INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	Rebecca Vitsmun	**Sample type:**	Saliva	**Report date:**	22-NOV-2022
DOB:	12-FEB-1983	**Sample collection date:**	08-JUN-2021	**Invitae #:**	RQ2391657-1
Sex assigned at birth:	Female	**Sample accession date:**	25-SEP-2021	**Clinical team:**	Kenneth Corliss
Gender:					
Patient ID (MRN):					

Reason for testing

Diagnostic test for a personal history of disease

Test performed

Sequence analysis and deletion/duplication testing of the 328 genes listed in the Genes Analyzed section.

- Invitae Inherited Retinal Disorders Panel

ADDENDED REPORT

This report supersedes RQ2391657 (14-OCT-2021) and updates the interpretation of the variant(s) in the table below.

- The change in variant classification was made as a result of re-review of the evidence in light of new variant interpretation guidelines and/or new information. Updating variant classification may result in variant(s) being added to, removed from, or moved to a different section of the report.

Updated Interpretations

GENE	VARIANT	ZYGOSITY	PRIOR VARIANT CLASSIFICATION	NEW VARIANT CLASSIFICATION
ADGRV1	c.16537G>T (p.Ala5513Ser)	heterozygous	Uncertain Significance	Likely Benign
TTC21B	c.3415G>A (p.Val1139Ile)	heterozygous	Uncertain Significance	Likely Benign

RESULT: POSITIVE

Two Pathogenic variants identified in SLC24A1. SLC24A1 is associated with autosomal recessive congenital stationary night blindness.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
SLC24A1	c.754_755del (p.Met252Valfs*2)	homozygous	PATHOGENIC
CDH23	c.5901G>C (p.Glu1967Asp)	heterozygous	Uncertain Significance
COL11A1	c.4032G>A (Silent)	heterozygous	Uncertain Significance
PHYH	c.25C>G (p.Arg9Gly)	heterozygous	Uncertain Significance

About this test

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This diagnostic test evaluates 328 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Next steps

- This is a medically important result that should be discussed with a healthcare provider, such as a genetic counselor, to learn more about this result and the appropriate next steps for further evaluation, treatment and/or management. This result should be interpreted within the context of additional laboratory results, family history and clinical findings.
- Consider sharing this result with relatives as they may also be at risk. Details on our Family Variant Testing program can be found at **www.invitae.com/family**.
- Register your test at **www.invitae.com/patients** to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

Clinical summary

Two Pathogenic variants, c.754_755del (p.Met252Valfs*2) (homozygous), were identified in SLC24A1.

- The SLC24A1 gene is associated with autosomal recessive congenital stationary night blindness (CSNB) (MedGen UID:462543). Additionally, the SLC24A1 gene has preliminary evidence supporting a correlation with retinitis pigmentosa (PMID: 12037007).
- This result is consistent with a predisposition to, or diagnosis of, SLC24A1-related conditions.
- CSNB is a clinically and genetically heterogeneous disorder characterized by impaired night vision or delayed adaptation to dark environments (PMID: 25307992, 19578023). Other findings can include photophobia, myopia, poor visual acuity, eye movement disorders, and retinal abnormalities (PMID: 25307992).
- Biological relatives have a chance of being a carrier for or being at risk for autosomal recessive SLC24A1-related conditions. Testing should be considered if clinically appropriate. The chance of having a child with autosomal recessive SLC24A1-related conditions depends on the carrier state of this individual's partner.

A Variant of Uncertain Significance, c.5901G>C (p.Glu1967Asp), was identified in CDH23.

- The CDH23 gene is associated with autosomal recessive Usher syndrome type I (USH1) (MedGen UID: 322051) and autosomal recessive deafness (MedGen UID: 330455).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.4032G>A (Silent), was identified in COL11A1.

- The COL11A1 gene is associated with autosomal dominant Stickler syndrome (MedGen UID: 347615), Marshall syndrome (MRSHS) (MedGen UID: 82694), which is considered to be a phenotypic variant of Stickler syndrome by some experts (PMID: 10486316, 17236192), and non-syndromic deafness (MedGen UID: 1676950). COL11A1 is also associated with autosomal recessive fibrochondrogenesis (MedGen UID: 82700) as well as autosomal recessive forms of Stickler and Marshall syndromes (PMID: 22499343, 23922384).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.25C>G (p.Arg9Gly), was identified in PHYH.

- The PHYH gene is associated with autosomal recessive Refsum disease (MedGen UID: 11161).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

Variant details

SLC24A1, Exon 2, c.754_755del (p.Met252Valfs*2), homozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Met252Valfs*2) in the SLC24A1 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in SLC24A1 are known to be pathogenic (PMID: 20850105, 26822852).
- This variant is present in population databases (rs777989874, gnomAD 0.03%).

- This premature translational stop signal has been observed in individual(s) with macular degeneration (PMID: 12037007).
- ClinVar contains an entry for this variant (Variation ID: 560508).
- For these reasons, this variant has been classified as Pathogenic.

CDH23, Exon 45, c.5901G>C (p.Glu1967Asp), heterozygous, Uncertain Significance

- This sequence change replaces glutamic acid, which is acidic and polar, with aspartic acid, which is acidic and polar, at codon 1967 of the CDH23 protein (p.Glu1967Asp).
- This variant is present in population databases (rs758329598, gnomAD 0.002%).
- This variant has not been reported in the literature in individuals affected with CDH23-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1447479).
- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is not expected to disrupt CDH23 protein function.
- 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.

COL11A1, Exon 53, c.4032G>A (Silent), heterozygous, Uncertain Significance

- This sequence change affects codon 1344 of the COL11A1 mRNA. It is a 'silent' change, meaning that it does not change the encoded amino acid sequence of the COL11A1 protein. This variant also falls at the last nucleotide of exon 53, which is part of the consensus splice site for this exon.
- This variant is present in population databases (rs147637674, gnomAD 0.1%), and has an allele count higher than expected for a pathogenic variant.
- This variant has not been reported in the literature in individuals affected with COL11A1-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 166922).
- Variants that disrupt the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant is not likely to affect RNA splicing.
- 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.

PHYH, Exon 1, c.25C>G (p.Arg9Gly), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with glycine, which is neutral and non-polar, at codon 9 of the PHYH protein (p.Arg9Gly).
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with PHYH-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1495661).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Tolerated"; 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.

Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details. Results are negative unless otherwise indicated in the report. Benign and Likely Benign variants are not included in this report and in specific scenarios variants of uncertain significance in the requisitioned gene(s) may not be included in this report. These variants are available upon request.

GENE	TRANSCRIPT
ABCA4	NM_000350.2
ABCC6*	NM_001171.5
ABHD12	NM_001042472.2
ACBD5	NM_145698.4
ACO2	NM_001098.2
ADAM9	NM_003816.2
ADAMTS18	NM_199355.3
ADAMTSL4	NM_019032.5
ADGRA3	NM_145290.3
ADGRV1	NM_032119.3
ADIPOR1	NM_015999.5
AGBL5	NM_021831.5
AHI1	NM_017651.4
AHR	NM_001621.4
AIPL1	NM_014336.4
ALMS1	NM_015120.4
ARHGEF18	NM_001130955.1
ARL13B	NM_182896.2
ARL2BP	NM_012106.3
ARL3	NM_004311.3
ARL6	NM_177976.2
ARMC9*	NM_001271466.2
ARSG	NM_014960.4
ASRGL1	NM_001083926.1
ATF6	NM_007348.3
ATOH7	NM_145178.3
B9D1	NM_015681.3
BBIP1	NM_001195306.1
BBS1	NM_024649.4
BBS10	NM_024685.3
BBS12	NM_152618.2
BBS2	NM_031885.3
BBS4	NM_033028.4
BBS5	NM_152384.2
BBS7	NM_176824.2
BBS9*	NM_198428.2
BEST1	NM_004183.3
C10orf11	NM_032024.4
C12orf65	NM_152269.4
C1QTNF5	NM_015645.4
C8orf37	NM_177965.3
CA4	NM_000717.4
CABP4	NM_145200.3
CACNA1F	NM_005183.3
CACNA2D4	NM_172364.4
CAPN5	NM_004055.4
CC2D2A	NM_001080522.2
CCT2	NM_006431.2
CDH23	NM_022124.5
CDH3	NM_001793.5
CDHR1	NM_033100.3
CEP164	NM_014956.4
CEP19	NM_032898.4
CEP250	NM_007186.5
CEP290	NM_025114.3
CEP41	NM_018718.2
CEP78	NM_001098802.1
CEP83	NM_016122.2
CERKL	NM_001030311.2
CFAP410	NM_004928.2
CHM	NM_000390.2
CIB2	NM_006383.3
CISD2*	NM_001008388.4
CLCC1	NM_001048210.2
CLN3	NM_001042432.1
CLN5	NM_006493.2
CLN6	NM_017882.2
CLN8	NM_018941.3
CLRN1	NM_174878.2
CLUAP1	NM_015041.2
CNGA1	NM_000087.3
CNGA3	NM_001298.2
CNGB1	NM_001297.4
CNGB3	NM_019098.4
CNNM4	NM_020184.3
COL11A1*	NM_001854.3
COL11A2*	NM_080680.2
COL18A1	NM_130445.3;NM_030582.3
COL2A1	NM_001844.4
COL9A1	NM_001851.4
COL9A2	NM_001852.3
COL9A3*	NM_001853.3
CPLANE1	NM_023073.3
CRB1	NM_201253.2
CRX	NM_000554.4
CSPP1	NM_024790.6
CTNNA1	NM_001903.3
CTSD	NM_001909.4
CWC27	NM_005869.3
CYP4V2	NM_207352.3
DHDDS	NM_024887.3
DHX32	NM_018180.2
DHX38	NM_014003.3
DNAJC17	NM_018163.2
DRAM2	NM_178454.4
DSCAML1	NM_020693.3
DTHD1	NM_001136536.4
EFEMP1	NM_001039348.2
ELOVL4	NM_022726.3
EMC1	NM_015047.2
ERCC6	NM_000124.3
EXOSC2	NM_014285.6

GENE	TRANSCRIPT
EYS	NM_001142800.1
FAM161A	NM_001201543.1
FBLN5	NM_006329.3
FLVCR1	NM_014053.3
FRMD7	NM_194277.2
FSCN2	NM_001077182.2
FZD4	NM_012193.3
GDF6	NM_001001557.2
GNAT1	NM_144499.2
GNAT2	NM_005272.3
GNB3	NM_002075.3
GNPTG	NM_032520.4
GNS	NM_002076.3
GPR143	NM_000273.2
GPR179	NM_001004334.3
GPR45	NM_007227.3
GRM6	NM_000843.3
GRN	NM_002087.3
GUCA1A	NM_000409.4
GUCA1B	NM_002098.5
GUCY2D	NM_000180.3
HARS	NM_002109.5
HGSNAT	NM_152419.2
HK1	NM_000188.2
HMCN1	NM_031935.2
HMX1	NM_018942.2
IDH3A	NM_005530.2
IDH3B	NM_006899.4
IFT140	NM_014714.3
IFT172	NM_015662.2
IFT27	NM_006860.4
IFT43	NM_052873.2
IFT74	NM_001099222.1
IFT80	NM_020800.2
IFT81	NM_014055.3
IFT88	NM_175605.4
IMPDH1	NM_000883.3
IMPG1	NM_001563.3
IMPG2	NM_016247.3
INPP5E	NM_019892.4
INVS	NM_014425.3
IQCB1	NM_001023570.2
ITM2B	NM_021999.4
JAG1	NM_000214.2
KCNJ13	NM_002242.4
KCNV2	NM_133497.3
KIAA0586	NM_001244189.1
KIAA1549	NM_001164665.1
KIF11	NM_004523.3
KIF7	NM_198525.2
KIZ	NM_018474.4
KLHL7	NM_001031710.2
LCA5	NM_181714.3
LRAT	NM_004744.4
LRIT3	NM_198506.4
LRP2	NM_004525.2
LRP5	NM_002335.3
LYST	NM_000081.3
LZTFL1	NM_020347.3
MAK	NM_001242957.2
MAPKAPK3	NM_001243926.1
MERTK	NM_006343.2
MFN2	NM_014874.3
MFRP	NM_031433.3
MFSD8	NM_152778.2
MIR204	NR_029621.1
MKKS	NM_018848.3
MKS1	NM_017777.3
MPDZ	NM_003829.4
MTPAP	NM_018109.3
MTTP	NM_000253.3
MYO7A	NM_000260.3
NAGLU	NM_000263.3
NBAS	NM_015909.3
NDP	NM_000266.3
NEK2	NM_002497.3
NEUROD1	NM_002500.4
NMNAT1	NM_022787.3
NPHP1	NM_000272.3
NPHP3	NM_153240.4
NPHP4	NM_015102.4
NR2E3	NM_014249.3
NR2F1	NM_005654.5
NRL	NM_006177.3
NYX	NM_022567.2
OAT*	NM_000274.3
OCA2	NM_000275.2
OFD1	NM_003611.2
OPA1	NM_015560.2;NM_130837.2
OPA3	NM_025136.3
OPN1SW	NM_001708.2
OR2W3	NM_001001957.2
OTX2	NM_172337.2
P3H2	NM_018192.3
PAX2	NM_003988.3
PAX6	NM_000280.4
PCARE	NM_001029883.2
PCDH15	NM_033056.3
PCYT1A	NM_005017.3
PDE6A	NM_000440.2
PDE6B	NM_000283.3
PDE6C	NM_006204.3
PDE6D	NM_002601.3
PDE6G	NM_002602.3
PDE6H	NM_006205.2
PDZD7	NM_001195263.1
PEX1	NM_000466.2
PEX10	NM_153818.1
PEX11B	NM_003846.2
PEX12	NM_000286.2
PEX13	NM_002618.3
PEX14	NM_004565.2
PEX16	NM_004813.2
PEX19	NM_002857.3
PEX2	NM_000318.2
PEX26	NM_017929.5
PEX3	NM_003630.2

GENE	TRANSCRIPT
PEX5	NM_001131025.1
PEX6	NM_000287.3
PEX7	NM_000288.3
PHYH	NM_006214.3
PITPNM3	NM_031220.3
PLA2G5	NM_000929.2
PLK4	NM_014264.4
PNPLA6	NM_006702.4
POC1B	NM_172240.2
POC5	NM_001099271.1
POMGNT1	NM_017739.3
PPT1	NM_000310.3
PRCD	NM_001077620.2
PRDM13	NM_021620.3
PROM1*	NM_006017.2
PRPF3	NM_004698.2
PRPF31	NM_015629.3
PRPF4	NM_004697.4
PRPF6	NM_012469.3
PRPF8	NM_006445.3
PRPH2	NM_000322.4
PRPS1	NM_002764.3
RAB28	NM_004249.3
RAX2	NM_032753.3
RBP1	NM_002899.3
RBP3	NM_002900.2
RBP4	NM_006744.3
RCBTB1	NM_018191.3
RD3	NM_183059.2
RDH11	NM_016026.3
RDH12	NM_152443.2
RDH5	NM_002905.3
REEP6	NM_001329556.1
RGR	NM_001012720.1
RGS9	NM_003835.3
RGS9BP	NM_207391.2
RHO	NM_000539.3
RIMS1	NM_014989.5
RLBP1	NM_000326.4

GENE	TRANSCRIPT
ROM1	NM_000327.3
RP1	NM_006269.1
RP1L1*	NM_178857.5
RP2	NM_006915.2
RP9*	NM_203288.1
RPE65	NM_000329.2
RPGRIP1	NM_020366.3
RPGRIP1L	NM_015272.2
RS1	NM_000330.3
RTN4IP1	NM_032730.4
SAG	NM_000541.4
SAMD11	NM_152486.2
SCLT1	NM_144643.3
SDCCAG8	NM_006642.3
SEMA4A	NM_022367.3
SGSH	NM_000199.3
SIX6	NM_007374.2
SLC24A1	NM_004727.2
SLC24A5	NM_205850.2
SLC45A2	NM_016180.4
SLC7A14	NM_020949.2
SNRNP200	NM_014014.4
SPATA7	NM_018418.4
SPP2	NM_006944.2
TCTN1	NM_001082538.2
TCTN2	NM_024809.4
TCTN3	NM_015631.5
TEAD1	NM_021961.5
TIMM8A	NM_004085.3
TIMP3	NM_000362.4
TMED7	NM_181836.5
TMEM107	NM_032354.3
TMEM126A	NM_032273.3
TMEM138	NM_016464.4
TMEM216	NM_001173990.2
TMEM231	NM_001077416.2
TMEM237	NM_001044385.2
TMEM67	NM_153704.5
TOPORS	NM_005802.4

GENE	TRANSCRIPT
TPP1	NM_000391.3
TRAF3IP1	NM_015650.3
TREX1	NM_033629.4
TRIM32	NM_012210.3
TRNT1	NM_182916.2
TRPM1	NM_002420.5
TSPAN12	NM_012338.3
TTC21B	NM_024753.4
TTC8	NM_198309.3
TTLL5	NM_015072.4
TTPA	NM_000370.3
TUB	NM_003320.4
TUBGCP4*	NM_001286414.2
TUBGCP6	NM_020461.3
TULP1	NM_003322.4
TYR*	NM_000372.4
TYRP1	NM_000550.2
UNC119	NM_005148.3
USH1C*	NM_005709.3
USH1G	NM_173477.4
USH2A*	NM_206933.2
VCAN	NM_004385.4
VPS13B	NM_017890.4
WDPCP	NM_015910.5
WDR19	NM_025132.3
WDR34	NM_052844.3
WFS1	NM_006005.3
WHRN	NM_015404.3
ZNF408	NM_024741.2
ZNF423	NM_015069.3
ZNF513	NM_144631.5

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 10bp of flanking intronic sequence (20bp for BRCA1/2), and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed (indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Confirmation of the presence and location of reportable variants is performed based on stringent criteria established by Invitae (1400 16th Street, San Francisco, CA 94103, #05D2040778), as needed, using one of several validated orthogonal approaches (PubMed ID 30610921). The following analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). For C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation Reference Ranges: Benign (Normal Range): <25 repeat units, Uncertain: 25-30 repeat units, Pathogenic (Full Mutation): >=31 repeat units. A second round of RP-PCR utilizing a non-overlapping set of primers is used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For RNA analysis of the genes indicated in the Genes Analyzed table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific gene sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is assessed quantitatively and compared to the usage seen in control specimens. Abnormal exon junction usage is evaluated as evidence in the Sherloc variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing. RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2094793). Technical component of Fibroblast cell-culturing and gDNA extraction from skin punch biopsy is performed by Invitae Corporation (5 Technology Drive, Irvine CA 92618, #05D1052995).
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at **http://www.ncbi.nlm.nih.gov/pubmed**.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (**http://exac.broadinstitute.org**), gnomAD (**http://gnomad.broadinstitute.org**), and dbSNP (**http://ncbi.nlm.nih.gov/SNP**).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at **http://www.ncbi.nlm.nih.gov/medgen**. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance of Man (OMIM). Search by OMIM number at **http://omim.org/**.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full

exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination. Invitae's RNA analysis is not designed for use as a stand-alone diagnostic method and cannot determine absolute RNA levels.

OAT: Deletion/duplication analysis is not offered for exon 2. COL11A2: Deletion/duplication analysis is not offered for exon 36. ARMC9: Deletion/duplication analysis is not offered for exons 1-2, 5-6. PROM1: Deletion/duplication analysis is not offered for exons 20-21. TUBGCP4: Sequencing analysis for exons 9 includes only cds +/- 10 bp. USH1C: Deletion/duplication analysis is not offered for exons 5-6. RP1L1: Sequencing analysis is not offered for exon 4. BBS9: Deletion/duplication analysis is not offered for exon 4. RP9: Deletion/duplication and sequencing analysis is not offered for exon 6. COL11A1: Deletion/duplication analysis is not offered for exons 16-17 and sequencing analysis is not offered for exon 57. COL9A3: Deletion/duplication analysis is not offered for exon 12. ABCC6: Deletion/duplication and sequencing analysis is not offered for exons 1-9. USH2A: Deletion/duplication analysis is not offered for exon 59. CISD2: Deletion/duplication and sequencing analysis is not offered for exon 3. TYR: Deletion/duplication and sequencing analysis is not offered for exon 5.

For Addended, Amended and Corrected reports, orthogonal confirmation may not have been performed on variants that would have otherwise met criteria for confirmation at the time of the original analysis.

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been reviewed and approved by:

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Clinical Molecular Geneticist

INVITAE

POSITIVE RESULTS GUIDE

What positive results mean for you

Your genetic test results were positive. This means that you have a significant genetic change(s) in one or more of the genes tested. On your test report, this is called likely pathogenic variant or pathogenic variant ("mutation").

Create a plan with your healthcare provider

Whether or not you develop a disease is not determined by your genetics alone. However, your results are important. There may be tests and treatments available to help you prevent or manage a condition caused by a genetic variant. It is important to share these results with your healthcare provider so you can make informed medical decisions together.

What positive results mean for your family

Relatives can share genetic features. Your first-degree relatives (parents, children, and siblings), and even more distant relatives, may also have the same variant(s). We encourage you to share your test results with your relatives so they may discuss their potential health risks with their own healthcare providers. The medical community recommends genetic counseling and testing for family members who may be affected.

We (and others) are here to help

Genetic counseling is recommended to help you clearly and accurately understand your results so it's important to talk to your genetic counselor or other healthcare provider about your test results.

Log in to your patient portal (invitae.com) to view your results, search for a local or Invitae genetic counselor, or join Invitae's Patient Insight Network (PIN), a community where you can connect with other patients and share your experience.

This information in this results guide is meant to be used along with your genetic test results and other health information. It is not meant to replace a discussion with your healthcare provider and should not be considered or interpreted as medical advice.

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