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INVITAE CARRIER SCREEN RESULTS

Patient name:	Robert Dilella	**Sample type:**	Blood	**Report date:**	06-NOV-2023
DOB:	07-DEC-1964	**Sample collection date:**	01-MAR-2023	**Invitae #:**	RQ4755765-1
Sex assigned at birth:	Male	**Sample accession date:**	02-MAR-2023	**Clinical team:**	Yezenia Robles Connie Alford
Gender:	Man				
Patient ID (MRN):	44550				

Reason for testing

Patient/partner is planning for pregnancy

Test performed

Invitae Comprehensive Carrier Screen

- Primary Panel (CF, SMA)
- Add-on Comprehensive Carrier Screen genes

ADDENDED REPORT

This report supersedes RQ4755765 (09-MAR-2023) 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
SLC45A2	c.1504G>A (p.Gly502Arg)	heterozygous	Uncertain Significance	Likely Pathogenic

RESULT: POSITIVE

This carrier test evaluated 556 gene(s) for genetic changes (variants) that are associated with an increased risk of having a child with a genetic condition. Knowledge of carrier status for one of these conditions may provide information that can be used to assist with family planning and/or preparation. Carrier screening is not intended for diagnostic purposes. To identify a potential genetic basis for a condition in the individual being tested, diagnostic testing for the gene(s) of interest is recommended.

This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below. No other clinically significant changes were identified in the remaining genes evaluated with this test.

RESULTS	GENE	VARIANT(S)	INHERITANCE	PARTNER TESTING RECOMMENDED
Carrier: Oculocutaneous albinism type 4	SLC45A2	c.1504G>A (p.Gly502Arg)	Autosomal recessive	Yes

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Next steps

- See the table above for recommendations regarding testing of this individual's reproductive partner.
- Even for genes that have a negative test result, there is always a small risk that an individual could still be a carrier. This is called "residual risk." See the Carrier detection rates and residual risks document.
- Discussion with a physician and/or genetic counselor is recommended to further review the implications of this test result and to understand these results in the context of any family history of a genetic condition.
- All patients, regardless of result, may wish to consider additional screening for hemoglobinopathies by complete blood count (CBC) and hemoglobin electrophoresis, if this has not already been completed.
- Individuals can register their tests at **https://www.invitae.com/patients/** to access online results, educational resources, and next steps.

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Clinical summary

RESULT: CARRIER

Oculocutaneous albinism type 4

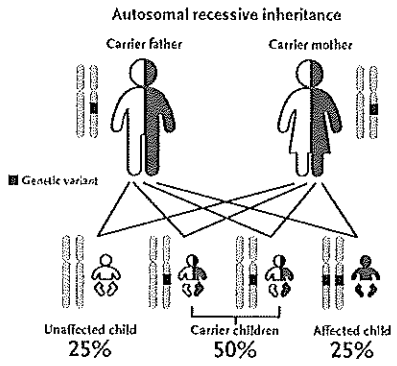
A single Likely Pathogenic variant, c.1504G>A (p.Gly502Arg), was identified in SLC45A2.

What is oculocutaneous albinism type 4?

Oculocutaneous albinism (OCA) is a condition that causes decreased color (hypopigmentation) of the hair, skin, and eyes. Affected individuals produce a reduced amount of melanin, the pigment that gives skin, hair, and eyes their color, resulting in hypopigmentation. Additional symptoms of OCA include reduced visual acuity (farsightedness or nearsightedness), increased sensitivity to light (photophobia), involuntary eye movements (nystagmus), and eyes that do not look in the same direction (strabismus). Other eye findings, such as reduced pigmentation of the light-sensitive tissue that lines the back of the eye (retina) and misrouting of the nerves of the eye (optic nerves), are seen on ophthalmologic exam. Individuals with fair complexions have an increased risk for skin cancers. Intelligence is not typically affected. Individuals with oculocutaneous albinism type 4 (OCA4) are often diagnosed during the first year of life, based on hypopigmentation, nystagmus, and strabismus. The range of skin pigmentation ranges from minimal to near normal. Vision typically stabilizes after childhood. Treatment is aimed at correcting vision and providing visual aids, or other visual resources. Sun protection is essential due to the increased risk for skin cancer.

Next steps

Carrier testing for the reproductive partner is recommended.



⊕ If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the SLC45A2 gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.

⊖ If your partner tests negative:

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for oculocutaneous albinism type 4. These values are provided only as a guide, are based on the detection rate for the condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the numbers provided apply to the recessive condition(s) associated with the gene.

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Oculocutaneous albinism type 4 (AR) NM_016180.4	SLC45A2	Pan-ethnic	1 in 158	1 in 15700

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Results to note

FMR1

- Normal triplet repeats observed: 29. CGG repeat ranges: normal (<45 CGG repeats), intermediate (45-54 CGG repeats), premutation (55-200 CGG repeats), full mutation (>200 CGG repeats).

SMN1

- Negative result. SMN1: 2 copies; c.*3+80T>G not detected.

Pseudodeficiency allele(s)

- Benign change, c.742G>A (p.Asp248Asn), known to be a pseudodeficiency allele, identified in the GALC gene. Pseudodeficiency alleles are not known to be associated with disease, including Krabbe disease.
- The presence of a pseudodeficiency allele does not impact this individual's risk to be a carrier. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, including newborn screening. However, pseudodeficiency alleles are not known to cause disease, even when there are two copies of the variant (homozygous) or when in combination with another disease-causing variant (compound heterozygous). Carrier testing for the reproductive partner is not indicated based on this result.

Variant details

SLC45A2, Exon 7, c.1504G>A (p.Gly502Arg), heterozygous, Likely Pathogenic

- This sequence change replaces glycine, which is neutral and non-polar, with arginine, which is basic and polar, at codon 502 of the SLC45A2 protein (p.Gly502Arg).
- This variant is present in population databases (rs147355272, gnomAD 0.003%).
- This missense change has been observed in individual(s) with ocular albinism (PMID: 27734839).
- ClinVar contains an entry for this variant (Variation ID: 2203616).
- 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 expected to disrupt SLC45A2 protein function with a positive predictive value of 80%.
- In summary, the currently available evidence indicates that the variant is pathogenic, but additional data are needed to prove that conclusively. Therefore, this variant has been classified as Likely Pathogenic.

Residual risk

No carrier test can detect 100% of carriers. There still remains a small risk of being a carrier after a negative test (residual risk). Residual risk values assume a negative family history and are inferred from published carrier frequencies and estimated detection rates based on testing technologies used at Invitae. You can view Invitae's complete Carrier detection rates and residual risks document (containing all carrier genes) online at https://www.invitae.com/carrier-residual-risks/. Additionally, the order-specific information for this report is available to download in the portal (under this order's documents) or can be requested by contacting Invitae Client Services. The complete Carrier detection rates and residual risks document will not be applicable for any genes with specimen-specific limitations in sequencing and/or deletion/duplication coverage. Please see the final bullet point in the Limitations section of this report to view if this specimen had any gene-specific coverage gaps.

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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.

GENE	TRANSCRIPT
AAAS	NM_015665.5
ABCA12	NM_173076.2
ABCA3	NM_001089.2
ABCA4	NM_000350.2
ABCB11	NM_003742.2
ABCB4	NM_000443.3
ABCC2*	NM_000392.4
ABCC8	NM_000352.4
ABCD1	NM_000033.3
ACAD9	NM_014049.4
ACADM	NM_000016.5
ACADVL	NM_000018.3
ACAT1	NM_000019.3
ACOX1	NM_004035.6
ACSF3	NM_174917.4
ADA	NM_000022.2
ADAMTS2	NM_014244.4
ADAMTSL4	NM_019032.5
ADGRG1	NM_005682.6
ADGRV1	NM_032119.3
AGA	NM_000027.3
AGL	NM_000642.2
AGPS	NM_003659.3
AGXT	NM_000030.2
AHI1	NM_017651.4
AIPL1*	NM_014336.4
AIRE	NM_000383.3
ALDH3A2	NM_000382.2
ALDH7A1	NM_001182.4
ALDOB	NM_000035.3
ALG1	NM_019109.4
ALG13	NM_001099922.2
ALG6	NM_013339.3
ALMS1	NM_015120.4
ALPL	NM_000478.5
AMN*	NM_030943.3
AMT	NM_000481.3
ANO10*	NM_018075.3
AP1S1	NM_001283.3
AQP2	NM_000486.5
AR*	NM_000044.3
ARG1	NM_000045.3
ARL6	NM_177976.2
ARSA	NM_000487.5
ARSB	NM_000046.3
ARSE	NM_000047.2
ARX*	NM_139058.2
ASL	NM_000048.3
ASNS	NM_133436.3
ASPA	NM_000049.2
ASS1	NM_000050.4
ATM*	NM_000051.3
ATP6V1B1	NM_001692.3
ATP7A	NM_000052.6
ATP7B	NM_000053.3
ATP8B1*	NM_005603.4
ATRX	NM_000489.4
AVPR2	NM_000054.4
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
BCKDHA	NM_000709.3
BCKDHB	NM_183050.2
BCS1L	NM_004328.4
BLM	NM_000057.3
BLOC1S3	NM_212550.4
BLOC1S6	NM_012388.3
BMP1	NM_006129.4;NM_001199.3
BRIP1	NM_032043.2
BSND	NM_057176.2
BTK	NM_000061.2
CAD	NM_004341.4
CANT1	NM_138793.3
CAPN3	NM_000070.2
CASQ2	NM_001232.3
CBS	NM_000071.2
CC2D1A	NM_017721.5
CC2D2A	NM_001080522.2
CCDC103	NM_213607.2
CCDC39	NM_181426.1
CCDC88C	NM_001080414.3
CD3D	NM_000732.4
CD3E	NM_000733.3
CD40	NM_001250.5
CD40LG	NM_000074.2
CD59	NM_203330.2
CDH23	NM_022124.5
CEP152	NM_014985.3
CEP290	NM_025114.3
CERKL	NM_001030311.2
CFTR*	NM_000492.3
CHAT	NM_020549.4
CHM	NM_000390.2
CHRNE	NM_000080.3
CHRNG	NM_005199.4
CIITA	NM_000246.3
CLCN1	NM_000083.2
CLN3	NM_001042432.1
CLN5	NM_006493.2
CLN6	NM_017882.2
CLN8	NM_018941.3
CLRN1	NM_174878.2
CNGB3	NM_019098.4

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GENE	TRANSCRIPT
COL11A2*	NM_080680.2
COL17A1	NM_000494.3
COL27A1	NM_032888.3
COL4A3	NM_000091.4
COL4A4	NM_000092.4
COL4A5	NM_000495.4
COL7A1	NM_000094.3
COX15	NM_004376.6
CPS1	NM_001875.4
CPT1A	NM_001876.3
CPT2	NM_000098.2
CRB1	NM_201253.2
CRTAP	NM_006371.4
CTNS	NM_004937.2
CTSA	NM_000308.3
CTSC	NM_001814.5
CTSD	NM_001909.4
CTSK	NM_000396.3
CYBA	NM_000101.3
CYBB	NM_000397.3
CYP11A1	NM_000781.2
CYP11B1	NM_000497.3
CYP11B2	NM_000498.3
CYP17A1	NM_000102.3
CYP19A1	NM_031226.2
CYP1B1	NM_000104.3
CYP21A2*	NM_000500.7
CYP27A1	NM_000784.3
CYP27B1	NM_000785.3
CYP7B1	NM_004820.3
DBT	NM_001918.3
DCAF17	NM_025000.3
DCLRE1C	NM_001033855.2
DDX11*	NM_030653.3
DFNB59	NM_001042702.3
DGAT1	NM_012079.5
DGUOK	NM_080916.2
DHCR7	NM_001360.2
DHDDS	NM_024887.3

GENE	TRANSCRIPT
DKC1	NM_001363.4
DLD	NM_000108.4
DLL3	NM_016941.3
DMD	NM_004006.2
DNAH11	NM_001277115.1
DNAH5	NM_001369.2
DNAI1	NM_012144.3
DNAI2	NM_023036.4
DNMT3B	NM_006892.3
DOK7	NM_173660.4
DUOX2*	NM_014080.4
DYNC2H1	NM_001080463.1
DYSF	NM_003494.3
EDA	NM_001399.4
EIF2AK3	NM_004836.6
EIF2B1	NM_001414.3
EIF2B2	NM_014239.3
EIF2B3	NM_020365.4
EIF2B4	NM_015636.3
EIF2B5	NM_003907.2
ELP1	NM_003640.3
EMD	NM_000117.2
EPG5	NM_020964.2
ERCC2	NM_000400.3
ERCC6	NM_000124.3
ERCC8	NM_000082.3
ESCO2	NM_001017420.2
ETFA	NM_000126.3
ETFB	NM_001985.2
ETFDH	NM_004453.3
ETHE1	NM_014297.3
EVC	NM_153717.2
EVC2	NM_147127.4
EXOSC3	NM_016042.3
EYS*	NM_001142800.1
F9	NM_000133.3
FAH*	NM_000137.2
FAM161A	NM_001201543.1
FANCA	NM_000135.2

GENE	TRANSCRIPT
FANCB	NM_001018113.1
FANCC	NM_000136.2
FANCD2*	NM_033084.3
FANCE	NM_021922.2
FANCG	NM_004629.1
FANCI	NM_001113378.1
FANCL*	NM_018062.3
FBP1	NM_000507.3
FBXO7	NM_012179.3
FH*	NM_000143.3
FHL1	NM_001449.4
FKBP10	NM_021939.3
FKRP	NM_024301.4
FKTN	NM_001079802.1
FMO3	NM_006894.6
FMR1*	NM_002024.5
FOXN1	NM_003593.2
FOXRED1	NM_017547.3
FRAS1	NM_025074.6
FREM2	NM_207361.5
FUCA1	NM_000147.4
G6PC	NM_000151.3
G6PC3	NM_138387.3
GAA	NM_000152.3
GALC*	NM_000153.3
GALE*	NM_000403.3
GALK1	NM_000154.1
GALNS	NM_000512.4
GALNT3	NM_004482.3
GALT	NM_000155.3
GAMT	NM_000156.5
GATM	NM_001482.2
GBA*	NM_001005741.2
GBE1	NM_000158.3
GCDH	NM_000159.3
GCH1	NM_000161.2
GDF5	NM_000557.4
GFM1	NM_024996.5
GHR*	NM_000163.4

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GENE	TRANSCRIPT
GJB1	NM_000166.5
GJB2	NM_004004.5
GLA	NM_000169.2
GLB1	NM_000404.2
GLDC	NM_000170.2
GLE1	NM_001003722.1
GNE*	NM_001128227.2
GNPAT	NM_014236.3
GNPTAB	NM_024312.4
GNPTG	NM_032520.4
GNS	NM_002076.3
GORAB	NM_152281.2
GRHPR	NM_012203.1
GRIP1	NM_021150.3
GSS	NM_000178.2
GUCY2D	NM_000180.3
GUSB	NM_000181.3
HADH	NM_005327.4
HADHA	NM_000182.4
HADHB	NM_000183.2
HAMP	NM_021175.2
HAX1	NM_006118.3
HBA1*	NM_000558.4
HBA2	NM_000517.4
HBB	NM_000518.4
HCFC1	NM_005334.2
HEXA	NM_000520.4
HEXB	NM_000521.3
HGSNAT	NM_152419.2
HJV	NM_213653.3
HLCS	NM_000411.6
HMGCL	NM_000191.2
HMOX1	NM_002133.2
HOGA1	NM_138413.3
HPD	NM_002150.2
HPRT1	NM_000194.2
HPS1	NM_000195.4
HPS3	NM_032383.4
HPS4	NM_022081.5

GENE	TRANSCRIPT
HPS5	NM_181507.1
HPS6	NM_024747.5
HSD17B10	NM_004493.2
HSD17B3	NM_000197.1
HSD17B4	NM_000414.3
HSD3B2	NM_000198.3
HYAL1	NM_153281.1
HYLS1	NM_145014.2
IDS*	NM_000202.6
IDUA	NM_000203.4
IGHMBP2	NM_002180.2
IKBKB	NM_001556.2
IL2RG	NM_000206.2
IL7R	NM_002185.3
INVS	NM_014425.3
ITGA6	NM_000210.3
ITGB3	NM_000212.2
ITGB4	NM_001005731.2
IVD	NM_002225.3
JAK3	NM_000215.3
KCNJ1	NM_000220.4
KCNJ11	NM_000525.3
L1CAM	NM_000425.4
LAMA2	NM_000426.3
LAMA3	NM_000227.4
LAMB3	NM_000228.2
LAMC2	NM_005562.2
LARGE1	NM_004737.4
LCA5	NM_181714.3
LDLR	NM_000527.4
LDLRAP1	NM_015627.2
LHX3	NM_014564.4
LIFR*	NM_002310.5
LIG4	NM_002312.3
LIPA	NM_000235.3
LMBRD1	NM_018368.3
LOXHD1	NM_144612.6
LPL	NM_000237.2
LRAT	NM_004744.4

GENE	TRANSCRIPT
LRP2	NM_004525.2
LRPPRC	NM_133259.3
LYST	NM_000081.3
MAK	NM_001242957.2
MAN2B1	NM_000528.3
MANBA	NM_005908.3
MCEE	NM_032601.3
MCOLN1	NM_020533.2
MCPH1	NM_024596.4
MECP2	NM_004992.3;NM_001110792.1
MECR	NM_016011.3
MED17	NM_004268.4
MESP2	NM_001039958.1
MFSD8	NM_152778.2
MID1*	NM_000381.3
MKKS	NM_018848.3
MKS1	NM_017777.3
MLC1*	NM_015166.3
MLYCD	NM_012213.2
MMAA	NM_172250.2
MMAB	NM_052845.3
MMACHC	NM_015506.2
MMADHC	NM_015702.2
MOCS1	NM_001358530.2
MOCS2A	NM_176806.3
MOCS2B	NM_004531.4
MPI	NM_002435.2
MPL	NM_005373.2
MPV17	NM_002437.4
MRE11	NM_005591.3
MTHFR*	NM_005957.4
MTM1	NM_000252.2
MTR	NM_000254.2
MTRR	NM_002454.2
MTTP	NM_000253.3
MUSK	NM_005592.3
MUT	NM_000255.3
MVK	NM_000431.3
MYO15A	NM_016239.3

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GENE	TRANSCRIPT
MYO7A	NM_000260.3
NAGA	NM_000262.2
NAGLU	NM_000263.3
NAGS	NM_153006.2
NBN	NM_002485.4
NCF2	NM_000433.3
NDRG1	NM_006096.3
NDUFAF2	NM_174889.4
NDUFAF5	NM_024120.4
NDUFS4	NM_002495.3
NDUFS6	NM_004553.4
NDUFS7	NM_024407.4
NDUFV1	NM_007103.3
NEB*	NM_001271208.1
NEU1	NM_000434.3
NGLY1	NM_018297.3
NPC1	NM_000271.4
NPC2	NM_006432.3
NPHP1	NM_000272.3
NPHS1	NM_004646.3
NPHS2	NM_014625.3
NR0B1	NM_000475.4
NR2E3	NM_014249.3
NSMCE3	NM_138704.3
NTRK1	NM_001012331.1
OAT*	NM_000274.3
OCA2	NM_000275.2
OCRL	NM_000276.3
OPA3	NM_025136.3
OSTM1	NM_014028.3
OTC	NM_000531.5
OTOA*	NM_144672.3
OTOF	NM_194248.2;NM_194323.2
P3H1	NM_022356.3
PAH	NM_000277.1
PANK2	NM_153638.2
PC	NM_000920.3
PCBD1	NM_000281.3
PCCA	NM_000282.3
PCCB	NM_000532.4
PCDH15	NM_033056.3
PCNT	NM_006031.5
PDHA1	NM_000284.3
PDHB	NM_000925.3
PEPD	NM_000285.3
PET100	NM_001171155.1
PEX1*	NM_000466.2
PEX10	NM_153818.1
PEX12	NM_000286.2
PEX13	NM_002618.3
PEX16	NM_004813.2
PEX2	NM_000318.2
PEX26	NM_017929.5
PEX5	NM_001131025.1
PEX6	NM_000287.3
PEX7	NM_000288.3
PFKM	NM_000289.5
PGM3	NM_001199917.1
PHGDH	NM_006623.3
PHKB	NM_000293.2;NM_001031835.2
PHKG2	NM_000294.2
PHYH	NM_006214.3
PIGN	NM_176787.4
PKHD1*	NM_138694.3
PLA2G6	NM_003560.2
PLEKHG5	NM_020631.4
PLOD1	NM_000302.3
PLP1	NM_000533.4
PMM2	NM_000303.2
PNPO	NM_018129.3
POLG	NM_002693.2
POLH	NM_006502.2
POMGNT1	NM_017739.3
POMT1	NM_007171.3
POMT2	NM_013382.5
POR	NM_000941.2
POU1F1	NM_000306.3
PPT1	NM_000310.3
PRCD	NM_001077620.2
PRDM5	NM_018699.3
PRF1	NM_001083116.1
PROP1	NM_006261.4
PRPS1	NM_002764.3
PSAP	NM_002778.3
PTPRC*	NM_002838.4
PTS	NM_000317.2
PUS1	NM_025215.5
PYGM	NM_005609.3
QDPR	NM_000320.2
RAB23	NM_183227.2
RAG1	NM_000448.2
RAG2	NM_000536.3
RAPSN	NM_005055.4
RARS2	NM_020320.3
RDH12	NM_152443.2
RLBP1	NM_000326.4
RMRP	NR_003051.3
RNASEH2A	NM_006397.2
RNASEH2B	NM_024570.3
RNASEH2C	NM_032193.3
RP2	NM_006915.2
RPE65	NM_000329.2
RPGRIP1L	NM_015272.2
RS1	NM_000330.3
RTEL1	NM_001283009.1
RXYLT1	NM_014254.2
RYR1	NM_000540.2
SACS	NM_014363.5
SAMD9	NM_017654.3
SAMHD1	NM_015474.3
SCO2	NM_005138.2
SEC23B	NM_006363.4
SEPSECS	NM_016955.3
SGCA	NM_000023.2
SGCB	NM_000232.4
SGCD	NM_000337.5
SGCG	NM_000231.2

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GENE	TRANSCRIPT
SGSH	NM_000199.3
SKIV2L	NM_006929.4
SLC12A1	NM_000338.2
SLC12A3	NM_000339.2
SLC12A6	NM_133647.1
SLC17A5	NM_012434.4
SLC19A2	NM_006996.2
SLC19A3	NM_025243.3
SLC1A4	NM_003038.4
SLC22A5	NM_003060.3
SLC25A13	NM_014251.2
SLC25A15	NM_014252.3
SLC25A20	NM_000387.5
SLC26A2	NM_000112.3
SLC26A3	NM_000111.2
SLC26A4	NM_000441.1
SLC27A4	NM_005094.3
SLC35A3	NM_012243.2
SLC37A4	NM_001164277.1
SLC38A8	NM_001080442.2
SLC39A4	NM_130849.3
SLC45A2	NM_016180.4
SLC4A11	NM_032034.3
SLC5A5	NM_000453.2
SLC6A8	NM_005629.3
SLC7A7	NM_001126106.2
SMARCAL1	NM_014140.3
SMN1*	NM_000344.3
SMPD1	NM_000543.4
SNAP29	NM_004782.3
SPG11	NM_025137.3
SPR	NM_003124.4
SRD5A2	NM_000348.3
ST3GAL5	NM_003896.3
STAR	NM_000349.2
STX11	NM_003764.3
STXBP2	NM_006949.3
SUMF1	NM_182760.3
SUOX	NM_000456.2

GENE	TRANSCRIPT
SURF1	NM_003172.3
SYNE4	NM_001039876.2
TANGO2	NM_152906.6
TAT	NM_000353.2
TAZ	NM_000116.4
TBCD	NM_005993.4
TBCE*	NM_003193.4
TCIRG1	NM_006019.3
TCN2	NM_000355.3
TECPR2	NM_014844.3
TERT	NM_198253.2
TF	NM_001063.3
TFR2	NM_003227.3
TG*	NM_003235.4
TGM1	NM_000359.2
TH	NM_199292.2
TK2	NM_004614.4
TMC1	NM_138691.2
TMEM216	NM_001173990.2
TMEM67	NM_153704.5
TMPRSS3	NM_024022.2
TPO	NM_000547.5
TPP1	NM_000391.3
TREX1	NM_033629.4
TRIM32	NM_012210.3
TRIM37	NM_015294.4
TRMU	NM_018006.4
TSEN54	NM_207346.2
TSFM*	NM_001172696.1
TSHB	NM_000549.4
TSHR	NM_000369.2
TTC37	NM_014639.3
TTPA	NM_000370.3
TULP1	NM_003322.4
TYMP	NM_001953.4
TYR*	NM_000372.4
TYRP1	NM_000550.2
UBR1	NM_174916.2
UNC13D	NM_199242.2

GENE	TRANSCRIPT
USH1C*	NM_005709.3
USH2A	NM_206933.2
VDR	NM_001017535.1
VLDLR	NM_003383.4
VPS11	NM_021729.5
VPS13A*	NM_033305.2
VPS13B	NM_017890.4
VPS45	NM_007259.4
VPS53*	NM_001128159.2
VRK1	NM_003384.2
VSX2	NM_182894.2
WAS	NM_000377.2
WISP3	NM_003880.3
WNT10A	NM_025216.2
WRN*	NM_000553.4
XPA	NM_000380.3
XPC	NM_004628.4
ZBTB24	NM_014797.2
ZFYVE26	NM_015346.3
ZNF469	NM_001127464.2

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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 in the Genes Analyzed table. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, 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. 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. Invitae utilizes a classification methodology to identify next-generation sequencing (NGS)-detected variants that require orthogonal confirmation (Lincoln, et al. J Mol Diagn. 2019 Mar;21(2):318-329). Confirmation of the presence and location of reportable variants is performed as needed based on stringent criteria using one of several validated orthogonal approaches (PubMed ID 30610921). Sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).

  The following additional analyses are performed if relevant to the requisition. For GBA the reference genome has been modified to mask the sites of polymorphic paralog sequence variants (PSVs) in both the gene and pseudogene. For CYP21A2 and GBA, if one or more reportable variants, gene conversion, or fusion event is identified via our NGS pipeline (see Limitations), these variants are confirmed by PacBio sequencing of an amplicon generated by long-range PCR and subsequent short-range PCR. In some cases, it may not be possible to disambiguate between the gene and pseudogene. For GJB2, the reportable range includes large upstream deletions overlapping GJB6. For HBA1/2, the reference genome has been modified to force some sequencing reads derived from HBA1 to align to HBA2, and variant calling algorithms are modified to support an expectation of 4 alleles in these regions. HBA1/2 copy number calling is performed by a custom hypothesis testing algorithm which generates diplotype calls. If sequence data for a sample does not support a unique high confidence match from among hypotheses tested, that sample is flagged for manual review. Copy number variation is only reported for coding sequence of HBA1 and HBA2 and the HS-40 region. This assay does not distinguish among the -α3.7 subtypes, and all -α3.7 variants are called as HBA1 deletions. This assay may not detect overlapping copy gain and copy loss events when the breakpoints of those events are similar. For FMR1, cytosine-guanine-guanine (CGG) triplet repeats in the 5' untranslated region (5' UTR) of the FMR1 gene are detected by triplet repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Reference ranges: Normal: <45 CGG repeats, intermediate: 45-54 CGG repeats, premutation: 55-200 CGG repeats, full mutation: >200 CGG repeats. For alleles with 55-90 triplet repeats, the region surrounding the FMR1 repeat is amplified by PCR. The PCR amplicons are then processed through PacBio SMRTBell library prep and sequenced using PacBio long read technology. The number of AGG interruptions within the 55-90 triplet repeat is read directly from the resulting DNA sequences.

- This report only includes variants that have a clinically significant association with the conditions tested as of the report date. Variants of uncertain significance, benign variants, and likely benign variants are not included in this report. However, if additional evidence becomes available to indicate that the clinical significance of a variant has changed, Invitae may update this report and provide notification.
- 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**).

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

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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.

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.
- FMR1 testing is limited to repeat expansion analysis only, and does not include coding region sequence, CNV analysis or FMR1 methylation. Sizing accuracy is expected to be +/-1 for CGG repeat alleles less than or equal to 90 repeat units and +/-3 for CGG repeat alleles greater than 90 repeat units. If the two CGG repeat counts listed are the same, it most likely indicates homozygosity; however, in very rare scenarios it could be the result of biological or technical reasons including, but not limited to, sex chromosome anomalies, allelic dropout, or sample submission errors. This test is not intended to diagnose sex chromosome aneuploidy, although evidence of such incidental findings may be present in the analysis and reported. The number of AGG interruptions is only determined for females ≥12 years of age with triplet repeat sizes of 55-90. Due to somatic mosaicism and/or repeat instability of expanded alleles, repeat size identified in DNA isolated from peripheral blood, buccal cells, or saliva may not reflect the repeat size in untested tissues (e.g. brain, gonads). In addition, a negative result does not definitively rule out the presence of an expansion in the mosaic state, as the current test is not validated to detect low-level mosaic variants. 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. AIPL1: Sequencing analysis for exons 2 includes only cds +/- 10 bp. FANCL: Sequencing analysis for exons 4, 10 includes only cds +/- 10 bp. FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp. GALC: Deletion/duplication analysis is not offered for exon 6. GNE: Sequencing analysis for exons 8 includes only cds +/- 10 bp. VPS53: Sequencing analysis for exons 14 includes only cds +/- 5 bp. TG: Deletion/duplication analysis is not offered for exon 18. Sequencing analysis for exons 44 includes only cds +/- 0 bp. EYS: Sequencing analysis for exons 30 includes only cds +/- 0 bp. HBA1/2: This assay is designed to detect deletions and duplications of HBA1 and/or HBA2, resulting from the -alpha20.5, --MED, --SEA, --FIL/--THAI, -alpha3.7, -alpha4.2, anti3.7 and anti4.2. Sensitivity to detect other copy number variants may be reduced. Detection of overlapping deletion and duplication events will be limited to combinations of events with significantly differing boundaries. In addition, deletion of the enhancer element HS-40 and the sequence variant, Constant Spring (NM_000517.4:c.427T>C), can be identified by this assay. USH1C: Deletion/duplication analysis is not offered for exons 5-6. FAH: Deletion/duplication analysis is not offered for exon 14. LIFR: Sequencing analysis for exons 3 includes only cds +/- 5 bp. MLC1: Sequencing analysis for exons 11 includes only cds +/- 10 bp. MTHFR: The NM_005957.4:c.665C>T (p.Ala222Val) (aka 677C>T) and c.1286A>C (p.Glu429Ala) (aka 1298A>C) variants are not reported in our primary report. NEB: Deletion/duplication analysis is not offered for exons 82-105. NEB variants in this region with no evidence towards pathogenicity are not included in this report, but are available upon request. PEX1: Sequencing analysis for exons 16 includes only cds +/- 0 bp. PKHD1: Deletion/duplication analysis is not offered for exon 13. CYP21A2: Analysis includes the most common variants (c.92C>T(p.Pro31Leu), c.293-13C>G (intronic), c.332_339delGAGACTAC (p.Gly111Valfs*21), c.518T>A (p.Ile173Asn), c.710T>A (p.Ile237Asn), c.713T>A (p.Val238Glu), c.719T>A (p.Met240Lys), c.844G>T (p.Val282Leu), c.923dupT (p.Leu308Phefs*6), c.955C>T (p.Gln319*), c.1069C>T(p.Arg357Trp), c.1360C>T (p.Pro454Ser) and the 30Kb deletion) as well as select rare HGMD variants only (list available upon request). Full gene duplications are reported only in the presence of a pathogenic variant(s). When a duplication and a pathogenic variant(s) is identified, phase (cis/trans) cannot be determined. Full gene deletion analysis is not offered. Sensitivity to detect these variants, if they result from complex gene conversion/fusion events, may be reduced. ABCC2: Deletion/duplication analysis is not offered for exons 24-25. GHR: Deletion/duplication and sequencing analysis is not offered for exon 3. GALE: Sequencing analysis for exons 10 includes only cds +/- 5 bp. BBS9: Deletion/duplication analysis is not offered for exon 4. WRN: Deletion/

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duplication analysis is not offered for exons 10-11. Sequencing analysis for exons 8, 10-11 includes only cds +/- 10 bp. OTOA: Deletion/duplication and sequencing analysis is not offered for exons 20-28. DUOX2: Deletion/duplication and sequencing analysis is not offered for exons 6-7. FANCD2: Deletion/duplication analysis is not offered for exons 14-17, 22 and sequencing analysis is not offered for exons 15-17. Sequencing analysis for exons 6, 14, 18, 20, 23, 25, 34 includes only cds +/- 10 bp. ARX: Analysis is validated to detect polyalanine expansions but sensitivity may be reduced. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. TSFM: Sequencing analysis is not offered for exon 5. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28. AR: CAG repeat numbers are not determined. ATP8B1: Sequencing analysis for exons 19 includes only cds +/- 10 bp. IDS: Detection of complex rearrangements not offered (PMID: 7633410, 20301451). TYR: Deletion/duplication and sequencing analysis is not offered for exon 5. PTPRC: Sequencing analysis is not offered for exons 3, 15. ANO10: Sequencing analysis for exons 8 includes only cds +/- 0 bp. TBCE: Sequencing analysis for exons 2 includes only cds +/- 10 bp. CFTR: Sequencing analysis for exons 7 includes only cds +/- 10 bp. GBA: c.84dupG (p.Leu29Alafs*18), c.115+1G>A (Splice donor), c.222_224delTAC (p.Thr75del), c.475C>T (p.Arg159Trp), c.595_596delCT (p.Leu199Aspfs*62), c.680A>G (p.Asn227Ser), c.721G>A (p.Gly241Arg), c.754T>A (p.Phe252Ile), c.1226A>G (p.Asn409Ser), c.1246G>A (p.Gly416Ser), c.1263_1317del (p.Leu422Profs*4), c.1297G>T (p.Val433Leu), c.1342G>C (p.Asp448His), c.1343A>T (p.Asp448Val), c.1448T>C (p.Leu483Pro), c.1504C>T (p.Arg502Cys), c.1505G>A (p.Arg502His), c.1603C>T (p.Arg535Cys), c.1604G>A (p.Arg535His) variants only. Rarely, sensitivity to detect these variants may be reduced. When sensitivity is reduced, zygosity may be reported as "unknown". DDX11: NM_030653.3:c.1763-1G>C variant only. COL11A2: Deletion/duplication analysis is not offered for exon 36. SMN1: Systematic exon numbering is used for all genes, including SMN1, and for this reason the exon typically referred to as exon 7 in the literature (PMID: 8838816) is referred to as exon 8 in this report. This assay unambiguously detects SMN1 exon 8 copy number. The presence of the g.27134T>G variant (also known as c.*3+80T>G) is reported if SMN1 copy number = 2. SMN1 or SMN2: NM_000344.3:c.*3+80T>G variant only. AMN: Deletion/duplication analysis is not offered for exon 1. MID1: Sequencing analysis for exons 3 includes only cds +/- 0 bp. OAT: Deletion/duplication analysis is not offered for exon 2.

- 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.

This report has been reviewed and approved by:

Rupa Udani, PhD, FACMG
Clinical Molecular Geneticist

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