Dante Labs Inc
325 5th Ave, Suite 38A
New York City , United States
10016
WGS

dante labs

Provider Information
Institution
Dante Labs Inc
Patient Id
Case Id

Sample Information

Sample Type
Human DNA - germline
Collection Method
DNA Genotek - DNA saliva collection kit Oragene OGD-500
Panel Coverage
WGS: Full DNA(introns and exons)
Avg. Read Depth
WGS 30X
Report Date
2/4/2019

Results

Dante Labs ranks the variants according to the ClinVar database.
ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence.
(https://www.ncbi.nlm.nih.gov/clinvar/intro/)

For a representation of clinical significance in ClinVar:
https://www.ncbi.nlm.nih.gov/clinvar/docs/clinsig/#conflicts

Negative: No variants with established pathogenicity detected in genes surveyed.

Affected Genes

AIPL1 **(1)**	***CEP290*** **(1)**	*CRB1* (0)	*CRX* (0)	*GDF6* (0)	*GUCY2D* (0)	*IQCB1* (0)	*KCNJ13* (0)	***LCA5*** **(1)**	*LRAT* (0)	*NMAT1* (0)
OTX2 (0)	*PRPH2* (0)	***RD3*** **(1)**	*RDH12* (0)	*RPE65* (0)	***RPGRIP1*** **(1)**	*SPATA7* (0)	*TULP1* (0)			

Primary Findings

Gene	Zygosity	Variant	Exon	Pathogenicity
CEP290	Heterozygous	NM_025114.3:c.226G>A(NP_079390.3:p.Ala76Thr)	4	Conflicting
RPGRIP1	Homozygous Variant	NM_020366.3:c.1639G>T(NP_065099.3:p.Ala547Ser)	13	Conflicting
AIPL1	Heterozygous	NM_014336.4:c.905G>T(NP_055151.3:p.Arg302Leu)	6	Conflicting
RD3	Heterozygous	NM_183059.2:c.-297_-296delAC(?)	1	Uncertain Significance
LCA5	Heterozygous	NM_181714.3:c.*1300G>A(?)	9	Uncertain Significance

Recommendations

Dante Labs suggests you to discuss your results with a doctor/geneticist or Genetic Counselor in order to correctly interpret the relevance of the variants. As Science progresses, variants may be subject to score changes or reclassification. Dante Labs decided to provide customers with unbiased information about variants by reporting findings as they have been originally reported in ClinVar.

Individual Variant Interpretations

NP_079390.3:p.Ala76Thr in Exon 4 of *CEP290* (NM_025114.3:c.226G>A) Conflicting

This is a Missense Variant located in the CEP290 gene.

The CEP290 gene encodes a centrosomal protein involved in ciliary assembly and ciliary trafficking (summary by Coppieters et al., 2010).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Bardet-Biedl syndrome 14, Joubert syndrome 5, Leber congenital amaurosis 10, Meckel syndrome 4, and Senior-Loken syndrome 6.

ClinVar Assessment from Invitae

Classified as Uncertain Significance on 2017-07-10 for Not Provided

This sequence change replaces alanine with threonine at codon 76 of the CEP290 protein (p.Ala76Thr). The alanine residue is moderately conserved and there is a small physicochemical difference between alanine and threonine. This variant is present in population databases (rs373913704, ExAC 0.09%), including at least one homozygous and/or hemizygous individual. This variant has not been reported in the literature in individuals with CEP290-related disease. ClinVar contains an entry for this variant (Variation ID: 166841). Algorithms developed to predict the effect of missense changes on protein structure and function do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0"). In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

ClinVar Assessment from GeneDx

Classified as Likely Benign on 2017-10-20 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

NP_065099.3:p.Ala547Ser in Exon 13 of *RPGRIP1* (NM_020366.3:c.1639G>T) Conflicting

This is a Missense Variant located in the RPGRIP1 gene.

In 3 Pakistani families, Hameed et al. (2003) found that recessive cone-rod dystrophy (CORD13; 608194) segregated with homozygosity for a 1639G-T transversion in exon 13 of the RPGRIP1 gene, which changed codon 547 from GCT (ala) to TCT (ser).

It has been associated with Cone-rod dystrophy 13 and Leber congenital amaurosis 6.

ClinVar Assessment from GeneDx

Classified as Benign on 2016-10-21 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

NP_055151.3:p.Arg302Leu in Exon 6 of *AIPL1* (NM_014336.4:c.905G>T) Conflicting

This is a Missense Variant located in the AIPL1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cone-rod dystrophy, Leber congenital amaurosis 4, and Retinitis pigmentosa juvenile.

5 Prime UTR Variant in *RD3* (NM_183059.2:c.-297_-296delAC) Uncertain Significance

This is a 5 Prime UTR Variant located in the RD3 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Leber congenital amaurosis 12.

3 Prime UTR Variant in *LCA5* (NM_181714.3:c.*1300G>A) Uncertain Significance

This is a 3 Prime UTR Variant located in the LCA5 gene.

It has been associated with Leber congenital amaurosis 5.

References

Additional Information

Test

Dante Labs_Eye Diseases Panel_1

Indication

Data produced by tertiary bioinformatic analysis on WGS 30X

Background

WGS was performed using Next-Generation-Sequencing Technology.Variants are reported according to the HGVS nomenclature (www.hgvs.org/mutnomen) and ACMG Guidelines (https://www.acmg.net/)

Method

Whole genome sequencing

The qualified genomic DNA sample was randomly fragmented by Covaris technology and the fragment of 350bp was obtained after fragment selection. The end repair of DNA fragments was performed and an "A" base was added at the 3'-end of each strand. Adapters were then ligated to both ends of the end repaired/dA tailed DNA fragments, then amplification by ligation-mediated PCR (LM-PCR), then single strand separation and cyclization. The rolling circle amplification (RCA) was performed to produce DNA Nanoballs (DNBs). The qualified DNBs were loaded into the patterned nanoarrays and pair-end read were read through on the BGISEQ-500 platform and high-throughput sequencing are performed for each library to ensure that each sample meet the average sequencing coverage requirement. Sequencing-derived raw image files were processed by BGISEQ-500 basecalling Software for base-calling with default parameters and the sequence data of each individual is generated as paired-end reads, which is defined as "raw data" and stored in FASTQ format.

Sequencing of this individual's genome was performed and covered an average of 30X. 99.66% on average of the whole genome excluding gap regions were covered by at least 1X coverage, 99.27% had at least 4X coverage and 98.28% had at least 10X coverage.

Bioinformatic analysis

Reads were aligned to the human reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). The GATK Variant Quality Score Recalibration (VQSR) that uses machine learning algorithm was used to filter the raw variant callset. The SNPs and InDels marked PASS in the output VCF file were high-confident variation set. All the variants with pathogenic or unknown significance for causing or contributing to diseases are reported.

Data Quality Control

The strict data quality control (QC) was performed in the whole analysis pipeline for the clean data , the mapping data, the variant calling, etc. Several quality control items for each sample were checked.

Variant classification

The classification of variants is largely based on the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., Genet. Med., 2015, http://www.ncbi.nlm.nih.gov/pubmed/25741868, and Richards et al.,Genet. Med., 2008, http://www.ncbi.nlm.nih.gov/pubmed/18414213). Based on the evidence available, a given variant will be classified according to the weighted classification system as set out by the ACMG (for more information about the specific criteria, see also tables 3 and 4 in http://www.ncbi.nlm.nih.gov/pubmed/25741868). In general, variant evidence can comprise previous reports and functional data about that specific variant if available (e.g. described as pathogenic, reports about the effect of that specific variant on protein expression and function, as verified in functional in vitro or in vivo experiments), reports and functional data about other similar variants within the same gene (e.g. information about the type of known pathogenic and benign variants within a specific gene, known mutational hot spots or certain protein domains, are also taken into account when classifying a variant within the same gene), phenotype data (e.g. the clinical phenotype of the patient is taken into account when classifying a variant, the match between the phenotype in the patient and the gene's disease association is of relevance), population data (e.g. variant and disease population frequencies), segregation data (e.g. whether the variant co-segregates with the disease in a family), and computational data (e.g. in silico predictive algorithms).

Limitations

CNVs are not included into the report.

Disclaimer

The genetic analysis and reporting conducted by the Dante Labs are based on information from one or more published third- party scientific and medical studies. We do not independently judge the validity or accuracy of such published scientific information. Because 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, epidemiologic data aren'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 to ask help to 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 FDA has determined that such clearance or approval is not necessary.

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Provider Information
Institution
Dante Labs Inc
Patient Id
Case Id

Sample Information

Sample Type
Human DNA - germline
Collection Method
DNA Genotek - DNA saliva collection kit Oragene OGD-500
Panel Coverage
WGS: Full DNA(introns and exons)
Avg. Read Depth
WGS 30X
Report Date
2/4/2019

Results

Dante Labs ranks the variants according to the ClinVar database.
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For a representation of clinical significance in ClinVar:
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Positive: Variants with established pathogenicity detected in genes surveyed.

Affected Genes

ABCB6 (0)	*ABCC6* (0)	*ABHD12* (0)	*ADAM9* (0)	*ADAMTS18* (0)	*ADGRV1* (0)	*AGK* (0)	*AHI1* (0)	***AIPL1*** **(1)**	***ALMS1*** **(1)**	*ARL13B* (0)
ARL6 (0)	*B3GLCT* (0)	*BBS1* (0)	*BBS10* (0)	*BBS12* (0)	*BBS2* (0)	*BBS4* (0)	*BBS5* (0)	*BBS7* (0)	*BBS9* (0)	*BCOR* (0)
BEST1 (0)	*BFSP2* (0)	*BMP4* (0)	*C19ORF12* (0)	*C1QTNF5* (0)	*C8ORF37* (0)	*CA4* (0)	*CABP4* (0)	*CACNA1F* (0)	*CACNA2D4* (0)	*CC2D2A* (0)
CDH23 **(1)**	*CDH3* (0)	***CDHR1*** **(1)**	***CEP290*** **(1)**	***CEP41*** **(1)**	*CERKL* (0)	*CFH* (0)	*CHM* (0)	*CHMP4B* (0)	*CHST6* (0)	*CIB2* (0)
CLN3 (0)	*CLN5* (0)	***CLN6*** **(1)**	*CLN8* (0)	***CLRN1*** **(1)**	*CNGA1* (0)	*CNGA3* (0)	***CNGB1*** **(1)**	*CNGB3* (0)	*CNNM4* (0)	***COL11A1*** **(2)**

COL11A2 (0)	*COL2A1* (0)	*COL4A1* (0)	*COL8A2* (0)	*COL9A1* (0)	*COL9A2* (0)	*CRB1* (0)	*CRX* (0)	*CRYAA* (0)	*CRYAB* (0)	*CRYBA1* (0)
CRYBA4 (0)	*CRYBB1* (0)	*CRYBB2* (0)	*CRYBB3* (0)	*CRYGB* (0)	*CRYGC* (0)	*CRYGD* (0)	*CRYGS* (0)	*CTDP1* (0)	*CTSD* (0)	***CYP1B1*** **(2)**
CYP4V2 **(1)**	*DCN* (0)	*DHDDS* (0)	*EFEMP1* (0)	*ELOVL4* (0)	*EPHA2* (0)	*EYS* (0)	*FAM161A* (0)	***FLVCR1*** **(3)**	***FRAS1*** **(1)**	***FREM1*** **(1)**
FREM2 **(1)**	*FSCN2* (0)	*FTL* (0)	***FYCO1*** **(3)**	***FZD4*** **(3)**	*GALK1* (0)	***GALT*** **(1)**	*GDF3* (0)	*GDF6* (0)	*GFER* (0)	*GIPC3* (0)
GJA1 (0)	*GJA3* (0)	*GNAT1* (0)	*GNAT2* (0)	*GNPTG* (0)	*GPR143* (0)	*GPR179* (0)	*GRIP1* (0)	*GRK1* (0)	*GRM6* (0)	*GRN* (0)
GSN **(1)**	*GUCA1A* (0)	*GUCA1B* (0)	*GUCY2D* (0)	*HARS* (0)	*HCCS* (0)	*HMX1* (0)	*HSF4* (0)	*IDH3B* (0)	*IFT140* (0)	*IMPDH1* (0)
IMPG2 **(1)**	***INVS*** **(1)**	*IQCB1* (0)	*ITM2B* (0)	*JAG1* (0)	*JAM3* (0)	*KCNJ13* (0)	*KIF11* (0)	*KIF7* (0)	*KLHL7* (0)	*KRT12* (0)
KRT3 (0)	*LAMA1* (0)	***LCA5*** **(1)**	*LIM2* (0)	*LRAT* (0)	*LRP5* (0)	*LZTFL1* (0)	*MAK* (0)	*MERTK* (0)	*MFN2* (0)	*MFRP* (0)
MFSD8 (0)	*MIP* (0)	*MKKS* (0)	*MKS1* (0)	*MTTP* (0)	*MVK* (0)	*MYO7A* (0)	*MYOC* (0)	*NAA10* (0)	*NDP* (0)	*NHS* (0)
NMNAT1 (0)	*NPHP1* (0)	*NPHP3* (0)	*NPHP4* (0)	***NR2E3*** **(1)**	*NRL* (0)	*NYX* (0)	***OAT*** **(1)**	*OFD1* (0)	*OPA1* (0)	***OPA3*** **(3)**
OPN1MW (0)	*OTX2* (0)	*PANK2* (0)	*PAX2* (0)	*PAX6* (0)	*PCARE* (0)	***PCDH15*** **(1)**	***PDE6A*** **(1)**	*PDE6B* (0)	*PDE6C* (0)	*PDE6G* (0)
PDE6H (0)	*PDZD7* (0)	*PEX7* (0)	*PHYH* (0)	*PIKFYVE* (0)	***PITPNM3*** **(3)**	*PITX2* (0)	*PITX3* (0)	*PLA2G5* (0)	*PPT1* (0)	*PRCD* (0)
PRDM5 (0)	*PROM1* (0)	*PRPF3* (0)	*PRPF31* (0)	*PRPF6* (0)	*PRPF8* (0)	*PRPH2* (0)	*PRSS56* (0)	*RAB28* (0)	*RAX2* (0)	*RBP3* (0)
RBP4 (0)	***RD3*** **(1)**	*RDH12* (0)	*RDH5* (0)	*RGR* (0)	*RGS9* (0)	*RGS9BP* (0)	*RHO* (0)	*RIMS1* (0)	*RLBP1* (0)	*ROM1* (0)
RP1 (0)	*RP1L1* (0)	*RP2* (0)	*RP9* (0)	*RPE65* (0)	*RPGR* (0)	***RPGRIP1*** **(1)**	*RPGRIP1L* (0)	*RS1* (0)	*SAG* (0)	*SDCCAG8* (0)

SEMA4A (0)	*SIX6* (0)	*SLC24A1* (0)	*SLC45A2* (0)	*SLC4A11* (0)	*SMOC1* (0)	***SNRNP200*** **(1)**	*SOX2* (0)	*SPATA7* (0)	*STRA6* (0)	*TACSTD2* (0)
TCTN1 (0)	*TCTN2* (0)	*TDRD7* (0)	*TEAD1* (0)	*TGFBI* (0)	*TIMM8A* (0)	***TIMP3*** **(1)**	*TMEM126A* (0)	*TMEM138* (0)	*TMEM216* (0)	*TMEM237* (0)
TMEM67 (0)	***TOPORS*** **(1)**	***TPP1*** **(1)**	*TREX1* (0)	*TRIM32* (0)	*TRPM1* (0)	*TSPAN12* (0)	*TTC21B* (0)	*TTC8* (0)	*TULP1* (0)	*TYR* (0)
TYRP1 (0)	*UBIAD1* (0)	*UNC119* (0)	*USH1C* (0)	*USH1G* (0)	***USH2A*** **(1)**	*VAX1* (0)	*VCAN* (0)	*VIM* (0)	*VPS13B* (0)	*VSX1* (0)
VSX2 **(1)**	*WDPCP* (0)	*WDR19* (0)	***WFS1*** **(1)**	*WHRN* (0)	*YAP1* (0)	*ZEB1* (0)	*ZNF469* (0)	*ZNF513* (0)	*ZNF644* (0)	

Primary Findings

Gene	Zygosity	Variant	Exon	Pathogenicity
COL11A1	Heterozygous	NM_001854.3:c.3817-14_3817-13dupTT(?)	51	Conflicting
COL11A1	Heterozygous	NM_001854.3:c.3817-13dupT(?)	51	Conflicting
FLVCR1	Heterozygous	NM_014053.3:c.*2077_*2080dupCACA(?)	10	Conflicting
FLVCR1	Heterozygous	NM_014053.3:c.*2077_*2080dupCACA(?)	10	Conflicting
USH2A	Heterozygous	NM_206933.2:c.6240G>T(NP_996816.2:p.Lys2080Asn)	32	Conflicting
CYP1B1	Heterozygous	NM_000104.3:c.685G>A(NP_000095.2:p.Glu229Lys)	2	Conflicting
ALMS1	Heterozygous	NM_015120.4:c.72_74dupGGA(NP_055935.4:p.Glu28_Ala29insGlu)	1	Conflicting
GALT	Heterozygous	NM_000155.3:c.940A>G(NP_000146.2:p.Asn314Asp)	10	Conflicting
PCDH15	Heterozygous	NM_033056.3:c.546A>G(NP_149045.3:p.Gly182=)	6	Conflicting
CDH23	Homozygous Variant	NM_022124.5:c.-35_-31dupAGGCG(?)	1	Conflicting
CEP290	Heterozygous	NM_025114.3:c.226G>A(NP_079390.3:p.Ala76Thr)	4	Conflicting
RPGRIP1	Homozygous Variant	NM_020366.3:c.1639G>T(NP_065099.3:p.Ala547Ser)	13	Conflicting
CLN6	Homozygous Variant	NM_017882.2:c.*159_*160dupGT(?)	7	Conflicting
AIPL1	Heterozygous	NM_014336.4:c.905G>T(NP_055151.3:p.Arg302Leu)	6	Conflicting
OPA3	Heterozygous	NM_025136.3:c.*4720_*4723dupATAA(?)	2	Conflicting
OPA3	Heterozygous	NM_025136.3:c.*4720_*4723dupATAA(?)	2	Conflicting
CYP1B1	Homozygous Variant	NM_000104.3:c.1294G>C(NP_000095.2:p.Val432Leu)	3	Drug Response
WFS1	Homozygous Variant	NM_006005.3:c.713-1075C>G(?)	7	Pathogenic
RD3	Heterozygous	NM_183059.2:c.-297_-296delAC(?)	1	Uncertain Significance
FLVCR1	Heterozygous	NM_014053.3:c.-156delT(?)	1	Uncertain Significance
SNRNP200	Heterozygous	NM_014014.4:c.*331G>C(?)	45	Uncertain Significance
FYCO1	Heterozygous	NM_024513.3:c.*2695_*2696insT(?)	18	Uncertain Significance
FYCO1	Heterozygous	NM_024513.3:c.*2695_*2696insTT(?)	18	Uncertain Significance
FYCO1	Heterozygous	NM_024513.3:c.*2695_*2696insT(?)	18	Uncertain Significance
IMPG2	Heterozygous	NM_016247.3:c.*740_*743dupTATA(?)	19	Uncertain Significance
CLRN1	Homozygous Variant	NM_174878.2:c.*301_*304delGTGT(?)	3	Uncertain Significance
FRAS1	Heterozygous	NM_025074.6:c.380C>G(NP_079350.5:p.Pro127Arg)	5	Uncertain Significance
CYP4V2	Homozygous Variant	NM_207352.3:c.*1061_*1064dupCACA(?)	11	Uncertain Significance
PDE6A	Heterozygous	NM_000440.2:c.*2068delG(?)	22	Uncertain Significance
LCA5	Heterozygous	NM_181714.3:c.*1300G>A(?)	9	Uncertain Significance
CEP41	Heterozygous	NM_018718.2:c.*1384dupA(?)	11	Uncertain Significance
FREM1	Heterozygous	NM_144966.5:c.-149A>G(?)	3	Uncertain Significance
TOPORS	Heterozygous	NM_005802.4:c.*139dupT(?)	3	Uncertain Significance
INVS	Heterozygous	NM_014425.4:c.*504_*505delCA(?)	17	Uncertain Significance
GSN	Heterozygous	NM_000177.4:c.*136dupT(?)	17	Uncertain Significance
CDHR1	Heterozygous	NM_033100.3:c.159C>A(NP_149091.1:p.His53Gln)	3	Uncertain Significance
OAT	Heterozygous	NM_000274.3:c.-30+8C>T(?)	1	Uncertain Significance
TPP1	Homozygous Variant	NM_000391.3:c.887-6delA(?)	8	Uncertain Significance
FZD4	Heterozygous	NM_012193.3:c.*3937_*3940delTTTG(?)	2	Uncertain Significance

Gene	Zygosity	Variant	Exon	Pathogenicity
FZD4	Heterozygous	NM_012193.3:c.*3925_*3940del(?)	2	Uncertain Significance
FZD4	Heterozygous	NM_012193.3:c.*3925_*3940del(?)	2	Uncertain Significance
FREM2	Heterozygous	NM_207361.5:c.*5610_*5611dupGA(?)	24	Uncertain Significance
VSX2	Heterozygous	NM_182894.2:c.-43dupG(?)	1	Uncertain Significance
NR2E3	Heterozygous	NM_014249.3:c.-139G>A(?)	1	Uncertain Significance
CNGB1	Heterozygous	NM_001297.4:c.105G>A(NP_001288.3:p.Ala35=)	2	Uncertain Significance
PITPNM3	Heterozygous	NM_031220.3:c.*3464dupG(?)	20	Uncertain Significance
PITPNM3	Homozygous Variant	NM_031220.3:c.*3445_*3446insT(?)	20	Uncertain Significance
PITPNM3	Homozygous Variant	NM_031220.3:c.*2334_*2335delGA(?)	20	Uncertain Significance
OPA3	Heterozygous	NM_025136.3:c.*4716_*4723dupATAAATAA(?)	2	Uncertain Significance
OPA3	Heterozygous	NM_025136.3:c.*4720_*4723dupATAA(?)	2	Uncertain Significance
SYN3, TIMP3	Heterozygous	NM_003490.3:c.711+4001delA(?)	5,5	Uncertain Significance

Recommendations

Dante Labs suggests you to discuss your results with a doctor/geneticist or Genetic Counselor in order to correctly interpret the relevance of the variants. As Science progresses, variants may be subject to score changes or reclassification. Dante Labs decided to provide customers with unbiased information about variants by reporting findings as they have been originally reported in ClinVar.

Individual Variant Interpretations

Intron Variant in *COL11A1* (NM_001854.3:c.3817-14_3817-13dupTT) Conflicting

This is a Intron Variant located in the COL11A1 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Fibrochondrogenesis 1, Marshall syndrome, Stickler syndrome type II, and Lumbar disc herniation susceptibility to.

ClinVar Assessment from GeneDx

Classified as Benign on 2017-11-01 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

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3 Prime UTR Variant in *FLVCR1* (NM_014053.3:c.*2077_*2080dupCACA) Conflicting

This is a 3 Prime UTR Variant located in the FLVCR1 gene.

The FLVCR1 gene encodes the feline leukemia virus subgroup C receptor 1, a heme-transporter protein (Quigley et al., 2004).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ataxia posterior column with retinitis pigmentosa.

3 Prime UTR Variant in *FLVCR1* (NM_014053.3:c.*2077_*2080dupCACA) Conflicting

This is a 3 Prime UTR Variant located in the FLVCR1 gene.

The FLVCR1 gene encodes the feline leukemia virus subgroup C receptor 1, a heme-transporter protein (Quigley et al., 2004).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ataxia posterior column with retinitis pigmentosa.

NP_996816.2:p.Lys2080Asn in Exon 32 of *USH2A* (NM_206933.2:c.6240G>T) Conflicting

This is a Missense Variant located in the USH2A gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Retinitis pigmentosa 39 and Usher syndrome type 2A.

ClinVar Assessment from Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine

Classified as Benign on 2012-05-14 for Not Specified

Lys2080Asn in Exon 32 of USH2A: This variant is not expected to have clinical significance because it has been identified in 1.1% (41/3738) of African American chromosomes from a broad population by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS; dbSNP rs114402911). As expected, this variant has been reported in equal frequencies in cases and controls (Booij 2010, Clark 2010, Dreyer 2008, McGee 2010).

NP_000095.2:p.Glu229Lys in Exon 2 of *CYP1B1* (NM_000104.3:c.685G>A) Conflicting

This is a Missense Variant located in the CYP1B1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Anterior segment dysgenesis 6 multiple subtypes and Glaucoma 3A primary open angle congenital juvenile or adult onset.

NP_055935.4:p.Glu28_Ala29insGlu in Exon 1 of *ALMS1* (NM_015120.4:c.72_74dupGGA) Conflicting

This is a Inframe Insertion located in the ALMS1 gene.

ALMS1 localizes to the centrosome and appears to have a role in centriole structure and function (Knorz et al., 2010).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Alstrom syndrome.

NP_000146.2:p.Asn314Asp in Exon 10 of *GALT* (NM_000155.3:c.940A>G) Conflicting

This is a Missense Variant located in the GALT gene.

This polymorphism was identified by Reichardt and Woo (1991). The asn314-to-asp (N314D; {dbSNP rs2070074}) substitution results from a 940A-G transition in exon 10 of the GALT gene. In 111 biochemically unphenotyped controls with no history of galactosemia, Elsas et al. (1994) identified 13 N314D alleles. Using G for the allele causing classic galactosemia and D for the Duarte allele, Elsas et al. (1994) proposed that the D/N, D/D, and D/G genotypes show approximately 75%, 50%, and 25% of normal GALT activity, respectively. In addition, the Duarte allele is associated with an isoform of the enzyme that has more acidic pI than normal. This variant is known as Duarte, Duarte-2, or D2 (Holton et al., 2001).

Ashino et al. (1995) identified the N314D substitution in Japanese patients with GALT deficiency and speculated that the mutation arose before Asian and Caucasian peoples diverged. Carney et al. (2009) reported that the frequency of the D314 allele in the CEPH HapMap sample is 11.3%, which is unusually high compared with Yoruba, Chinese, and Japanese populations, which each exhibit frequencies of D314 well under 3%.

The characteristic Duarte isoform is also associated with a variant allele (652C-T; L218L; {606999.0012}), yielding the 'Los Angeles (LA) phenotype,' which has nearly normal or increased GALT enzyme activity. Podskarbi et al. (1996) referred to the 'Los Angeles variant' as Duarte-1 (D1), and noted that the N314D substitution was associated with a silent L218L substitution. They found the same substitution, N314D, in conjunction with 2 regulatory intronic mutations, 1105G-C and 1391G-A, in the D2 variant. Although D1 and D2 have identical electrophoretic mobility and isoelectric focusing points, their GALT activities differ: D1 variants show 110% to 130% of normal RBC activity, but D2 variants show only 40% to 50%. The N314D polymorphism occurs in both variants. Podskarbi et al. (1996) suggested that the decrease in GALT activity in D2 may be due to regulation of GALT gene expression by the intronic mutations. They suggested that the 1105G-C site may be critical to the function of erythroid transcription factor NFE1 (305371), since it flanks the core consensus sequence for 1 of its binding sites. Alternatively, both intronic mutations may be involved in aberrant splice processing, possibly resulting in a low level of correctly spliced mRNA.

Langley et al. (1997) evaluated GALT enzyme activity and screened the GALT genes of 145 patients with 1 or more N314D-containing alleles. They found 7 with the 'LA' biochemical phenotype, and all had the The 652C-T transition in exon 7 in cis with the N314D substitution. In pedigree analyses, this 652C-T transition segregated with the LA phenotype of increased GALT activity in 3 different biochemical phenotypes: LA/N, LA/G, and LA/D. From other studies, Langley et al. (1997) concluded that the 652C-T transition increases GALT activity by increasing GALT protein abundance without increasing transcription or decreasing thermolability. They postulated a favorable codon bias for the mutated codon with consequently increased translation rates.

Kozak et al. (1999) found that the Duarte allele is linked to a 4-bp deletion 5-prime to the translation start site (-119_-116delGTCA; {606999.0016}) of GALT. Elsas et al. (2001) found that this 4-bp deletion conferred reduced luciferase activity when transfected into cell lines. Additionally, human lymphoblasts derived from patients with the Duarte allele had reduced GALT mRNA. In the Los Angeles variant, the promoter is intact. Trbusek et al. (2001) presented evidence that the 4-bp promoter deletion is a crucial factor in reduction of Duarte allele enzyme activity.

Carney et al. (2009) reported that the N314D protein was functionally neutral in mammalian cell and yeast expression studies. In contrast, the 5-prime 4-bp deletion characteristic of D2 alleles appeared to be functionally impaired in reporter gene transfection studies. Allele-specific quantitative RT-PCR revealed that D2 alleles expressed less mRNA in vivo than their wildtype counterparts. The 4-bp deletion appeared to be exclusive to D2 alleles amongst GG, NN, and DG populations. Carney et al. (2009) concluded that the 4-bp 5-prime deletion is the causal mutation in Duarte galactosemia and suggested that direct tests for this deletion could enhance or supplant current tests.

Galactose-1-phosphate uridylyltransferase (GALT; {EC 2.7.7.12}) is the second enzyme in the evolutionarily conserved galactose metabolic pathway. It facilitates the simultaneous conversion of uridine diphosphoglucose and galactose-1-phosphate to uridine diphosphogalactose and glucose-1-phosphate, respectively (summary by Tang et al., 2014).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Galactosemia.

ClinVar Assessment from GeneDx

Classified as Pathogenic on 2017-07-26 for Not Provided

The N314D variant has been reported in various populations with a frequency ranging from 1% to 13% by the NHLBI ESP Exome Sequencing Project and the 1000 Genomes Project. When N314D is present on the same GALT allele (in cis) as the c.-119_116delGTCA promoter variant (Duarte-2 variant), the result is an impaired regulatory domain of the GALT enzyme and approximately 50% of normal galactose-1-phosphate uridyltransferase (GALT) activity (Bosch et al., 2005). Newborns who are compound heterozygotes for the Duarte-2 variant (D variant) and a variant associated with classic galactosemia (G variant) are considered to have Duarte-2 variant galactosemia or D/G galactosemia which may be identified by newborn screening programs and is associated with approximately 50% of control galactosyltransferase activity, on average (Berry, 2014).

NP_149045.3:p.Gly182= in Exon 6 of *PCDH15* (NM_033056.3:c.546A>G) Conflicting

This is a Synonymous Variant located in the PCDH15 gene.

This gene has been observed to exhibit Autosomal recessive and Digenic recessive inheritance pattern.

It has been associated with Deafness autosomal recessive 23, Usher syndrome type 1D/F digenic, and Usher syndrome type 1F.

ClinVar Assessment from Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine

Classified as Benign on 2010-07-25 for Not Specified

This variant is not expected to have clinical significance because it does not alter an amino acid residue, is not located near a splice junction and is listed in dbSNP(rs34164469 - 2 submissions). In addition, this variant has been identified by our laboratory in an individual who has a homozygous pathogenic variant in another gene that the causes hearing loss.

ClinVar Assessment from GeneDx

Classified as Benign on 2013-02-11 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

5 Prime UTR Variant in *CDH23* (NM_022124.5:c.-35_-31dupAGGCG) Conflicting

This is a 5 Prime UTR Variant located in the CDH23 gene.

The CDH23 gene encodes a member of the cadherin superfamily, which comprises calcium-dependent cell-cell adhesion glycoproteins (summary by Zhang et al., 2017).

This gene has been observed to exhibit Autosomal recessive, Digenic recessive, and Autosomal dominant inheritance pattern.

It has been associated with Deafness autosomal recessive 12, Usher syndrome type 1D, Usher syndrome type 1D/F digenic, and Pituitary adenoma 5 multiple types.

ClinVar Assessment from Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine

Classified as Likely Benign on 2016-03-28 for Not Specified

Variant identified in a genome or exome case(s) and assessed due to predicted null impact of the variant or pathogenic assertions in the literature or databases. Disclaimer: This variant has not undergone full assessment. The following are preliminary notes: Outside ROI, common in our data set

NP_079390.3:p.Ala76Thr in Exon 4 of *CEP290* (NM_025114.3:c.226G>A) Conflicting

This is a Missense Variant located in the CEP290 gene.

The CEP290 gene encodes a centrosomal protein involved in ciliary assembly and ciliary trafficking (summary by Coppieters et al., 2010).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Bardet-Biedl syndrome 14, Joubert syndrome 5, Leber congenital amaurosis 10, Meckel syndrome 4, and Senior-Loken syndrome 6.

ClinVar Assessment from Invitae

Classified as Uncertain Significance on 2017-07-10 for Not Provided

This sequence change replaces alanine with threonine at codon 76 of the CEP290 protein (p.Ala76Thr). The alanine residue is moderately conserved and there is a small physicochemical difference between alanine and threonine. This variant is present in population databases (rs373913704, ExAC 0.09%), including at least one homozygous and/or hemizygous individual. This variant has not been reported in the literature in individuals with CEP290-related disease. ClinVar contains an entry for this variant (Variation ID: 166841). Algorithms developed to predict the effect of missense changes on protein structure and function do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0"). In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

ClinVar Assessment from GeneDx

Classified as Likely Benign on 2017-10-20 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

NP_065099.3:p.Ala547Ser in Exon 13 of *RPGRIP1* (NM_020366.3:c.1639G>T) Conflicting

This is a Missense Variant located in the RPGRIP1 gene.

In 3 Pakistani families, Hameed et al. (2003) found that recessive cone-rod dystrophy (CORD13; 608194) segregated with homozygosity for a 1639G-T transversion in exon 13 of the RPGRIP1 gene, which changed codon 547 from GCT (ala) to TCT (ser).

It has been associated with Cone-rod dystrophy 13 and Leber congenital amaurosis 6.

ClinVar Assessment from GeneDx

Classified as Benign on 2016-10-21 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

3 Prime UTR Variant in *CLN6* (NM_017882.2:c.*159_*160dupGT) Conflicting

This is a 3 Prime UTR Variant located in the CLN6 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ceroid lipofuscinosis neuronal 6 and Ceroid lipofuscinosis neuronal Kufs type adult onset.

NP_055151.3:p.Arg302Leu in Exon 6 of *AIPL1* (NM_014336.4:c.905G>T) Conflicting

This is a Missense Variant located in the AIPL1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cone-rod dystrophy, Leber congenital amaurosis 4, and Retinitis pigmentosa juvenile.

3 Prime UTR Variant in *OPA3* (NM_025136.3:c.*4720_*4723dupATAA) Conflicting

This is a 3 Prime UTR Variant located in the OPA3 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with 3-methylglutaconic aciduria type III and Optic atrophy 3 with cataract.

3 Prime UTR Variant in *OPA3* (NM_025136.3:c.*4720_*4723dupATAA) Conflicting

This is a 3 Prime UTR Variant located in the OPA3 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with 3-methylglutaconic aciduria type III and Optic atrophy 3 with cataract.

NP_000095.2:p.Val432Leu in Exon 3 of *CYP1B1* (NM_000104.3:c.1294G>C) Drug Response

This is a Missense Variant located in the CYP1B1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Anterior segment dysgenesis 6 multiple subtypes and Glaucoma 3A primary open angle congenital juvenile or adult onset.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2016-05-18 for Paclitaxel Response - Efficacy

PharmGKB Level of Evidence 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Intron Variant in *WFS1* (NM_006005.3:c.713-1075C>G) Pathogenic

This is a Intron Variant located in the WFS1 gene.

For discussion of the {dbSNP rs6446482} in the WFS1 gene that was found in an association study for type 2 diabetes (125853) by Sandhu et al. (2007), see {606201.0021}.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Cataract 41, Deafness autosomal dominant 6/14/38, Wolfram syndrome 1, Wolfram-like syndrome autosomal dominant, and Diabetes mellitus noninsulin-dependent association with.

5 Prime UTR Variant in *RD3* (NM_183059.2:c.-297_-296delAC) Uncertain Significance

This is a 5 Prime UTR Variant located in the RD3 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Leber congenital amaurosis 12.

5 Prime UTR Variant in *FLVCR1* (NM_014053.3:c.-156delT) Uncertain Significance

This is a 5 Prime UTR Variant located in the FLVCR1 gene.

The FLVCR1 gene encodes the feline leukemia virus subgroup C receptor 1, a heme-transporter protein (Quigley et al., 2004).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ataxia posterior column with retinitis pigmentosa.

3 Prime UTR Variant in *SNRNP200* (NM_014014.4:c.*331G>C) Uncertain Significance

This is a 3 Prime UTR Variant located in the SNRNP200 gene.

Many of the factors involved in the splicing of RNA molecules are conserved in eukaryotes, including the small nuclear ribonuclear particles (snRNPs) U1, U2, U4/U6 and U5, and a number of non-snRNP splicing factors. The snRNPs contain both RNA and protein. During the presplicing reaction, U1 and U2 snRNA are involved in distinguishing intron from exon sequence. U4/U6 and U5 act as a tri-snRNP complex (U4/U6.U5) to align RNA during splice reactions. The RNA to be spliced undergoes several conformational changes during spliceosome assembly and the splicing reactions. A group of non-snRNP splicing factors have been identified in yeast and may be involved in the dynamic changes associated with splicing. These proteins fall into 2 classes; Prp5 and Prp28 belong to the DEAD-box of putative ATP-dependent RNA helicases, and Prp2, Prp16, and Prp22 belong to a family of putative RNA helicases containing a DEAH box. DEAD and DEAH refer to a sequence motif present in these proteins (asp-glu-ala-asp or asp-glu-ala-his) (summary by Lauber et al., 1996).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Retinitis pigmentosa 33.

3 Prime UTR Variant in *FYCO1* (NM_024513.3:c.*2695_*2696insT) Uncertain Significance

This is a 3 Prime UTR Variant located in the FYCO1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cataract 18 autosomal recessive.

3 Prime UTR Variant in *FYCO1* (NM_024513.3:c.*2695_*2696insTT) Uncertain Significance

This is a 3 Prime UTR Variant located in the FYCO1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cataract 18 autosomal recessive.

3 Prime UTR Variant in *FYCO1* (NM_024513.3:c.*2695_*2696insT) Uncertain Significance

This is a 3 Prime UTR Variant located in the FYCO1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cataract 18 autosomal recessive.

3 Prime UTR Variant in *IMPG2* (NM_016247.3:c.*740_*743dupTATA) Uncertain Significance

This is a 3 Prime UTR Variant located in the IMPG2 gene.

Interphotoreceptor matrix proteoglycan-2 is part of an extracellular complex occupying the interface between photoreceptors and the retinal pigment epithelium in the fundus of the eye (summary by Acharya et al., 2000).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Macular dystrophy vitelliform 5 and Retinitis pigmentosa 56.

3 Prime UTR Variant in *CLRN1* (NM_174878.2:c.*301_*304delGTGT) Uncertain Significance

This is a 3 Prime UTR Variant located in the CLRN1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Retinitis pigmentosa 61 and Usher syndrome type 3A.

NP_079350.5:p.Pro127Arg in Exon 5 of *FRAS1* (NM_025074.6:c.380C>G) Uncertain Significance

This is a Missense Variant located in the FRAS1 gene.

The FRAS1 gene encodes a putative extracellular matrix (ECM) protein (McGregor et al., 2003).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Fraser syndrome 1.

3 Prime UTR Variant in *CYP4V2* (NM_207352.3:c.*1061_*1064dupCACA) Uncertain Significance

This is a 3 Prime UTR Variant located in the CYP4V2 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Bietti crystalline corneoretinal dystrophy.

3 Prime UTR Variant in *PDE6A* (NM_000440.2:c.*2068delG) Uncertain Significance

This is a 3 Prime UTR Variant located in the PDE6A gene.

It has been associated with Retinitis pigmentosa 43.

3 Prime UTR Variant in *LCA5* (NM_181714.3:c.*1300G>A) Uncertain Significance

This is a 3 Prime UTR Variant located in the LCA5 gene.

It has been associated with Leber congenital amaurosis 5.

3 Prime UTR Variant in *CEP41* (NM_018718.2:c.*1384dupA) Uncertain Significance

This is a 3 Prime UTR Variant located in the CEP41 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Joubert syndrome 15.

5 Prime UTR Variant in *FREM1* (NM_144966.5:c.-149A>G) Uncertain Significance

This is a 5 Prime UTR Variant located in the FREM1 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Bifid nose with or without anorectal and renal anomalies, Manitoba oculotrichoanal syndrome, and Trigonocephaly 2.

3 Prime UTR Variant in *TOPORS* (NM_005802.4:c.*139dupT) Uncertain Significance

This is a 3 Prime UTR Variant located in the TOPORS gene.

It has been associated with Retinitis pigmentosa 31.

3 Prime UTR Variant in *INVS* (NM_014425.4:c.*504_*505delCA) Uncertain Significance

This is a 3 Prime UTR Variant located in the INVS gene.

INVS is part of a complex of ciliary proteins required for renal and cardiovascular development (Hoff et al., 2013).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Nephronophthisis 2 infantile.

3 Prime UTR Variant in *GSN* (NM_000177.4:c.*136dupT) Uncertain Significance

This is a 3 Prime UTR Variant located in the GSN gene.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Amyloidosis Finnish type.

NP_149091.1:p.His53Gln in Exon 3 of *CDHR1* (NM_033100.3:c.159C>A) Uncertain Significance

This is a Missense Variant located in the CDHR1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cone-rod dystrophy 15 and Retinitis pigmentosa 65.

Splice Region Variant in *OAT* (NM_000274.3:c.-30+8C>T) Uncertain Significance

This is a Splice Region Variant located in the OAT gene.

Ornithine aminotransferase (OAT; {EC 2.6.1.13}) is a mitochondrial matrix enzyme that catalyzes the reversible transamination of ornithine to glutamate semialdehyde (Valle and Simell, 1983).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Gyrate atrophy of choroid and retina with or without ornithinemia.

Splice Region Variant in *TPP1* (NM_000391.3:c.887-6delA) Uncertain Significance

This is a Splice Region Variant located in the TPP1 gene.

TPP1 ({EC 3.4.14.9}) is a lysosomal exopeptidase that sequentially removes tripeptides from the N termini of proteins. It also has a minor endoprotease activity (Golabek et al., 2005).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ceroid lipofuscinosis neuronal 2 and Spinocerebellar ataxia autosomal recessive 7.

3 Prime UTR Variant in *FZD4* (NM_012193.3:c.*3937_*3940delTTTG) Uncertain Significance

This is a 3 Prime UTR Variant located in the FZD4 gene.

Members of the 'frizzled' (FZ) gene family (see 606143) encode 7-transmembrane domain proteins that are receptors for Wnt (see Wnt5A; 164975) signaling proteins.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Exudative vitreoretinopathy 1 and Retinopathy of prematurity.

3 Prime UTR Variant in *FZD4* (NM_012193.3:c.*3925_*3940del) Uncertain Significance

This is a 3 Prime UTR Variant located in the FZD4 gene.

Members of the 'frizzled' (FZ) gene family (see 606143) encode 7-transmembrane domain proteins that are receptors for Wnt (see Wnt5A; 164975) signaling proteins.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Exudative vitreoretinopathy 1 and Retinopathy of prematurity.

3 Prime UTR Variant in *FZD4* (NM_012193.3:c.*3925_*3940del) Uncertain Significance

This is a 3 Prime UTR Variant located in the FZD4 gene.

Members of the 'frizzled' (FZ) gene family (see 606143) encode 7-transmembrane domain proteins that are receptors for Wnt (see Wnt5A; 164975) signaling proteins.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Exudative vitreoretinopathy 1 and Retinopathy of prematurity.

3 Prime UTR Variant in *FREM2* (NM_207361.5:c.*5610_*5611dupGA) Uncertain Significance

This is a 3 Prime UTR Variant located in the FREM2 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Fraser syndrome 2.

5 Prime UTR Variant in *VSX2* (NM_182894.2:c.-43dupG) Uncertain Significance

This is a 5 Prime UTR Variant located in the VSX2 gene.

It has been associated with Microphthalmia with coloboma 3 and Microphthalmia isolated 2.

5 Prime UTR Variant in *NR2E3* (NM_014249.3:c.-139G>A) Uncertain Significance

This is a 5 Prime UTR Variant located in the NR2E3 gene.

PNR, also known as NR2E3, encodes a retinal nuclear receptor that is a ligand-dependent transcription factor. The NR2E3 protein is part of a large family of nuclear receptor transcription factors involved in signaling pathways. Nuclear receptors have been shown to regulate pathways involved in embryonic development, as well as maintenance of proper cell function in adults. Members of this family are characterized by discrete domains that function in DNA and ligand binding.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Enhanced S-cone syndrome and Retinitis pigmentosa 37.

NP_001288.3:p.Ala35= in Exon 2 of *CNGB1* (NM_001297.4:c.105G>A) Uncertain Significance

This is a Synonymous Variant located in the CNGB1 gene.

The CNGB1 and CNGA1 (123825) gene products form the heterotetrameric rod photoreceptor cyclic nucleotide-gated (CNG) channel, which conducts a cation current in response to changes in intracellular levels of cGMP and mediates the electrical response to light (summary by Kondo et al., 2004).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Retinitis pigmentosa 45.

3 Prime UTR Variant in *PITPNM3* (NM_031220.3:c.*3464dupG) Uncertain Significance

This is a 3 Prime UTR Variant located in the PITPNM3 gene.

PITPNM3 belongs to a family of membrane-associated phosphatidylinositol transfer domain-containing proteins that share homology with the Drosophila retinal degeneration B (rdgB) protein (Ocaka et al., 2005).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Cone-rod dystrophy 5.

3 Prime UTR Variant in *PITPNM3* (NM_031220.3:c.*3445_*3446insT) Uncertain Significance

This is a 3 Prime UTR Variant located in the PITPNM3 gene.

PITPNM3 belongs to a family of membrane-associated phosphatidylinositol transfer domain-containing proteins that share homology with the Drosophila retinal degeneration B (rdgB) protein (Ocaka et al., 2005).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Cone-rod dystrophy 5.

3 Prime UTR Variant in *PITPNM3* (NM_031220.3:c.*2334_*2335delGA) Uncertain Significance

This is a 3 Prime UTR Variant located in the PITPNM3 gene.

PITPNM3 belongs to a family of membrane-associated phosphatidylinositol transfer domain-containing proteins that share homology with the Drosophila retinal degeneration B (rdgB) protein (Ocaka et al., 2005).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Cone-rod dystrophy 5.

3 Prime UTR Variant in *OPA3* (NM_025136.3:c.*4716_*4723dupATAAATAA) Uncertain Significance

This is a 3 Prime UTR Variant located in the OPA3 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with 3-methylglutaconic aciduria type III and Optic atrophy 3 with cataract.

3 Prime UTR Variant in *OPA3* (NM_025136.3:c.*4720_*4723dupATAA) Uncertain Significance

This is a 3 Prime UTR Variant located in the OPA3 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with 3-methylglutaconic aciduria type III and Optic atrophy 3 with cataract.

Intron Variant in *SYN3* (NM_003490.3:c.711+4001delA) Uncertain Significance

3 Prime UTR Variant in *TIMP3* (NM_000362.4:c.*1553delT) Uncertain Significance

This is a Intron Variant (NM_003490.3) and 3 Prime UTR Variant (NM_000362.4). It is located in the *SYN3 and TIMP3* genes.

References

Additional Information

Test

Dante Labs_Comprehensive Eye Diseases Panel_2

Indication

Data produced by tertiary bioinformatic analysis on WGS 30X

Background

WGS was performed using Next-Generation-Sequencing Technology.Variants are reported according to the HGVS nomenclature (www.hgvs.org/mutnomen) and ACMG Guidelines (https://www.acmg.net/)

Method

Whole genome sequencing

The qualified genomic DNA sample was randomly fragmented by Covaris technology and the fragment of 350bp was obtained after fragment selection. The end repair of DNA fragments was performed and an "A" base was added at the 3'-end of each strand. Adapters were then ligated to both ends of the end repaired/dA tailed DNA fragments, then amplification by ligation-mediated PCR (LM-PCR), then single strand separation and cyclization. The rolling circle amplification (RCA) was performed to produce DNA Nanoballs (DNBs). The qualified DNBs were loaded into the patterned nanoarrays and pair-end read were read through on the BGISEQ-500 platform and high-throughput sequencing are performed for each library to ensure that each sample meet the average sequencing coverage requirement. Sequencing-derived raw image files were processed by BGISEQ-500 basecalling Software for base-calling with default parameters and the sequence data of each individual is generated as paired-end reads, which is defined as "raw data" and stored in FASTQ format.

Sequencing of this individual's genome was performed and covered an average of 30X. 99.66% on average of the whole genome excluding gap regions were covered by at least 1X coverage, 99.27% had at least 4X coverage and 98.28% had at least 10X coverage.

Bioinformatic analysis

Reads were aligned to the human reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). The GATK Variant Quality Score Recalibration (VQSR) that uses machine learning algorithm was used to filter the raw variant callset. The SNPs and InDels marked PASS in the output VCF file were high-confident variation set. All the variants with pathogenic or unknown significance for causing or contributing to diseases are reported.

Data Quality Control

The strict data quality control (QC) was performed in the whole analysis pipeline for the clean data , the mapping data, the variant calling, etc. Several quality control items for each sample were checked.

Variant classification

The classification of variants is largely based on the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., Genet. Med., 2015, http://www.ncbi.nlm.nih.gov/pubmed/25741868, and Richards et al.,Genet. Med., 2008, http://www.ncbi.nlm.nih.gov/pubmed/18414213). Based on the evidence available, a given variant will be classified according to the weighted classification system as set out by the ACMG (for more information about the specific criteria, see also tables 3 and 4 in http://www.ncbi.nlm.nih.gov/pubmed/25741868). In general, variant evidence can comprise previous reports and functional data about that specific variant if available (e.g. described as pathogenic, reports about the effect of that specific variant on protein expression and function, as verified in functional in vitro or in vivo experiments), reports and functional data about other similar variants within the same gene (e.g. information about the type of known pathogenic and benign variants within a specific gene, known mutational hot spots or certain protein domains, are also taken into account when classifying a variant within the same gene), phenotype data (e.g. the clinical phenotype of the patient is taken into account when classifying a variant, the match between the phenotype in the patient and the gene's disease association is of relevance), population data (e.g. variant and disease population frequencies), segregation data (e.g. whether the variant co-segregates with the disease in a family), and computational data (e.g. in silico predictive algorithms).

Limitations

CNVs are not included into the report.

Disclaimer

The genetic analysis and reporting conducted by the Dante Labs are based on information from one or more published third- party scientific and medical studies. We do not independently judge the validity or accuracy of such published scientific information. Because 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, epidemiologic data aren'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 to ask help to 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 FDA has determined that such clearance or approval is not necessary.