INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	Viktoriya Polyuha	**Sample type:**	gDNA	**Report date:**	02/23/2021
DOB:	03/29/2020	**Sample collection date:**	02/09/2021	**Invitae #:**	RQ1999310
Sex:	Female	**Sample accession date:**	02/10/2021	**Clinical team:**	Halyna Makukh
MRN:					

Reason for testing

Diagnostic test for a personal history of disease

Test performed

Sequence analysis and deletion/duplication testing of the 362 genes listed in the Genes Analyzed section.
Multiple panels/genes ordered: see Methods for complete list.

RESULT: POSITIVE

Two Pathogenic variants identified in SMN1. SMN1 is associated with autosomal recessive spinal muscular atrophy.

SMN2 copy number = 3.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
SMN1	Deletion (Entire coding sequence)	homozygous	PATHOGENIC
ALDOA	c.958A>T (p.Asn320Tyr)	heterozygous	Uncertain Significance
BIN1	c.1201G>A (p.Val401Met)	heterozygous	Uncertain Significance
DMD	c.2617T>C (p.Cys873Arg)	heterozygous	Uncertain Significance
MICAL1	c.225C>A (p.Asn75Lys)	heterozygous	Uncertain Significance
SPG11	c.4327G>A (p.Glu1443Lys)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 362 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.

Laboratory Director: Kristin Gibson, PhD, FACMG, NYCQ, CGMB, ErCLG
Invitae 1400 16th Street, San Francisco, CA 94103 · clientservices@invitae.com · 800.436.3037

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, Deletion (Entire coding sequence) (homozygous), were identified in SMN1.

- The SMN1 gene is associated with autosomal recessive spinal muscular atrophy (SMA) (MedGen UID: 21913, 101816, 95975, 325364).
- This result is consistent with a diagnosis of spinal muscular atrophy.
- Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by the loss of neurons within the spinal cord, which results in progressive muscle weakness and atrophy (PMID: 10679938, 18572081). Other features of SMA may include muscle fasciculations, tremor, poor weight gain, sleeping difficulties, pneumonia, scoliosis, joint contractures, and congenital heart disease (PMID: 18662980, 7658877). Four clinical SMA subtypes have been distinguished: severe infantile acute SMA type I (also referred to as Wednig-Hoffman disease), infantile chronic SMA type II, juvenile SMA type III (also referred to as Wohlfard-Kugelberg-Welander disease), and adult-onset SMA type IV (PMID: 10679938, 18572081). The age of onset, phenotype, prognosis, and life expectancy display marked inter- and intrafamilial variability, between and also within subtypes (PMID: 6855803). For SMA clinical management guidelines, refer to PMID: 17761659.
- Biological relatives have a chance of being a carrier for or being at risk for autosomal recessive spinal muscular atrophy. Testing should be considered if clinically appropriate. The chance of having a child with autosomal recessive spinal muscular atrophy depends on the carrier state of this individual's partner.

This individual has 3 copies of SMN2 exon 8, typically referred to as exon 7, which is expected to reflect SMN2 copy number.

- While the SMN2 gene alone is not associated with disease, variation in SMN2 copy number can modify the phenotype of SMN1-related SMA (PMID: 15378550). Accumulating evidence indicates that, in individuals with homozygous Pathogenic deletions in SMN1, the presence of two or fewer copies of SMN2 may be associated with a more severe phenotype compared to the presence of three or more copies of SMN2, which may be associated with a milder phenotype (PMID: 8824882, 9199562, 9837824, 11839954). Unaffected individuals with five copies of SMN2 and a homozygous deletion in SMN1 have been reported, suggesting that five copies of SMN2 may compensate for the lack of SMN1 expression (PMID: 15378550).

A Variant of Uncertain Significance, c.958A>T (p.Asn320Tyr), was identified in ALDOA.

- The ALDOA gene is associated with autosomal recessive glycogen storage disease (GSD) XII (MedGen UID: 82895).
- 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.1201G>A (p.Val401Met), was identified in BIN1.

- The BIN1 gene is associated with autosomal dominant and recessive centronuclear myopathy (MedGen UID: 98049).
- 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.2617T>C (p.Cys873Arg), was identified in DMD.

- The DMD gene is associated with X-linked Duchenne Muscular Dystrophy (DMD) (MedGen UID: 3925), Becker Muscular Dystrophy (BMD) (MedGen UID: 182959) and dilated cardiomyopathy 3B (CMD3B) (MedGen UID: 777148).
- 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.225C>A (p.Asn75Lys), was identified in MICAL1.

- The MICAL1 gene is associated with autosomal dominant familial temporal lobe epilepsy (ETL1) (MedGen UID: 1643229). Additionally, the MICAL1 gene currently has preliminary evidence supporting a correlation with autosomal dominant Charcot-Marie-Tooth disease (PMID: 26752306).

- 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.4327G>A (p.Glu1443Lys), was identified in SPG11.

- The SPG11 gene is associated with autosomal recessive hereditary spastic paraplegia 11 (SPG11) (MedGen UID: 388073), juvenile amyotrophic lateral sclerosis 5 (ALS5) (MedGen UID: 356388) and Charcot-Marie-Tooth disease type 2X (CMT2X) (MedGen UID: 895625).
- 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

SMN1, Deletion (Entire coding sequence), homozygous, PATHOGENIC

- This variant is a gross deletion of the genomic region encompassing exon 8 (conventionally referred to as exon 7) of the SMN1 gene. Due to the sequence similarity between other exons of SMN1 and SMN2, the presence of this variant is used to infer a whole-gene deletion of SMN1.
- This variant is clearly defined as a spinal muscular atrophy (SMA) causative allele (PMID: 11839954, 18572081). It has been reported in the homozygous state in approximately 96.4% of individuals affected with 5q13-linked SMA, and in the compound heterozygous state with a second loss-of-function SMN1 allele in the remaining 3.6% of affected individuals (PMID: 10679938).
- For these reasons, this variant has been classified as Pathogenic.

ALDOA, Exon 13, c.958A>T (p.Asn320Tyr), heterozygous, Uncertain Significance

- This sequence change replaces asparagine with tyrosine at codon 320 of the ALDOA protein (p.Asn320Tyr). The asparagine residue is highly conserved and there is a large physicochemical difference between asparagine and tyrosine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with ALDOA-related conditions.
- Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, Align-GVGD) all suggest that this variant is likely to be disruptive, but these predictions have not been confirmed by published functional studies and their clinical significance is uncertain.
- 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.

BIN1, Exon 13, c.1201G>A (p.Val401Met), heterozygous, Uncertain Significance

- This sequence change replaces valine with methionine at codon 401 of the BIN1 protein (p.Val401Met). The valine residue is moderately conserved and there is a small physicochemical difference between valine and methionine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with BIN1-related conditions.
- 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: "Deleterious"; PolyPhen-2: "Possibly 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.

DMD, Exon 20, c.2617T>C (p.Cys873Arg), heterozygous, Uncertain Significance

- This sequence change replaces cysteine with arginine at codon 873 of the DMD protein (p.Cys873Arg). The cysteine residue is highly conserved and there is a large physicochemical difference between cysteine and arginine.
- This variant is present in population databases (rs200872948, ExAC 0.004%), including at least one homozygous and/or hemizygous individual.
- This variant has been reported in individuals in the Leiden Open-source Variation Database (PMID: 21520333). ClinVar contains an entry for this variant (Variation ID: 382670).
- 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: "Deleterious"; PolyPhen-2: "Possibly 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.

MICAL1, Exon 2, c.225C>A (p.Asn75Lys), heterozygous, Uncertain Significance

- This sequence change replaces asparagine with lysine at codon 75 of the MICAL1 protein (p.Asn75Lys). The asparagine residue is moderately conserved and there is a moderate physicochemical difference between asparagine and lysine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with MICAL1-related conditions.
- 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: "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.

SPG11, Exon 25, c.4327G>A (p.Glu1443Lys), heterozygous, Uncertain Significance

- This sequence change replaces glutamic acid with lysine at codon 1443 of the SPG11 protein (p.Glu1443Lys). The glutamic acid residue is moderately conserved and there is a small physicochemical difference between glutamic acid and lysine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with SPG11-related conditions.
- Algorithms developed to predict the effect of missense changes on protein structure and function output the following: SIFT: "Tolerated"; PolyPhen-2: "Benign"; Align-GVGD: "Class C0". The lysine amino acid residue is found in multiple mammalian species, suggesting that this missense change does not adversely affect protein function. These predictions have not been confirmed by published functional studies and their clinical significance is uncertain.
- 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. Results are negative unless otherwise indicated in the report. Benign and Likely Benign variants are not included in this report but are available upon request. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

GENE	TRANSCRIPT
AARS	NM_001605.2
ABCD1	NM_000033.3
ACAD9	NM_014049.4
ACADM	NM_000016.5
ACADVL	NM_000018.3
ACTA1	NM_001100.3
ADGRB2	NM_001294336.1
ADSSL1	NM_199165.2
AGL	NM_000642.2
AGRN	NM_198576.3
AIFM1	NM_004208.3
ALDH18A1	NM_002860.3
ALDOA	NM_000034.3
ALG14	NM_144988.3
ALG2	NM_033087.3
ALS2	NM_020919.3
AMACR	NM_014324.5
AMPD1	NM_000036.2
AMPD2	NM_001257360.1
ANO5	NM_213599.2
AP4B1	NM_006594.3
AP4E1	NM_007347.4
AP4M1	NM_004722.3
AP4S1	NM_007077.4
AP5Z1	NM_014855.2
APOA1	NM_000039.2
ARG1	NM_000045.3
ARHGEF10	NM_014629.3
ARL6IP1	NM_015161.2
ARSI	NM_001012301.2
ASAH1	NM_177924.3
ATL1	NM_015915.4
ATL3	NM_015459.4
ATP13A2	NM_022089.3
ATP1A1*	NM_000701.7
ATP2A1	NM_173201.3
ATP2B4	NM_001001396.2
ATP7A	NM_000052.6
ATP7B	NM_000053.3
B3GALNT2	NM_152490.4
B4GALNT1	NM_001478.4
B4GAT1	NM_006876.2
BAG3	NM_004281.3
BICD2	NM_001003800.1
BIN1	NM_139343.2
BSCL2	NM_032667.6
C12orf65	NM_152269.4
C19orf12*	NM_001031726.3
CACNA1S	NM_000069.2
CAPN1	NM_001198868.1
CAPN3*	NM_000070.2
CASQ1	NM_001231.4
CAV3	NM_033337.2
CCDC78	NM_001031737.2
CCT5	NM_012073.4
CFL2	NM_021914.7
CHAT	NM_020549.4
CHCHD10	NM_213720.2
CHKB	NM_005198.4
CHRNA1	NM_000079.3
CHRNB1	NM_000747.2
CHRND	NM_000751.2
CHRNE	NM_000080.3
CLCN1	NM_000083.2
CNTN1	NM_001843.3
COL12A1	NM_004370.5
COL13A1	NM_001130103.1
COL6A1	NM_001848.2
COL6A2	NM_001849.3
COL6A3	NM_004369.3
COLQ	NM_005677.3
COQ8A	NM_020247.4
COQ9	NM_020312.3
COX6A1	NM_004373.3
CPT1A	NM_001876.3
CPT1C	NM_001136052.2
CPT2	NM_000098.2
CRYAB	NM_001885.2
CTDP1*	NM_004715.4
CYP27A1	NM_000784.3
CYP2U1	NM_183075.2
CYP7B1	NM_004820.3
DAG1	NM_004393.5
DCTN1	NM_004082.4
DDHD1	NM_001160147.1
DDHD2	NM_015214.2
DES	NM_001927.3
DGUOK	NM_080916.2
DHTKD1	NM_018706.6
DMD	NM_004006.2
DNAJB2	NM_001039550.1
DNAJB6	NM_058246.3
DNM2	NM_001005360.2
DNMT1	NM_001130823.1
DOK7	NM_173660.4
DPAGT1	NM_001382.3
DPM1	NM_003859.1
DPM2	NM_003863.3
DPM3	NM_153741.1
DRP2	NM_001939.2
DST	NM_001723.5;NM_015548.4
DSTYK	NM_015375.2
DYNC1H1	NM_001376.4
DYSF	NM_003494.3
EGR2	NM_000399.3

GENE	TRANSCRIPT
ELP1	NM_003640.3
EMD	NM_000117.2
ENO3	NM_053013.3
ENTPD1	NM_001776.5
ERLIN1	NM_006459.3
ERLIN2	NM_007175.6
ETFA	NM_000126.3
ETFB	NM_001985.2
ETFDH	NM_004453.3
EXOSC3	NM_016042.3
EXOSC9	NM_001034194.1
FA2H	NM_024306.4
FARS2	NM_006567.3
FBLN5	NM_006329.3
FBXO38	NM_030793.4
FDX2	NM_001031734.3
FGD4	NM_139241.3
FHL1	NM_001449.4
FIG4	NM_014845.5
FKBP14	NM_017946.3
FKRP	NM_024301.4
FKTN	NM_001079802.1
FLAD1	NM_025207.4
FLNC*	NM_001458.4
GAA	NM_000152.3
GAN	NM_022041.3
GARS	NM_002047.2
GBA2	NM_020944.2
GBE1	NM_000158.3
GDAP1	NM_018972.2
GFPT1	NM_001244710.1
GJB1	NM_000166.5
GJC2	NM_020435.3
GLA	NM_000169.2
GMPPB	NM_021971.2
GNB4	NM_021629.3
GNE	NM_001128227.2
GOSR2	NM_004287.3
GSN	NM_000177.4

GENE	TRANSCRIPT
GYG1	NM_004130.3
GYS1	NM_002103.4
HACD1	NM_014241.3
HACE1	NM_020771.3
HADH	NM_005327.4
HADHA	NM_000182.4
HADHB	NM_000183.2
HARS	NM_002109.5
HEXA	NM_000520.4
HINT1	NM_005340.6
HMBS	NM_000190.3
HNRNPA2B1	NM_031243.2
HNRNPDL	NM_031372.3
HSPB1	NM_001540.3
HSPB3	NM_006308.2
HSPB8	NM_014365.2
HSPD1	NM_002156.4
IBA57	NM_001010867.3
IGHMBP2	NM_002180.2
INF2	NM_022489.3
ISCU	NM_213595.3
ISPD	NM_001101426.3
ITGA7	NM_002206.2
KBTBD13	NM_001101362.2
KCNA2	NM_004974.3
KCNJ2	NM_000891.2
KDM5C	NM_004187.3
KIDINS220	NM_020738.2
KIF1A	NM_004321.6
KIF1C	NM_006612.5
KIF5A	NM_004984.2
KLC2	NM_022822.2
KLHL40	NM_152393.3
KLHL41	NM_006063.2
KLHL9	NM_018847.3
L1CAM	NM_000425.4
LAMA2	NM_000426.3
LAMB2	NM_002292.3
LAMP2	NM_002294.2

GENE	TRANSCRIPT
LARGE1	NM_004737.4
LAS1L	NM_031206.4
LDB3	NM_001080116.1;NM_001171610.1;NM_007078.3
LDHA	NM_005566.3
LIMS2	NM_001136037.2
LITAF	NM_004862.3
LMNA	NM_170707.3
LMOD3	NM_198271.4
LPIN1	NM_145693.2
LRP4	NM_002334.3
LRSAM1	NM_138361.5
MAG	NM_002361.3
MAP3K20	NM_016653.2
MARS	NM_004990.3
MATR3	NM_199189.2
MCM3AP	NM_003906.4
MED25	NM_030973.3
MEGF10	NM_032446.2
MFN2	NM_014874.3
MICAL1	NM_001286613.1
MICU1	NM_006077.3
MME*	NM_007289.2
MORC2	NM_001303256.2
MPZ	NM_000530.6
MTM1	NM_000252.2
MTMR14	NM_022485.4
MTMR2	NM_016156.5
MUSK	NM_005592.3
MYH2	NM_017534.5
MYH7	NM_000257.3
MYL2	NM_000432.3
MYO18B	NM_032608.6
MYOT	NM_006790.2
MYPN	NM_032578.3
NDRG1	NM_006096.3
NEB*	NM_001271208.1
NEFH	NM_021076.3
NEFL	NM_006158.4

GENE	TRANSCRIPT
NGF	NM_002506.2
NIPA1	NM_144599.4
NKX6-2	NM_177400.2
NT5C2	NM_012229.4
NTRK1	NM_001012331.1
OPA1	NM_015560.2;NM_130837.2
OPA3	NM_025136.3
ORAI1	NM_032790.3
PDK3	NM_001142386.2
PDSS2	NM_020381.3
PFKM	NM_000289.5
PGAM2	NM_000290.3
PGAP1	NM_024989.3
PGK1	NM_000291.3
PGM1*	NM_002633.2
PHKA1	NM_002637.3
PHKB	NM_000293.2;NM_001031835.2
PLEC	NM_000445.4;NM_201378.3
PLEKHG5	NM_020631.4
PLP1	NM_000533.4
PMP2	NM_002677.3
PMP22	NM_000304.3
PNPLA2	NM_020376.3
PNPLA6	NM_006702.4
POLG	NM_002693.2
POLG2	NM_007215.3
POMGNT1	NM_017739.3
POMGNT2	NM_032806.5
POMK	NM_032237.4
POMT1	NM_007171.3
POMT2	NM_013382.5
PRDM12	NM_021619.2
PREPL	NM_006036.4
PRPS1	NM_002764.3
PRX	NM_181882.2
PYGM	NM_005609.3
PYROXD1	NM_024854.3
RAB3GAP2	NM_012414.3
RAB7A	NM_004637.5
RAPSN	NM_005055.4
RBCK1	NM_031229.3
REEP1	NM_022912.2
REEP2	NM_001271803.1
RETREG1	NM_001034850.2
RRM2B	NM_015713.4
RTN2	NM_005619.4
RXYLT1	NM_014254.2
RYR1	NM_000540.2
SACS	NM_014363.5
SBF1	NM_002972.3
SBF2	NM_030962.3
SCN10A	NM_006514.3
SCN11A*	NM_014139.2
SCN4A	NM_000334.4
SCN9A	NM_002977.3
SDHA*	NM_004168.3
SELENON	NM_020451.2
SEPT9	NM_006640.4
SGCA	NM_000023.2
SGCB	NM_000232.4
SGCD	NM_000337.5
SGCG	NM_000231.2
SGPL1	NM_003901.3
SH3TC2	NM_024577.3
SIGMAR1	NM_005866.3
SIL1	NM_022464.4
SLC12A6	NM_133647.1
SLC16A1	NM_003051.3
SLC16A2	NM_006517.4
SLC18A3	NM_003055.2
SLC22A5	NM_003060.3
SLC25A20	NM_000387.5
SLC25A21	NM_030631.3
SLC25A32	NM_030780.4
SLC25A46	NM_138773.2
SLC33A1	NM_004733.3
SLC52A1	NM_017986.3
SLC52A2	NM_024531.4
SLC52A3	NM_033409.3
SLC5A7	NM_021815.2
SMCHD1	NM_015295.2
SMN1	NM_000344.3
SMN2	NM_017411.3
SNAP25	NM_130811.2
SPART	NM_015087.4
SPAST	NM_014946.3
SPEG	NM_005876.4
SPG11	NM_025137.3
SPG21	NM_016630.6
SPG7	NM_003119.3
SPTLC1	NM_006415.3
SPTLC2	NM_004863.3
SQSTM1	NM_003900.4
STAC3	NM_145064.2
STIM1	NM_003156.3
SUCLA2	NM_003850.2
SUCLG1	NM_003849.3
SUN1	NM_001130965.2
SUN2	NM_015374.2
SURF1	NM_003172.3
SYNE1	NM_033071.3
SYNE2	NM_182914.2
SYT2	NM_177402.4
TANGO2	NM_152906.6
TAZ	NM_000116.4
TCAP	NM_003673.3
TECPR2	NM_014844.3
TFG	NM_006070.5
TIA1	NM_022173.2
TK2	NM_004614.4
TMEM43	NM_024334.2
TNNT1	NM_003283.5
TNNT3	NM_006757.3
TNPO3	NM_012470.3
TOR1AIP1	NM_001267578.1
TPM2	NM_003289.3
TPM3*	NM_152263.3

GENE	TRANSCRIPT
TRAPPC11	NM_021942.5
TRIM2	NM_001130067.1
TRIM32	NM_012210.3
TRPV4	NM_021625.4
TSFM*	NM_001172696.1
TTN*	NM_001267550.2
TTR	NM_000371.3
TWNK	NM_021830.4
TYMP	NM_001953.4
UBA1	NM_003334.3
UCHL1	NM_004181.4
USP8	NM_005154.4
VAMP1	NM_014231.3
VAPB	NM_004738.4
VCP	NM_007126.3
VMA21	NM_001017980.3
VPS37A	NM_152415.2
VRK1	NM_003384.2
WASHC5	NM_014846.3
WNK1	NM_213655.4
YARS	NM_003680.3
ZFR	NM_016107.3
ZFYVE26	NM_015346.3
ZFYVE27	NM_001002261.3

Methods

- Complete list of tests performed: Invitae Comprehensive Neuropathies Panel, Add-on Preliminary-evidence Genes for Neuropathies, Invitae Hereditary Spastic Paraplegia Comprehensive Panel, Add-on Preliminary-evidence Genes for Hereditary Spastic Paraplegia, Invitae Comprehensive Neuromuscular Disorders Panel, Add-on Preliminary-evidence Genes for Neuromuscular Disorders, Invitae Congenital Myasthenic Syndrome Panel, Add-on Preliminary-evidence Genes for Congenital Myasthenic Syndrome, Invitae Comprehensive Muscular Dystrophy Panel, Add-on Preliminary-evidence Genes for Muscular Dystrophy, Invitae Limb-Girdle Muscular Dystrophy Panel, Add-on Preliminary-evidence Genes for Limb-Girdle Muscular Dystrophy, Invitae Comprehensive Myopathy Panel, Add-on Preliminary-evidence Genes for Myopathy, Invitae Hereditary Rhabdomyolysis Panel
- 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, 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. 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. All clinically significant observations are confirmed by orthogonal technologies, except individually validated variants and variants previously confirmed in a first-degree relative. Confirmation technologies include any of the following: Sanger sequencing, Pacific Biosciences SMRT sequencing, MLPA, MLPA-seq, Array CGH. Array CGH confirmation of NGS CNV calling performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). 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). 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

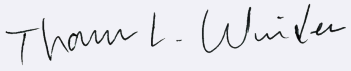
Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than 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. In very rare cases (such as circulating hematolymphoid neoplasm, bone marrow transplant, recent blood transfusion, or maternal cell contamination), the analyzed DNA may not represent the patient's constitutional genome.
CTDP1: c.863+389C>T variant only. PGM1: Deletion/duplication analysis is not offered for exon 11. FLNC: Deletion/duplication analysis is not offered for exon 47. Sensitivity and specificity for single nucleotide variants, insertions and deletions in exons 47-48 may be reduced due to the presence of segmental duplications overlapping the region. 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. SMN1 or SMN2: The SMN1 gene is identical to the SMN2 gene with the exception of exon 8 (typically referred to as exon 7). This assay unambiguously detects SMN1 exon 8 copy number and sequence variants. Sequence variants outside of exon 8 will also be detected, but this assay cannot determine whether the variant is located in SMN1 or SMN2. SMN2 exon 8 copy number will be reported for individuals with a positive result in SMN1. CNVs of exons 1-7 of SMN1 or SMN2 (typically referred to as exons 1-6 in the literature) will not be reported. Variants in all exons with no evidence towards pathogenicity are not reported, but are available upon request. This assay cannot detect silent carriers (individuals that have 2 functional copies of SMN1 on one chromosome and zero copies on the other). Therefore a negative result for carrier testing greatly reduces but does not eliminate the chance that a person is a carrier. For individuals with 2 copies of SMN1, the residual risk of being a carrier has been reported to be 1 in 121 in African Americans, 1 in 345 in Ashkenazi Jewish individuals, 1 in 628 in Asians, 1 in 632 in Caucasians, and 1 in 1061 in Hispanic individuals (PMID: 23788250). The SMA-STAT test does not detect sequence variants in SMN1 or SMN2, and therefore cannot be used to identify compound heterozygotes. SDHA: Deletion/duplication analysis is not offered for this gene and sequencing analysis is not offered for exon 14. Sequencing analysis for exons 6-8 includes only cds +/- 10 bp. TTN: Exons 45-46, 147, 149, 164, 172-201 (NM_001267550.2) are excluded from analysis. TTN variants are included in the primary report based on functional effect and/or location. A complete list of variants of uncertain significance, likely benign and benign variants in TTN is available upon request. Variants are named relative to the NM_001267550.2 (meta) transcript. Variants in the coding sequence and intronic boundaries of the clinically relevant NM_133378.4 (N2A) and fetal isoforms are reported (PMID: 25589632, 29598826, 29691892, 31660661), with the exception of the PEVK tandem repeat region (172-198) (PMID: 28040389). CAPN3: Deletion/duplication analysis is not offered for exon 24. SCN11A: Sequencing analysis for exons 1 includes only cds +/- 10 bp. MME: Deletion/duplication analysis is not offered for exons 5-6. TSFM: Sequencing analysis is not offered for exon 5. C19orf12: Deletion/duplication analysis is not offered for exon 1. ATP1A1: Deletion/duplication analysis is not offered for exon 1. TPM3: Deletion/duplication analysis is not offered for exon 10.

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:



Thomas L. Winder, Ph.D., FACMG
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.

1400 16th Street, San Francisco, CA 94103 • www.invitae.com • 800-436-3037 • 415-276-4164