INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	Bohdana Royik	**Sample type:**	Blood	**Report date:**	12/17/2020
DOB:	12/09/2019	**Sample collection date:**	12/07/2020	**Invitae #:**	RQ1844339
Sex:	Female	**Sample accession date:**	12/08/2020	**Clinical team:**	Halyna Makukh
MRN:					

Reason for testing

Test performed

Sequence analysis and deletion/duplication testing of the 223 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 = 2.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
SMN1	Deletion (Entire coding sequence)	homozygous	PATHOGENIC
CHCHD10	c.323A>C (p.Gln108Pro)	heterozygous	Uncertain Significance
LAMB2	c.1442G>A (p.Ser481Asn)	heterozygous	Uncertain Significance
TTN	c.106837T>G (p.Ser35613Ala)	heterozygous	Uncertain Significance
TTN	c.105145C>A (p.Pro35049Thr)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 223 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 2 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.323A>C (p.Gln108Pro), was identified in CHCHD10.

- The CHCHD10 gene is associated with autosomal dominant frontotemporal dementia and/or amyotrophic lateral sclerosis 2 (FTDALS2) (MedGen UID: 863085), spinal muscular atrophy, Jokela type (SMAJ) (MedGen UID: 767312), and isolated mitochondrial myopathy (IMMD) (MedGen UID: 863950).
- 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.1442G>A (p.Ser481Asn), was identified in LAMB2.

- The LAMB2 gene is associated with autosomal recessive nephrotic syndrome, type 5 (NPHS5) with or without ocular abnormalities (MedGen UID: 481743), and Pierson syndrome (MedGen UID: 373199). Additionally, the LAMB2 gene has preliminary evidence supporting a correlation with autosomal recessive congenital myasthenic syndrome (PMID: 19251977).
- 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.

Two Variants of Uncertain Significance, c.106837T>G (p.Ser35613Ala) and c.105145C>A (p.Pro35049Thr), were identified in TTN. The data from this test cannot definitively determine if these variants are on the same or opposite chromosomes.

- The TTN gene is associated with autosomal dominant dilated cardiomyopathy (DCM) (MedGen UID: 2880). Additionally, the TTN gene is associated with a diverse group of disorders affecting skeletal muscles, including autosomal dominant tibial muscular dystrophy (TMD) (MedGen UID: 333047) and autosomal recessive limb-girdle muscular dystrophy type 2J (LGMD2J) (MedGen UID: 324741), autosomal recessive centronuclear myopathy (CNM) (PMID: 23975875), and autosomal dominant hereditary myopathy with early respiratory failure (HMERF) (MedGen UID: 350930). Additional TTN-related conditions have also been reported (OMIM: 188840).

- 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 these variants 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.

CHCHD10, Exon 3, c.323A>C (p.Gln108Pro), heterozygous, Uncertain Significance

- This sequence change replaces glutamine with proline at codon 108 of the CHCHD10 protein (p.Gln108Pro). The glutamine residue is highly conserved and there is a moderate physicochemical difference between glutamine and proline.
- This variant is not present in population databases (ExAC no frequency).
- This variant has been observed in individual(s) with clinical features of

  CHCHD10-related conditions (PMID: 29789341).
- Experimental studies have shown that this variant affects CHCHD10 protein function (PMID: 29789341).
- 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.

LAMB2, Exon 11, c.1442G>A (p.Ser481Asn), heterozygous, Uncertain Significance

- This sequence change replaces serine with asparagine at codon 481 of the LAMB2 protein (p.Ser481Asn). The serine residue is weakly conserved and there is a small physicochemical difference between serine and asparagine.
- This variant is present in population databases (rs144230655, ExAC 0.02%) but has not been reported in the literature in individuals with a LAMB2-related disease.
- 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 tolerated, but these predictions have not been confirmed by published functional studies.
- In summary, this variant is a rare missense change that is not predicted to affect protein function, and is found in the population at an appreciable frequency. This variant is not anticipated to cause disease; however, the available evidence is currently insufficient to prove that conclusively. Therefore, it has been classified as a Variant of Uncertain Significance.

TTN, Exon 360, c.106837T>G (p.Ser35613Ala), heterozygous, Uncertain Significance

- This sequence change replaces serine with alanine at codon 35613 of the TTN protein (p.Ser35613Ala). There is a moderate physicochemical difference between serine and alanine.
- This variant is present in population databases (rs374405802, ExAC 0.01%).
- This variant has not been reported in the literature in individuals with TTN-related disease. ClinVar contains an entry for this variant (Variation ID: 47714).
- This variant identified in the TTN gene is located in the M band of the resulting protein (PMID: 25589632). It is unclear how this variant impacts the function of this protein.

- Algorithms developed to predict the effect of missense changes on protein structure and function are unavailable for the TTN gene.
- In summary, this variant is a rare missense change with unknown impact on protein function. Missense variants in this region of the TTN gene are typically not causative for cardiac disease, but may be relevant for neuromuscular disorders. However, the available evidence is currently insufficient to determine this variant's role in disease. Therefore, it has been classified as a Variant of Uncertain Significance

TTN, Exon 358, c.105145C>A (p.Pro35049Thr), heterozygous, Uncertain Significance

- This sequence change replaces proline with threonine at codon 35049 of the TTN protein (p.Pro35049Thr). There is a small physicochemical difference between proline and threonine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with TTN-related conditions.
- This variant is located in the M band of TTN (PMID: 25589632). Variants in this region may be relevant for neuromuscular disorders, but have not been definitively shown to cause cardiomyopathy (PMID: 23975875).
- Experimental studies and prediction algorithms are not available or were not evaluated, and the functional significance of this variant is currently unknown.
- 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
ACTA1	NM_001100.3
AGRN	NM_198576.3
AIFM1	NM_004208.3
ALG14	NM_144988.3
ALG2	NM_033087.3
ANO3	NM_031418.2
ANO5	NM_213599.2
ATL1	NM_015915.4
ATL3	NM_015459.4
ATP1A3	NM_152296.4
ATP2A1	NM_173201.3
ATP7A	NM_000052.6
ATP7B	NM_000053.3
B3GALNT2	NM_152490.4
B4GAT1	NM_006876.2
BAG3	NM_004281.3
BICD2	NM_001003800.1
BIN1	NM_139343.2
BSCL2	NM_032667.6
CACNA1S	NM_000069.2
CAPN3	NM_000070.2
CAV3	NM_033337.2
CCDC78	NM_001031737.2
CCT5	NM_012073.3
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
CIZ1	NM_012127.2
CLCN1	NM_000083.2
CNTN1	NM_001843.3
COL12A1	NM_004370.5
COL6A1	NM_001848.2
COL6A2	NM_001849.3
COL6A3	NM_004369.3
COLQ	NM_005677.3
CPT2	NM_000098.2
CRYAB	NM_001885.2
DAG1	NM_004393.5
DCTN1	NM_004082.4
DES	NM_001927.3
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
DRD2	NM_000795.3
DST	NM_001723.5;NM_015548.4
DYNC1H1	NM_001376.4
DYSF	NM_003494.3
EGR2	NM_000399.3
ELP1	NM_003640.3
EMD	NM_000117.2
FBXO38	NM_030793.4
FGD4	NM_139241.3
FHL1	NM_001449.4
FIG4	NM_014845.5
FKBP14	NM_017946.3
FKRP	NM_024301.4
FKTN	NM_001079802.1
FLNC*	NM_001458.4
FLRT1	NM_013280.4
GAA	NM_000152.3
GAN	NM_022041.3
GARS	NM_002047.2
GCH1	NM_000161.2
GDAP1	NM_018972.2
GFPT1	NM_001244710.1
GJB1	NM_000166.5
GMPPB	NM_021971.2
GNAL	NM_001142339.2
GNB4	NM_021629.3
GNE	NM_001128227.2
GYS1	NM_002103.4
HARS	NM_002109.5
HEXA	NM_000520.4
HINT1	NM_005340.6
HNRNPA2B1	NM_031243.2
HNRNPDL	NM_031372.3
HPCA	NM_002143.2
HSPB1	NM_001540.3
HSPB3	NM_006308.2
HSPB8	NM_014365.2
IGHMBP2	NM_002180.2
INF2	NM_022489.3
ISPD	NM_001101426.3
ITGA7	NM_002206.2
KBTBD13	NM_001101362.2
KCNJ2	NM_000891.2
KCTD17	NM_001282684.1
KIF1A	NM_004321.6
KLHL40	NM_152393.3
KLHL41	NM_006063.2
LAMA2	NM_000426.3
LAMB2	NM_002292.3

GENE	TRANSCRIPT
LAMP2	NM_002294.2
LARGE1	NM_004737.4
LAS1L	NM_031206.4
LDB3	NM_001080116.1;NM_001171610.1;NM_007078.2
LIMS2	NM_001136037.2
LITAF	NM_004862.3
LMNA	NM_170707.3
LMOD3	NM_198271.4
LRP4	NM_002334.3
LRSAM1	NM_138361.5
MARS	NM_004990.3
MATR3	NM_199189.2
MED25	NM_030973.3
MEGF10	NM_032446.2
MFN2	NM_014874.3
MORC2	NM_001303256.2
MPZ	NM_000530.6
MTM1	NM_000252.2
MTMR2	NM_016156.5
MUSK	NM_005592.3
MYF6	NM_002469.2
MYH2	NM_017534.5
MYH7	NM_000257.3
MYL2	NM_000432.3
MYOT	NM_006790.2
MYPN	NM_032578.3
NDRG1	NM_006096.3
NEB*	NM_001271208.1
NEFL	NM_006158.4
NGF	NM_002506.2
NTRK1	NM_001012331.1
PDK3	NM_001142386.2
PLEC	NM_000445.4;NM_201378.3
PLEKHG5	NM_020631.4
PMP22	NM_000304.3
PNKD	NM_015488.4
PNPLA2	NM_020376.3
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
PRKN	NM_004562.2
PRKRA	NM_003690.4
PRPS1	NM_002764.3
PRRT2	NM_145239.2
PRX	NM_181882.2
RAB7A	NM_004637.5
RAPSN	NM_005055.4
REEP1	NM_022912.2
RETREG1	NM_001034850.2
RXYLT1	NM_014254.2
RYR1	NM_000540.2
SBF2	NM_030962.3
SCN10A	NM_006514.3
SCN11A	NM_014139.2
SCN4A	NM_000334.4
SCN9A	NM_002977.3
SELENON	NM_020451.2
SETX	NM_015046.5
SGCA	NM_000023.2
SGCB	NM_000232.4
SGCD	NM_000337.5
SGCE	NM_003919.2
SGCG	NM_000231.2
SH3TC2	NM_024577.3
SIGMAR1	NM_005866.3
SLC25A46	NM_138773.2
SLC2A1	NM_006516.2
SLC52A2	NM_024531.4
SLC52A3	NM_033409.3
SLC5A7	NM_021815.2
SLC6A3	NM_001044.4
SMCHD1	NM_015295.2
SMN1*	NM_000344.3
SMN2	NM_017411.3
SNAP25	NM_130811.2
SPG11	NM_025137.3
SPR	NM_003124.4
SPTLC1	NM_006415.3
SPTLC2	NM_004863.3
SQSTM1	NM_003900.4
STAC3	NM_145064.2
STIM1	NM_003156.3
SUN1	NM_001130965.2
SUN2	NM_015374.2
SURF1	NM_003172.3
SYNE1	NM_033071.3
SYNE2	NM_182914.2
TAZ	NM_000116.4
TCAP	NM_003673.3
TFG	NM_006070.5
TH	NM_199292.2
THAP1	NM_018105.2
TIA1	NM_022173.2
TMEM43	NM_024334.2
TNNT1	NM_003283.5
TNPO3	NM_012470.3
TOR1A	NM_000113.2
TOR1AIP1	NM_001267578.1
TPM2	NM_003289.3
TPM3	NM_152263.3
TRAPPC11	NM_021942.5
TRIM2	NM_001130067.1
TRIM32	NM_012210.3
TRPV4	NM_021625.4
TTN*	NM_001267550.2
TTR	NM_000371.3
TUBB4A	NM_006087.3
UBA1	NM_003334.3
VAPB	NM_004738.4
VCP	NM_007126.3
VMA21	NM_001017980.3
VRK1	NM_003384.2
WNK1	NM_213655.4
YARS	NM_003680.3

Methods

- Complete list of tests performed: Invitae Comprehensive Neuropathies Panel, Add-on Preliminary-evidence Genes for Neuropathies, Add-on Spinal Muscular Atrophy Genes, Invitae Comprehensive Neuromuscular Disorders Panel, Add-on Preliminary-evidence Genes for Neuromuscular Disorders, Add-on Facioscapulohumeral Muscular Dystrophy Type 2 (FSHD2) Gene, Invitae Dystonia Comprehensive Panel, Add-on Preliminary-evidence Genes for Dystonia
- 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. 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.
SMN1, 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. 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. SMN1 or SMN2: Systematic exon numbering is used for all genes, including SMN1 and SMN2, 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 and SMN2 exon 8 copy number. Copy number of SMN2 exon 8 is expected to represent copy number for the entire SMN2 gene, and is reported only in individuals with a positive result in SMN1. Due to sequence similarity between SMN1 and SMN2, variants in exons 1-7 cannot be unambiguously mapped, and are therefore reported as occurring in "SMN1 or SMN2". Variants in all exons with no evidence towards pathogenicity are not included in this report, but are available upon request. TTN: Exons 153-155 (NM_133378.4) are excluded from analysis. TTN variants are reported 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, but only variants in the coding sequence and intronic boundaries of the clinically relevant NM_133378.4 (N2A) isoform are reported (PMID: 25589632). FLNC: Deletion/duplication analysis is not offered for exon 47. 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.

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:

Matteo Vatta, 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