1975675 | 1999338

The E6 oncoprotein derived from tumor-associated human papillomaviruses (HPVs) binds to and induces degradation of p53. Storey et al. (1998) investigated the effect of the P72R polymorphism on susceptibility of p53 to E6-mediated degradation and found that the arg72 form of p53 was significantly more susceptible than the pro72 form. Moreover, allelic analysis of patients with HPV-associated tumors revealed a striking overrepresentation of homozygous arg72 p53 compared with the normal population, indicating that individuals homozygous for arg72 are about 7 times more susceptible to HPV-associated tumorigenesis than heterozygotes.

PubMed 9607760

Using immunoprecipitation followed by SDS-PAGE, Thomas et al. (1999) found that the arg72 and pro72 p53 variants did not differ in their ability to bind DNA in a sequence-specific manner. They concluded that arg72 and pro72 are conformationally indistinguishable and that both can be considered wildtype. However, Thomas et al. (1999) noted that p53(pro) was a stronger inducer of transcription than p53(arg), whereas p53(arg) induced apoptosis faster and was a more potent suppressor of transformation than p53(pro).

PubMed 9891044

Marin et al. (2000) found that some tumor-derived p53 mutants bound and inactivated p73 (601990). The binding of such mutants was influenced by whether TP53 codon 72 encoded arginine or proline. The ability of p53 to bind p73, neutralize p73-induced apoptosis, and transform cells in cooperation with EJ-Ras (see 190020) was enhanced when codon 72 encoded arg. Marin et al. (2000) found that the arg-containing allele was preferentially mutated and retained in squamous cell tumors arising in arg/pro germline heterozygotes. They concluded that inactivation of p53 family members may contribute to the biologic properties of a subset of p53 mutants, and that a polymorphic residue within p53 affects mutant behavior.

PubMed 10802655

Laryngeal papillomatosis is caused by human papillomavirus and is associated with malignant transformation in 3 to 7% of cases. Aaltonen et al. (2001) found no difference in the prevalence of the P72R polymorphism between a group of patients with laryngeal papillomas and a control group.

PubMed 11403041

The pro72-to-arg polymorphism occurs in the proline-rich domain of p53, which is necessary for the protein to fully induce apoptosis. Dumont et al. (2003) found that in cell lines containing inducible versions of alleles encoding the pro72 and arg72 variants, and in cells with endogenous p53, the arg72 variant induced apoptosis markedly better than the pro72 variant. They suggested that at least 1 source of this enhanced apoptotic potential is the greater ability of the arg72 variant to localize to mitochondria; this localization was accompanied by release of cytochrome c into the cytosol.

PubMed 12567188

In 92 Caucasian MLH1 (120436) or MSH2 (609309) mutation carriers, including 47 with colorectal cancer, Jones et al. (2004) analyzed the p53 codon 72 genotype and found that arg/pro heterozygotes were 1.94 times more likely to get colorectal cancer during any age interval and developed it 13 years earlier than arg/arg homozygotes. The number of pro/pro homozygotes was too small to provide meaningful results.

PubMed 15355915

Kruger et al. (2005) studied the p53 genotype of 167 unrelated patients with hereditary nonpolyposis colon cancer (HNPCC; see 120435) with germline mutations in either MSH2 or MLH1 and found that the median age of onset was 41 years for arg/arg, 36 years for arg/pro, and 32 years for pro/pro individuals (p less than 0.0001). There was no difference in age of onset in 126 patients with microsatellite stable colorectal cancers. Kruger et al. (2005) concluded that in a mismatch repair-deficient background, p53 codon 72 genotypes are associated with the age of onset of colorectal carcinoma in a dose-dependent manner.

PubMed 16199549

Bougeard et al. (2006) studied the effect of the MDM2 SNP309 polymorphism (164785.0001) and the arg72-to-pro polymorphism of the p53 gene on cancer risk in 61 French carriers of the p53 germline mutation. The mean age of tumor onset in p53 codon 72 polymorphism arg allele carriers (21.8 years) was 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). 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.

PubMed 16258005

IASPP (607463) is among the most evolutionarily conserved inhibitors of p53, whereas ASPP1 (606455) and ASPP2 (602143) are activators of p53. Bergamaschi et al. (2006) showed that, in addition to the DNA-binding domain, the ASPP family members also bound to the proline-rich region of p53 containing the codon 72 polymorphism. Furthermore, the ASPP family members, particularly IASPP, bound to and regulated the activity of p53 pro72 more efficiently than that of p53 arg72.

PubMed 16964264

Orsted et al. (2007) stated that arg72 increases the ability of p53 to locate to mitochondria and induce cell death, whereas pro72 exhibits lower apoptotic potential but increases cellular arrest in G1 of the cell cycle. In a study of 9,219 Danish individuals, they found that overall 12-year survival was increased in p53 arg/pro heterozygotes by 3% (P of 0.003) and in pro/pro homozygotes by 6% (P of 0.002) compared with arg/arg homozygotes, corresponding to an increase in median survival of 3 years for pro/pro versus arg/arg homozygotes. Pro/pro homozygotes also showed increased survival after development of cancer, or even after development of other life-threatening diseases, compared with arg/arg homozygotes. The arg72-to-pro change was not associated with decreased risk of cancer.

PubMed 17535973

Among 254 patients with glioblastoma multiforme (see 137800), El Hallani et al. (2009) found an association between the pro72 allele and earlier age at onset. The pro/pro genotype was present in 20.6% of patients with onset before age 45 years, compared to in 6.5% of those with onset after age 45 years (p = 0.002) and 5.9% among 238 controls (p = 0.001). The findings were confirmed in an additional cohort of 29 patients. The variant did not have any impact on overall patient survival. Analysis of tumor DNA from 73 cases showed an association between the pro allele and a higher rate of somatic TP53 mutations.

PubMed 8242752

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 rs1042522 SNP, and found that the G allele was associated with smoking-related accelerated rate of decline in lung function (see 608852) (FEV1, p = 0.020; FEV1/FVC, p = 0.037).

PubMed 19521721

CR2 HGMD

1 207627693 T>C

rs3813946 - NM_001006658.3(CR2):c.-71T>C

ZYG HOM
MAF 0.13079
ACMG -
CLIN. SIG
HGMD Variant Class FP

Phenotype

Increased transcriptional activity

IKZF1

7 50466304 A>G

rs11978267 - NM_006060.6(IKZF1):c.851-1312A>G

ZYG HET
MAF 0.22664
ACMG -
CLIN. SIG Association [★]

Phenotypes

Leukemia, acute lymphoblastic 2

IKZF1

7 50470604 T>G

rs4132601 - NM_006060.6(IKZF1):c.*2279T>G

ZYG HET
MAF 0.22145
ACMG -
CLIN. SIG Association [★]

Phenotypes

Leukemia, acute lymphoblastic 2

TERT HGMD

5 1286516 C>A

rs2736100 - NM_198253.3(TERT):c.1574-3777G>T

ZYG HET
MAF 0.51538
ACMG -
CLIN. SIG Association
HGMD Variant Class DP

Phenotypes

Chronic osteomyelitis, Idiopathic pulmonary fibrosis: increased risk

TERT HGMD

5 1296486 A>G

rs2735940 - NM_198253.2(TERT):c.-1382T>C

ZYG HET
MAF 0.47264
ACMG -
CLIN. SIG Association
HGMD Variant Class DFP

Phenotypes

Chronic osteomyelitis, Coronary artery disease: protection against: association with

TERT Description

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

Matsubara et al. (2006) examined the -1327T-C promoter polymorphism in 104 Japanese male patients with coronary artery disease (CAD) and 115 age-matched male controls and found an association between the -1327 CC genotype and CAD (p = 0.0218). Among the 104 CAD patients, the CC genotype was also associated with shorter telomere length (p = 0.0287). Matsubara et al. (2006) suggested that the -1327 CC genotype is a risk factor for CAD and that it relates to shorter telomere length among CAD patients.

PubMed 16890917

Related Conditions:

- Breast-ovarian cancer, familial 1

Genes Analyzed

This report analyzed the following genes:

GNPTAB, GNAS, GALC, TCIRG1, IDUA, DKC1, PALB2, FANCB, DOCK8, SGSH, CIITA, FANCD2, KIF1B, TSR2, FGA, ICOS, RPS28, KCTD7, RPS7, ARSA, HAX1, PIK3CA, CTSF, MLH1, BRIP1, IRF2BP2, CHEK2, MTHFD1, CEBPA, TP53, LCP1, RPL18, GATA1, ATM, CLN3, GRN, MPL, RFX5, UROS, MTOR, RPS19, PARN, CTSD, GM2A, TPP2PPT1, FANCG, LYZ, IDH1, TYMS, FANCL, PMS2, BRAF, GBA1, SNX10, SH2D1A, MSH2, FANCC, NF1, CLN8, LIG4, ITGB3, RB1,

LRP5, SLX4, HNF1A, KRAS, IL7R, ALK, MYOC, TAP1, ERCC4, CYBA, TINF2, HEATR3, MYH7, CTNNA2, RPS26, UNC13D, IDH2, RAG2, RUNX1, SMARCA4, SLC35C1, PTPN11, CYBB, KMT2D, GATA2, NFKB1, TNFRSF13B, MSH6, RAG1, CLN5, ADA, PTEN, RHEB, LYST, AKT1, BRCA1, ABCD1, EPO, GBA, BLM, LIPA, CTC1, HGSNAT, WAS, CLCN7, OSMR, ITM2B, DCLRE1C, GLB1, NFKB2, MAD2L2, NBN, RPL11, TBX1, GNS, RFXANK, IKZF1, RAD51B, FANCF, B2M, BRCA2, XIAP, RPL35, RAD51, GALNS, MRE11, RPS17, TNFSF11, INPP4A, TNFRSF11A, RPS29, MITF, FLCN, TPP1, BARD1, TERC, TAP2, FERMT3, NRAS, AK2, MET, CBL, ITGB2, VHL, HPRT1, TERT, CA2, STX11, ARSB, CR2, HEXB, DROSHA, RPS15A, RFXAP, KLHDC8B, SMPD1, FANCM, NAGLU, UBE2T, RAC2, FGFR3, SMAD4, NOP10, JAK3, PRF1, FANCE, APP, RFWD3, FANCI, CD3G, IDS, PSAP, IKBKB, RAD50, RPL27, PLEKHM1, BCAR1, APOA1, MFSD8, CLN6, RPL5, CD19, WRAP53, STXBP2, IL31RA, TTR, GUSB, WIPF1, FGFR2, DNAJC5, MAN2B1, RMRP, SLC34A2, HEXA, RPS24, FANCA, SBDS, ITGA2B, RAD51C, PGM3, ERBB2, OSTM1, CDK4, GPNMB

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.

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 Pathogenecitity 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: 98Yv9m2vC7WAuzm2t9zvfmZsMos4T2x4
Clinvar Database Version: FgUM_0StTQ4PCkHW_E7OkqqE0l.5KRqI

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