INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	Dmytro Parhomchuk	**Sample type:**	gDNA	**Report date:**	05/10/2021
DOB:	11/08/2006	**Sample collection date:**	04/02/2021	**Invitae #:**	RQ2204714
Sex:	Male	**Sample accession date:**	04/14/2021	**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 761 genes listed in the Genes Analyzed section.
Multiple panels/genes ordered: see Methods for complete list.

RESULT: POSITIVE

One Pathogenic variant identified in ABCD1. ABCD1 is associated with X-linked adrenoleukodystrophy.

One Pathogenic variant identified in BTD. BTD is associated with autosomal recessive biotinidase deficiency.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ABCD1	c.1201C>T (p.Arg401Trp)	hemizygous	PATHOGENIC
BTD	c.1330G>C (p.Asp444His)	heterozygous	PATHOGENIC
ANK3	c.9935C>T (p.Ala3312Val)	heterozygous	Uncertain Significance
AP3B2	c.1096T>A (p.Ser366Thr)	heterozygous	Uncertain Significance
C19orf12	c.418G>A (p.Val140Ile)	heterozygous	Uncertain Significance
CNTN2	c.2345C>A (p.Thr782Lys)	heterozygous	Uncertain Significance
COL18A1	c.677G>A (p.Arg226His)	heterozygous	Uncertain Significance
DEAF1	c.56_79dup (p.Val19_Ala26dup)	heterozygous	Uncertain Significance
ERCC3	c.694A>G (p.Thr232Ala)	heterozygous	Uncertain Significance
GABRB2	c.1192-3C>T (Intronic)	heterozygous	Uncertain Significance
PNPT1	c.1027G>C (p.Val343Leu)	heterozygous	Uncertain Significance
RAI1	c.181G>C (p.Gly61Arg)	heterozygous	Uncertain Significance
SNORD118	NR_033294.1:n.37C>G (RNA change)	heterozygous	Uncertain Significance
GALC	c.1685T>C (p.Ile562Thr)	heterozygous	Benign (Pseudodeficiency allele)
GALC	c.550C>T (p.Arg184Cys)	heterozygous	Benign (Pseudodeficiency allele)
GALC	c.742G>A (p.Asp248Asn)	heterozygous	Benign (Pseudodeficiency allele)

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About this test

This diagnostic test evaluates 761 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Next steps

- This is a medically important result that should be discussed with a healthcare provider, such as a genetic counselor, to learn more about this result and the appropriate next steps for further evaluation, treatment and/or management. This result should be interpreted within the context of additional laboratory results, family history and clinical findings.
- Please see PMIDs: 1174883, 11204280 and 11558805 for management guidelines regarding ABCD1-related condition(s).
- 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**.
- One or more variants were identified that may generate a biochemical test result not known to cause disease. See the GALC variant(s) in the Variant Details section for more information.
- 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

A Pathogenic variant, c.1201C>T (p.Arg401Trp), was identified in ABCD1.

- The ABCD1 gene is associated with X-linked adrenoleukodystrophy (X-ALD) (MedGen UID: 57667).
- This result is consistent with a diagnosis of X-ALD.
- X-linked adrenoleukodystrophy is a metabolic disorder caused by impaired peroxisomal beta oxidation that leads to the accumulation of saturated very long chain fatty acids in numerous tissues throughout the body. The condition has a broad range of clinical phenotypes. Individuals with the same ABCD1 variant can have entirely different neurological and neuropathologic symptoms (PMID: 7811247, 8048932). Disease progression, over time, in any one specific individual cannot be predicted (PMID: 1174883). Affected individuals accumulate very long chain fatty acids (VLCFA) in all tissues (PMID: 16380594). The majority of males with X-ALD develop adrenocortical insufficiency (Addison's disease) in childhood, followed by progressive myelopathy and peripheral neuropathy in adulthood (PMID: 25115486). A subset of affected males develop a fatal childhood onset cerebral demyelinating disease, cerebral adrenoleukodystrophy (PMID: 25115486). Approximately 10% of males with childhood or adolescent onset cerebral X-ALD experience a plateau in disease progression, called chronic or arrested cerebral X-ALD, during which they can be stable for a decade or longer, but remain at risk for sudden onset of full progression to the neuroinflammatory stage of the disease (PMID: 1174883). Females who harbor a pathogenic variant may have biochemical and/or clinical manifestations. Approximately 85% of females with a pathogenic variant have an increased concentration of VLCFA in plasma and/or cultured skin fibroblasts while 20% of females have normal plasma concentration of VLCFA (PMID: 9894883). More than 20% of affected females develop progressive myelopathy, peripheral neuropathy, and progressive spastic paraparesis (PMID: 20301491). However, females typically present at a later age than males, and rarely develop adrenocortical insufficiency or cerebral adrenoleukodystrophy (PMID: 25115486).
- Biological relatives have a chance of being at risk for X-ALD and should consider testing if clinically appropriate.

A Pathogenic variant, c.1330G>C (p.Asp444His), was identified in BTD.

- The BTD gene is associated with autosomal recessive biotinidase deficiency (MedGen UID: 66323). The c.1330G>C (p.Asp444His) variant is associated with partial biotinidase deficiency.
- This individual is a carrier for autosomal recessive partial biotinidase deficiency. This result is insufficient to cause autosomal recessive partial biotinidase deficiency; however, carrier status does impact reproductive risk.
- Biotinidase deficiency is an inherited disorder of biotin recycling that can range from partial biotinidase deficiency to profound biotinidase deficiency. Individuals with profound biotinidase deficiency (<10% residual enzyme activity) can have metabolic acidosis, neurological symptoms including developmental delay, hypotonia, seizures, and ataxia, and skin rashes or alopecia. Individuals with partial biotinidase deficiency have one copy of the p.Asp444His variant and a second disease-causing variant in the BTD gene. These individuals have 10-30% residual enzyme activity, are mostly picked up on newborn screening and remain asymptomatic. Individuals that do have symptoms may have intermittent hypotonia, skin rashes, alopecia and/or acute episodes of metabolic decompensation with normal periods in between. Aside from low serum biotinidase activity, organic aciduria is variable but may include elevations of 3-hydroxyisovaleric acid, lactic acid, 3-hydroxypropionic acid, methylcitric acid, 3-methylcrotonylglycine, propionylglycine, and/or tiglylyglycine. This disorder is treatable with pharmacologic doses of biotin (PMID: 20129807). Clinical management guidelines may be found at PMID: 22241090. Note that individuals who are homozygous for the p.Asp444His variant have mild enzyme deficiency and may have mild abnormalities on biochemical testing, but do not have clinical symptoms of partial biotinidase deficiency.
- Biological relatives have a chance of being a carrier for autosomal recessive partial biotinidase deficiency. The chance of having a child with autosomal recessive BTD-related conditions depends on the carrier state of this individual's partner. The form of biotinidase deficiency depends on the specific BTD variants inherited from the reproductive parents.

A Variant of Uncertain Significance, c.9935C>T (p.Ala3312Val), was identified in ANK3.

- The ANK3 gene is associated with an autosomal recessive intellectual disability syndrome (MedGen UID: 816002). Additionally, the ANK3 gene has preliminary evidence supporting a correlation with autosomal dominant Tourette syndrome (MedGen UID: 21219) and a spectrum of autosomal dominant neurodevelopmental and cardiac disorders (PMID: 28687526, 28991257).
- 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.1096T>A (p.Ser366Thr), was identified in AP3B2.

- The AP3B2 gene is associated with autosomal recessive developmental and epileptic encephalopathy, also known as early infantile epileptic encephalopathy (MedGen UID: 934604).
- 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.418G>A (p.Val140Ile), was identified in C19orf12.

- The C19orf12 gene is associated with autosomal dominant and recessive mitochondrial membrane protein-associated neurodegeneration (MPAN) (MedGen UID: 482001). Additionally, the C19orf12 gene has preliminary evidence supporting a correlation with autosomal recessive hereditary spastic paraplegia 43 (SPG43) (MedGen UID: 760531).
- 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.2345C>A (p.Thr782Lys), was identified in CNTN2.

- The CNTN2 gene is associated with autosomal recessive myoclonic epilepsy (MedGen UID: 815704).
- 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.677G>A (p.Arg226His), was identified in COL18A1.

- The COL18A1 gene is associated with autosomal recessive Knobloch syndrome (MedGen UID: 1642123).
- 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.56_79dup (p.Val19_Ala26dup), was identified in DEAF1.

- The DEAF1 gene is associated with autosomal dominant and autosomal recessive neurodevelopmental disorders (MedGen UID: 862851, 934650).
- 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.694A>G (p.Thr232Ala), was identified in ERCC3.

- The ERCC3 gene is associated with autosomal recessive xeroderma pigmentosum/Cockayne syndrome (MedGen UID: 373493).
- 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.1192-3C>T (Intronic), was identified in GABRB2.

- The GABRB2 gene is associated with autosomal dominant intellectual disability and epilepsy (PMID: 27622563, 27789573, 29100083).
- 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.1027G>C (p.Val343Leu), was identified in PNPT1.

- The PNPT1 gene is associated with autosomal recessive combined oxidative phosphorylation deficiency 13 (COXPD13) (MedGen UID: 767043). Additionally, the PNPT1 gene has preliminary evidence supporting a correlation with autosomal recessive nonsyndromic deafness (DFNB) (MedGen UID: 760477).
- 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.181G>C (p.Gly61Arg), was identified in RAI1.

- The RAI1 gene is associated with autosomal dominant Smith-Magenis syndrome (MedGen UID: 162881) and is commonly deleted in the recurrent 17p11.2 microdeletion. Additionally, the RAI1 gene has preliminary evidence supporting a correlation with autosomal recessive non-syndromic deafness (PMID: 27082237).
- 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, NR_033294.1:n.37C>G (RNA change), was identified in SNORD118.

- The SNORD118 gene is associated with autosomal recessive leukoencephalopathy with brain calcifications and cysts (LCC) (MedGen UID: 482830).
- 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

ABCD1, Exon 3, c.1201C>T (p.Arg401Trp), hemizygous, PATHOGENIC

- This sequence change replaces arginine with tryptophan at codon 401 of the ABCD1 protein (p.Arg401Trp). The arginine residue is highly conserved and there is a moderate physicochemical difference between arginine and tryptophan.
- This variant is not present in population databases (ExAC no frequency).
- This variant has been observed in individual(s) with ABCD1-related conditions (PMID: 10190819, 21700483). In at least one individual the variant was observed to be de novo. ClinVar contains an entry for this variant (Variation ID: 488393).
- 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.
- This variant disrupts the p.Arg401 amino acid residue in ABCD1. Other variant(s) that disrupt this residue have been determined to be pathogenic (PMID: 8566952, 15811009, 21966424, 23419472 26388597). This suggests that this residue is clinically significant, and that variants that disrupt this residue are likely to be disease-causing
- For these reasons, this variant has been classified as Pathogenic.

BTD, Exon 4, c.1330G>C (p.Asp444His), heterozygous, PATHOGENIC

- This sequence change replaces aspartic acid with histidine at codon 444 of the BTD protein (p.Asp444His). The aspartic acid residue is highly conserved and there is a moderate physicochemical difference between aspartic acid and histidine.
- This variant is present in population databases (rs13078881, ExAC 5%).
- In the homozygous state this variant does not cause biotinidase deficiency or partial biotinidase deficiency (PMID: 28682309, 9654207). However, this variant in conjunction with another pathogenic variant is a common cause of partial biotinidase deficiency (PMID: 10206677, 9654207, 12227467, 23644139). This variant has also been observed in individuals affected with profound biotinidase deficiency when this variant is in cis

with the p.A171T variant and in trans with a third variant (PMID: 10206677, 9654207). ClinVar contains an entry for this variant (Variation ID: 16939).

- In individuals affected with partial biotinidase deficiency who harbor this variant in combination with another BTD variant, serum biotinidase activity was approximately 24% of the mean normal control activity (PMID: 9654207). In individuals affected with profound biotinidase deficiency who harbor this variant in cis with p.A171T and in trans with another BTD variant, serum biotinidase activity was <10% of the mean normal control activity (PMID: 10206677, 9654207). Individuals who are homozygous for this variant typically have an enzyme activity that is approximately 50% of normal (PMID: 20539236, 28682309, 9654207), similar to what is seen for a carrier of a profound allele.
- For these reasons, this variant has been classified as Pathogenic.

ANK3, Exon 37, c.9935C>T (p.Ala3312Val), heterozygous, Uncertain Significance

- This sequence change replaces alanine with valine at codon 3312 of the ANK3 protein (p.Ala3312Val). The alanine residue is weakly conserved and there is a small physicochemical difference between alanine and valine.
- This variant is present in population databases (rs201625904, ExAC 0.2%).
- This variant has not been reported in the literature in individuals with ANK3-related conditions. ClinVar contains an entry for this variant (Variation ID: 377485).
- 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: "Not Available"; PolyPhen-2: "Benign"; Align-GVGD: "Not Available").
- 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.

AP3B2, Exon 9, c.1096T>A (p.Ser366Thr), heterozygous, Uncertain Significance

- This sequence change replaces serine with threonine at codon 366 of the AP3B2 protein (p.Ser366Thr). The serine residue is highly conserved and there is a small physicochemical difference between serine 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 AP3B2-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 tolerated, 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.

C19orf12, Exon 3, c.418G>A (p.Val140Ile), heterozygous, Uncertain Significance

- This sequence change replaces valine with isoleucine at codon 140 of the C19orf12 protein (p.Val140Ile). The valine residue is weakly conserved and there is a small physicochemical difference between valine and isoleucine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with C19orf12-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 isoleucine 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.

CNTN2, Exon 18, c.2345C>A (p.Thr782Lys), heterozygous, Uncertain Significance

- This sequence change replaces threonine with lysine at codon 782 of the CNTN2 protein (p.Thr782Lys). The threonine residue is highly conserved and there is a moderate physicochemical difference between threonine 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 CNTN2-related conditions.

- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is not expected to disrupt CNTN2 protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

COL18A1, Exon 4, c.677G>A (p.Arg226His), heterozygous, Uncertain Significance

- This sequence change replaces arginine with histidine at codon 226 of the COL18A1 protein (p.Arg226His). The arginine residue is weakly conserved and there is a small physicochemical difference between arginine and histidine.
- This variant is present in population databases (rs201095161, ExAC 0.02%).
- This variant has not been reported in the literature in individuals with COL18A1-related conditions.
- 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.

DEAF1, Exon 1, c.56_79dup (p.Val19_Ala26dup), heterozygous, Uncertain Significance

- This variant, c.56_79dup, results in the insertion of 8 amino acid(s) to the DEAF1 protein (p.Val19_Ala26dup), but otherwise preserves the integrity of the reading frame.
- The frequency data for this variant in the population databases is considered unreliable, as metrics indicate insufficient coverage at this position in the ExAC database.
- This variant has not been reported in the literature in individuals with DEAF1-related conditions.
- 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.

ERCC3, Exon 6, c.694A>G (p.Thr232Ala), heterozygous, Uncertain Significance

- This sequence change replaces threonine with alanine at codon 232 of the ERCC3 protein (p.Thr232Ala). The threonine residue is moderately conserved and there is a small physicochemical difference between threonine and alanine.
- This variant is present in population databases (rs201383161, ExAC 0.03%).
- This variant has not been reported in the literature in individuals with ERCC3-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 tolerated, 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.

GABRB2, Intron 10, c.1192-3C>T (Intronic), heterozygous, Uncertain Significance

- This sequence change falls in intron 10 of the GABRB2 gene. It does not directly change the encoded amino acid sequence of the GABRB2 protein. It affects a nucleotide within the consensus splice site of the intron.
- This variant is present in population databases (rs773974056, ExAC 0.01%).
- This variant has not been reported in the literature in individuals with GABRB2-related conditions.
- Nucleotide substitutions within the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant is not likely to affect RNA splicing, but this prediction has not been confirmed by published transcriptional studies.
- 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.

PNPT1, Exon 12, c.1027G>C (p.Val343Leu), heterozygous, Uncertain Significance

- This sequence change replaces valine with leucine at codon 343 of the PNPT1 protein (p.Val343Leu). The valine residue is highly conserved and there is a small physicochemical difference between valine and leucine.
- This variant is present in population databases (rs766839497, ExAC 0.008%).
- This variant has not been reported in the literature in individuals with PNPT1-related conditions.
- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is not expected to disrupt PNPT1 protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

RAI1, Exon 3, c.181G>C (p.Gly61Arg), heterozygous, Uncertain Significance

- This sequence change replaces glycine with arginine at codon 61 of the RAI1 protein (p.Gly61Arg). The glycine residue is moderately conserved and there is a moderate physicochemical difference between glycine and arginine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with RAI1-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.

SNORD118, Exon 1, NR_033294.1:n.37C>G (RNA change), heterozygous, Uncertain Significance

- This variant occurs in the SNORD118 gene, which encodes an RNA molecule that does not result in a protein product.
- This variant is present in population databases (rs78363053, ExAC 0.04%).
- This variant has not been reported in the literature in individuals with SNORD118-related conditions.
- 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.

GALC, Exon 15, c.1685T>C (p.Ile562Thr), heterozygous, Benign (Pseudodeficiency allele)

- The GALC gene is associated with autosomal recessive Krabbe disease (MedGen UID: 44131). This variant is present in population databases (rs398607, gnomAD 60.5%), including many homozygous individuals, and occurs at a frequency higher than expected for Krabbe disease. This variant is a known pseudodeficiency allele and individuals with this variant can exhibit low galactocerebrosidase activity during enzyme analysis. On its own, this variant mildly reduces enzyme activity. However, it has been shown to further reduce GALC enzyme activity when it is located on the same chromosome (in cis) with pathogenic GALC variants (PMID: 26795590, 26865610, 27126738, 27638593). Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, but pseudodeficiency alleles are not known to cause disease. Although pseudodeficiency alleles do not cause disease, other carrier relatives may have abnormal enzyme testing. This variant is also known as p.Ile546Thr or p.I546T in the literature. For these reasons, this variant has been classified as Benign (Pseudodeficiency allele).

GALC, Exon 5, c.550C>T (p.Arg184Cys), heterozygous, Benign (Pseudodeficiency allele)

- The GALC gene is associated with autosomal recessive Krabbe disease (MedGen UID: 44131). This variant is a known pseudodeficiency allele (PMID: 26795590, 26865610, 8687180), and individuals with this variant can exhibit low galactocerebrosidase activity during enzyme analysis. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, but pseudodeficiency alleles are not known to cause disease. Although pseudodeficiency alleles do not cause disease, other carrier relatives may have abnormal enzyme testing. This variant is present in population databases (rs1805078, gnomAD 7%), including many homozygous individuals, and occurs at a frequency higher

than expected for Krabbe disease. This variant is also known as c.502T and p.R168C in the literature. For these reasons, this variant has been classified as Benign (Pseudodeficiency allele).

GALC, Exon 7, c.742G>A (p.Asp248Asn), heterozygous, Benign (Pseudodeficiency allele)

- The GALC gene is associated with autosomal recessive Krabbe disease (MedGen UID: 44131). This variant is a known pseudodeficiency allele (PMID: 24388568, 26795590, 27638593), and individuals with this variant can exhibit low galactocerebrosidase activity during enzyme analysis. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, but pseudodeficiency alleles are not known to cause disease. Although pseudodeficiency alleles do not cause disease, other carrier relatives may have abnormal enzyme testing. This variant is present in population databases (rs34362748, gnomAD 15.7%), including many homozygous individuals, and occurs at a frequency higher than expected for Krabbe disease. This variant is also known as p.D232N in the literature. For these reasons, this variant has been classified as Benign (Pseudodeficiency allele).

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
AARS2	NM_020745.3
ABAT	NM_020686.5
ABCA1	NM_005502.3
ABCD1	NM_000033.3
ACADM	NM_000016.5
ACADS	NM_000017.3
ACADVL	NM_000018.3
ACAT1	NM_000019.3
ACBD5	NM_145698.4
ACER3	NM_018367.6
ACO2	NM_001098.2
ACOX1	NM_004035.6
ACP5	NM_001111035.2
ACY1	NM_000666.2
ADAR	NM_001111.4
ADCY5	NM_183357.2
ADD3	NM_016824.4
ADGRG1	NM_005682.6
ADK	NM_001123.3
ADSL	NM_000026.2
AGA	NM_000027.3
AHDC1	NM_001029882.3
AHI1	NM_017651.4
AIFM1	NM_004208.3
AIMP1	NM_004757.3
AIMP2	NM_006303.3
AKT3	NM_005465.4
ALDH3A2	NM_000382.2
ALDH5A1	NM_001080.3
ALDH6A1	NM_005589.3
ALDH7A1	NM_001182.4
ALG1	NM_019109.4
ALG12	NM_024105.3
ALG13	NM_001099922.2
ALG2	NM_033087.3
ALG6	NM_013339.3
ALS2	NM_020919.3
AMACR	NM_014324.5
AMPD2	NM_001257360.1
AMT	NM_000481.3
ANK3	NM_020987.4
AP1S2	NM_003916.4
AP2M1	NM_004068.3
AP3B2	NM_004644.4
AP4B1	NM_006594.3
AP4E1	NM_007347.4
AP4M1	NM_004722.3
AP4S1	NM_007077.4
APOPT1	NM_032374.4
APP	NM_000484.3
APTX	NM_175073.2
ARCN1	NM_001655.4
ARG1	NM_000045.3
ARHGAP31	NM_020754.3
ARHGEF15	NM_173728.3
ARHGEF9	NM_015185.2;NM_001173479.1
ARNT2	NM_014862.3
ARSA	NM_000487.5
ARX*	NM_139058.2
ASAH1	NM_177924.3
ASL	NM_000048.3
ASNS	NM_133436.3
ASPA	NM_000049.2
ASS1	NM_000050.4
ASXL1	NM_015338.5
ASXL2	NM_018263.4
ATAD1	NM_001321967.1
ATM*	NM_000051.3
ATP13A2	NM_022089.3
ATP1A2	NM_000702.3
ATP1A3	NM_152296.4
ATP6AP2	NM_005765.2
ATP7A	NM_000052.6
ATP7B	NM_000053.3
ATP8A2	NM_016529.5
ATPAF2	NM_145691.3
ATRN	NM_139321.2
ATRX	NM_000489.4
AUH	NM_001698.2
B3GALNT2	NM_152490.4
BCAP31	NM_001139441.1
BCKDHA	NM_000709.3
BCKDHB	NM_183050.2
BCL11B	NM_138576.3
BCS1L	NM_004328.4
BMP4	NM_001202.3
BOLA3	NM_212552.2
BRAT1	NM_152743.3
BTD	NM_000060.3
C12orf57	NM_138425.3
C12orf65	NM_152269.4
C19orf12	NM_001031726.3
CACNA1A*	NM_001127221.1
CACNA1E	NM_000721.3
CACNA1H	NM_021098.2
CACNA2D2	NM_006030.3
CAD	NM_004341.4
CAMK2B	NM_001220.4
CARS2	NM_024537.3
CASK	NM_003688.3
CBS	NM_000071.2
CCDC88A	NM_001135597.1
CDKL5	NM_003159.2
CEP290	NM_025114.3

GENE	TRANSCRIPT
CERS1	NM_021267.4
CHD2	NM_001271.3
CHMP2B	NM_014043.3
CHRNA1	NM_000079.3
CHRNA2	NM_000742.3
CHRNA4	NM_000744.6
CHRNB2	NM_000748.2
CLCN2	NM_004366.5
CLCN4	NM_001830.3
CLCN6	NM_001286.3
CLCN7	NM_001287.5
CLN3	NM_001042432.1
CLN5	NM_006493.2
CLN6	NM_017882.2
CLN8	NM_018941.3
CLP1	NM_006831.2
CLPP	NM_006012.2
CLTC	NM_001288653.1
CNTN2	NM_005076.3
CNTNAP1	NM_003632.2
CNTNAP2	NM_014141.5
COASY	NM_025233.6
COG5	NM_006348.3
COL18A1	NM_130445.3;NM_030582.3
COL4A1	NM_001845.5
COL4A2*	NM_001846.3
COQ2	NM_015697.7
COQ4	NM_016035.4
COQ6	NM_182476.2
COQ7	NM_016138.4
COQ8A	NM_020247.4
COQ9	NM_020312.3
COX10*	NM_001303.3
COX14	NM_032901.3
COX15	NM_004376.6
COX20	NM_198076.5
COX6B1	NM_001863.4
COX7B	NM_001866.2
COX8A	NM_004074.2

GENE	TRANSCRIPT
CP	NM_000096.3
CPLX1	NM_006651.3
CPS1	NM_001875.4
CRAT	NM_000755.3
CSF1R	NM_005211.3
CSTB*	NM_000100.3
CTBP1	NM_001328.2
CTC1	NM_025099.5
CTDP1*	NM_004715.4
CTNNB1	NM_001904.3
CTNS	NM_004937.2
CTSA	NM_000308.3
CTSB	NM_001908.4
CTSD	NM_001909.4
CYFIP2	NM_001037333.2
CYP27A1	NM_000784.3
CYP2U1	NM_183075.2
CYP7B1	NM_004820.3
D2HGDH	NM_152783.4
DAG1	NM_004393.5
DARS	NM_001349.3
DARS2	NM_018122.4
DBH	NM_000787.3
DBT	NM_001918.3
DCAF17	NM_025000.3
DDC*	NM_000790.3
DDHD2	NM_015214.2
DDOST	NM_005216.4
DDX3X*	NM_001193416.2
DEAF1	NM_021008.3
DEGS1	NM_003676.3
DEPDC5	NM_001242896.1
DGKZ	NM_001105540.1
DGUOK	NM_080916.2
DHDDS	NM_024887.3
DHFR	NM_000791.3
DIAPH1	NM_005219.4
DLAT	NM_001931.4
DLD	NM_000108.4

GENE	TRANSCRIPT
DLL4	NM_019074.3
DMD	NM_004006.2
DNAJC12	NM_021800.2
DNAJC5	NM_025219.2
DNM1	NM_004408.3
DNM1L	NM_012062.4
DNM2	NM_001005360.2
DOCK6	NM_020812.3
DOCK7	NM_001271999.1
DPYS	NM_001385.2
DYNC1H1	NM_001376.4
DYRK1A	NM_001396.3
EARS2	NM_001083614.1
ECHS1	NM_004092.3
EDNRB	NM_000115.3
EEF1A2	NM_001958.3
EGR2	NM_000399.3
EHMT1	NM_024757.4
EIF2B1	NM_001414.3
EIF2B2	NM_014239.3
EIF2B3	NM_020365.4
EIF2B4	NM_015636.3
EIF2B5	NM_003907.2
ELOVL4	NM_022726.3
EMC1	NM_015047.2
ENTPD1	NM_001776.5
EPG5	NM_020964.2
EPHA4	NM_004438.4
EPM2A	NM_005670.3
EPRS	NM_004446.2
ERCC2	NM_000400.3
ERCC3	NM_000122.1
ERCC6	NM_000124.3
ERCC8	NM_000082.3
ETFA	NM_000126.3
ETFB	NM_001985.2
ETFDH	NM_004453.3
ETHE1	NM_014297.3
FA2H	NM_024306.4

GENE	TRANSCRIPT
FAM126A	NM_032581.3
FAR1	NM_032228.5
FARS2	NM_006567.3
FARSB	NM_005687.4
FASN	NM_004104.4
FASTKD2	NM_014929.3
FBXL4	NM_012160.4
FBXO11	NM_001190274.1
FDX2	NM_001031734.3
FGD4	NM_139241.3
FGF12	NM_021032.4
FGFRL1	NM_001004356.2
FH*	NM_000143.3
FIG4	NM_014845.5
FKRP	NM_024301.4
FKTN	NM_001079802.1
FLNA	NM_001456.3
FOLR1	NM_016725.2
FOXC1	NM_001453.2
FOXG1	NM_005249.4
FOXRED1	NM_017547.3
FRRS1L	NM_014334.2
FTL	NM_000146.3
FUCA1	NM_000147.4
GAA	NM_000152.3
GABBR2	NM_005458.7
GABRA1	NM_000806.5
GABRA2	NM_001330690.1
GABRB1	NM_000812.3
GABRB2	NM_021911.2
GABRB3	NM_000814.5
GABRG2	NM_000816.3
GAD1	NM_000817.2
GALC*	NM_000153.3
GALT	NM_000155.3
GAMT	NM_000156.5
GAN	NM_022041.3
GATAD2B	NM_020699.3
GATM	NM_001482.2
GBE1	NM_000158.3
GCDH	NM_000159.3
GCH1	NM_000161.2
GDAP1	NM_018972.2
GFAP	NM_002055.4;NM_001131019.2
GFM1	NM_024996.5
GFM2	NM_032380.4
GJA1	NM_000165.4
GJB1	NM_000166.5
GJC2	NM_020435.3
GLA	NM_000169.2
GLB1	NM_000404.2
GLDC	NM_000170.2
GLRA1	NM_000171.3
GLRB	NM_000824.4
GLRX5	NM_016417.2
GLUL	NM_002065.6
GLYCTK	NM_145262.3
GM2A	NM_000405.4
GNAO1	NM_020988.2
GNB1	NM_002074.4
GOSR2	NM_004287.3
GPAA1	NM_003801.3
GPHN	NM_020806.4
GPR88	NM_022049.2
GRIA3	NM_000828.4
GRIN1	NM_007327.3
GRIN2A	NM_000833.4
GRIN2B	NM_000834.3
GRIN2D	NM_000836.2
GRM7	NM_000844.3
GRN	NM_002087.3
GTF2H5	NM_207118.2
GTPBP2	NM_019096.4
GTPBP3	NM_133644.3
GUF1	NM_021927.2
HCN1	NM_021072.3
HEPACAM	NM_152722.4
HESX1	NM_003865.2
HEXA	NM_000520.4
HIBCH	NM_014362.3
HIKESHI	NM_016401.3
HK1	NM_000188.2
HLCS	NM_000411.6
HMGCL	NM_000191.2
HNRNPU	NM_031844.2
HPRT1	NM_000194.2
HSD17B10	NM_004493.2
HSD17B4	NM_000414.3
HSPD1	NM_002156.4
HTRA1	NM_002775.4
HTT*	NM_002111.8
IBA57	NM_001010867.3
IDH2	NM_002168.3
IDH3A	NM_005530.2
IDS*	NM_000202.6
IDUA	NM_000203.4
IER3IP1	NM_016097.4
IFIH1	NM_022168.3
IQSEC2	NM_001111125.2
ISCA1	NM_030940.3
ISCA2	NM_194279.3
ITPA	NM_033453.3
ITPR1	NM_002222.5
JAM3	NM_032801.4
KANK1	NM_015158.3
KANSL1*	NM_001193466.1
KARS	NM_001130089.1
KCNA1	NM_000217.2
KCNA2	NM_004974.3
KCNB1	NM_004975.2
KCNC1	NM_001112741.1
KCNC3*	NM_004977.2
KCND2	NM_012281.2
KCNH1	NM_172362.2
KCNH2	NM_000238.3
KCNH5	NM_139318.4
KCNJ10	NM_002241.4

GENE	TRANSCRIPT
KCNJ6	NM_002240.4
KCNK4	NM_001317090.1
KCNMA1	NM_002247.3
KCNQ2	NM_172107.2
KCNQ3	NM_004519.3
KCNQ5	NM_001160133.1
KCNT1	NM_020822.2
KCTD7	NM_153033.4
KDM5C	NM_004187.3
KIAA1161	NM_020702.4
KIDINS220	NM_020738.2
KIF1A	NM_004321.6
KIF2A	NM_001098511.2
KIF5A	NM_004984.2
KMT2C*	NM_170606.2
KPNA7	NM_001145715.1
L1CAM	NM_000425.4
L2HGDH	NM_024884.2
LAMA1	NM_005559.3
LAMA2	NM_000426.3
LAMB1	NM_002291.2
LAMC3	NM_006059.3
LARGE1	NM_004737.4
LETM1	NM_012318.2
LGI1	NM_005097.2
LIAS	NM_006859.3
LIPT1	NM_145199.2
LIPT2	NM_001144869.2
LMBRD1	NM_018368.3
LMNB1	NM_005573.3
LMNB2	NM_032737.3
LONP1	NM_004793.3
LRPPRC	NM_133259.3
LYRM7	NM_181705.3
MAG	NM_002361.3
MAN2B1	NM_000528.3
MAOA	NM_000240.3
MAPT	NM_005910.5
MARS2	NM_138395.3
MAT1A	NM_000429.2
MBD5	NM_018328.4
MCCC1	NM_020166.4
MCCC2	NM_022132.4
MCEE	NM_032601.3
MCOLN1	NM_020533.2
MDH2	NM_005918.3
MECP2	NM_004992.3;NM_001110792.1
MEF2C	NM_002397.4
MFSD8	NM_152778.2
MGP	NM_000900.3
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_001075098.3
MOCS2A	NM_176806.3
MOCS2B	NM_004531.4
MOCS3	NM_014484.4
MPC1	NM_016098.3
MPLKIP	NM_138701.3
MPV17	NM_002437.4
MPZ	NM_000530.6
MRPL44	NM_022915.3
MRPS16	NM_016065.3
MRPS22	NM_020191.2
MTFMT	NM_139242.3
MTHFR*	NM_005957.4
MTOR	NM_004958.3
MTR	NM_000254.2
MTRR	NM_002454.2
MTTP	NM_000253.3
MUT	NM_000255.3
NAA10	NM_003491.3
NACC1	NM_052876.3
NADK2	NM_001085411.2
NAGLU	NM_000263.3
NAGS	NM_153006.2
NAXD	NM_018210.3
NAXE	NM_144772.2
NBAS	NM_015909.3
NDRG1	NM_006096.3
NDUFA1	NM_004541.3
NDUFA10	NM_004544.3
NDUFA11	NM_175614.4
NDUFA12	NM_018838.4
NDUFA2	NM_002488.4
NDUFA9	NM_005002.4
NDUFAF1	NM_016013.3
NDUFAF2	NM_174889.4
NDUFAF3	NM_199069.1
NDUFAF4	NM_014165.3
NDUFAF5	NM_024120.4
NDUFAF6	NM_152416.3
NDUFB3	NM_002491.2
NDUFB8	NM_005004.3
NDUFB9	NM_005005.2
NDUFS1	NM_005006.6
NDUFS2	NM_004550.4
NDUFS3	NM_004551.2
NDUFS4	NM_002495.3
NDUFS6	NM_004553.4
NDUFS7	NM_024407.4
NDUFS8	NM_002496.3
NDUFV1	NM_007103.3
NDUFV2	NM_021074.4
NECAP1	NM_015509.3
NEDD4L	NM_015277.5
NEXMIF	NM_001008537.2
NFU1	NM_001002755.2
NGLY1	NM_018297.3
NHLRC1	NM_198586.2
NIPA1	NM_144599.4
NKX2-1	NM_001079668.2
NKX6-2	NM_177400.2
NOTCH1	NM_017617.3

GENE	TRANSCRIPT
NOTCH3	NM_000435.2
NPC1	NM_000271.4
NPC2	NM_006432.3
NPHP1	NM_000272.3
NPRL3	NM_001077350.2
NRXN1	NM_001135659.1
NTRK2	NM_006180.4
NUBPL	NM_025152.2
NUP62	NM_153719.3
NUS1	NM_138459.3
OCRL	NM_000276.3
OSGEP	NM_017807.3
OTC	NM_000531.5
PACS1*	NM_018026.3
PACS2	NM_001100913.2
PAFAH1B1	NM_000430.3
PAH	NM_000277.1
PAK3	NM_002578.4
PALM	NM_002579.2
PANK2	NM_153638.2
PARS2	NM_152268.3
PC	NM_000920.3
PCBD1	NM_000281.3
PCCA	NM_000282.3
PCCB	NM_000532.4
PCDH12	NM_016580.3
PCDH19	NM_001184880.1
PCLO	NM_033026.5
PDE10A	NM_001130690.2
PDE2A	NM_002599.4
PDHA1	NM_000284.3
PDHB	NM_000925.3
PDHX	NM_003477.2
PDP1	NM_018444.3
PDSS1	NM_014317.4
PDSS2	NM_020381.3
PDYN	NM_024411.4
PET100	NM_001171155.1
PEX1	NM_000466.2

GENE	TRANSCRIPT
PEX10	NM_153818.1
PEX11B	NM_003846.2
PEX12	NM_000286.2
PEX13	NM_002618.3
PEX14	NM_004565.2
PEX16	NM_004813.2
PEX19	NM_002857.3
PEX2	NM_000318.2
PEX26	NM_017929.5
PEX3	NM_003630.2
PEX5	NM_001131025.1
PEX6	NM_000287.3
PEX7	NM_000288.3
PGAP1	NM_024989.3
PGK1	NM_000291.3
PHGDH	NM_006623.3
PHYH	NM_006214.3
PIGA	NM_002641.3
PIGG	NM_001127178.2
PIGN	NM_176787.4
PIGO	NM_032634.3
PIGP	NM_153681.2
PIGQ	NM_004204.3
PIGV	NM_017837.3
PIGW	NM_178517.3
PIK3AP1	NM_152309.2
PIK3CA	NM_006218.2
PINK1	NM_032409.2
PLA2G6	NM_003560.2
PLAA	NM_001031689.2
PLCB1	NM_015192.3
PLEKHG2	NM_022835.2
PLP1	NM_000533.4
PLXNA2	NM_025179.3
PMP22	NM_000304.3
PNKD	NM_015488.4
PNKP	NM_007254.3
PNP	NM_000270.3
PNPO	NM_018129.3

GENE	TRANSCRIPT
PNPT1	NM_033109.4
POLG	NM_002693.2
POLG2	NM_007215.3
POLR1A	NM_015425.4
POLR1C	NM_203290.3
POLR3A	NM_007055.3
POLR3B	NM_018082.5
POMGNT1	NM_017739.3
POMK	NM_032237.4
POMT1	NM_007171.3
POMT2	NM_013382.5
PPP2CA	NM_002715.2
PPP2R1A	NM_014225.5
PPP2R5D	NM_006245.3
PPP3CA	NM_000944.4
PPT1	NM_000310.3
PRDM8	NM_020226.3
PRF1	NM_001083116.1
PRICKLE1	NM_153026.2
PRICKLE2	NM_198859.3
PRIMA1	NM_178013.3
PRKDC	NM_006904.6
PRNP*	NM_000311.3
PROSC	NM_007198.3
PRPS1	NM_002764.3
PRRT2	NM_145239.2
PSAP	NM_002778.3
PSAT1	NM_058179.3
PSEN1	NM_000021.3
PSPH*	NM_004577.3
PTEN*	NM_000314.4
PTPN23	NM_015466.3
PTS	NM_000317.2
PURA	NM_005859.4
PUS3	NM_031307.3
PYCR2	NM_013328.3
QARS	NM_005051.2
QDPR	NM_000320.2
RAB11A	NM_004663.4

GENE	TRANSCRIPT
RAB11B	NM_004218.3
RAI1	NM_030665.3
RALA	NM_005402.3
RANBP2*	NM_006267.4
RARS*	NM_002887.3
RBFOX1	NM_145891.2
RBFOX3	NM_001082575.2
RBPJ	NM_005349.3
RELN	NM_005045.3
REPS1	NM_001286611.1
RFT1	NM_052859.3
RHOBTB2	NM_001160036.1
RMND1	NM_017909.3
RNASEH2A	NM_006397.2
RNASEH2B	NM_024570.3
RNASEH2C	NM_032193.3
RNASET2	NM_003730.4
RNF13*	NM_007282.4
RNF216*	NM_207111.3
ROGDI	NM_024589.2
RORB	NM_006914.3
RPIA	NM_144563.2
RPS6KC1	NM_012424.4
RRM2B	NM_015713.4
RUSC2	NM_001135999.1
SAMHD1	NM_015474.3
SATB2	NM_015265.3
SCARB2	NM_005506.3
SCN1A	NM_001165963.1
SCN1B	NM_199037.3;NM_001037.4
SCN2A	NM_021007.2
SCN3A	NM_006922.3
SCN5A	NM_198056.2
SCN8A	NM_014191.3;NM_001330260.1
SCN9A	NM_002977.3
SCO1	NM_004589.3
SCO2	NM_005138.2
SCP2	NM_002979.4
SDHA*	NM_004168.3
SDHAF1	NM_001042631.2
SDHB	NM_003000.2
SDHD	NM_003002.3
SEPSECS	NM_016955.3
SERAC1	NM_032861.3
SERPINI1	NM_005025.4
SETBP1	NM_015559.2
SETD5	NM_001080517.2
SGCE	NM_003919.2
SGSH	NM_000199.3
SH3TC2	NM_024577.3
SHH	NM_000193.2
SHPK	NM_013276.2
SIK1*	NM_173354.3
SIX3	NM_005413.3
SLC12A5	NM_020708.4
SLC13A3	NM_022829.5
SLC13A5	NM_177550.4
SLC16A2	NM_006517.4
SLC17A5	NM_012434.4
SLC18A2	NM_003054.4
SLC19A3	NM_025243.3
SLC1A2	NM_004171.3
SLC1A4	NM_003038.4
SLC20A2	NM_006749.4
SLC25A1	NM_005984.4
SLC25A12	NM_003705.4
SLC25A15	NM_014252.3
SLC25A22	NM_024698.5
SLC25A4	NM_001151.3
SLC25A42	NM_178526.4
SLC2A1	NM_006516.2
SLC30A10	NM_018713.2
SLC33A1	NM_004733.3
SLC35A2	NM_001042498.2
SLC46A1	NM_080669.5
SLC6A1	NM_003042.3
SLC6A19	NM_001003841.2
SLC6A3	NM_001044.4
SLC6A5	NM_004211.3
SLC6A8	NM_005629.3
SLC6A9	NM_201649.3
SLC9A6	NM_006359.2
SMC1A	NM_006306.3
SNAP25	NM_130811.2
SNIP1	NM_024700.3
SNORD118	NR_033294.1
SNRPB	NM_198216.1
SNX27	NM_030918.5
SON	NM_032195.2
SOX10	NM_006941.3
SPART	NM_015087.4
SPAST	NM_014946.3
SPATA5	NM_145207.2
SPG11	NM_025137.3
SPG7	NM_003119.3
SPR	NM_003124.4
SPTAN1	NM_001130438.2
SPTBN2	NM_006946.2
SQSTM1	NM_003900.4
SSR4	NM_001204526.1
ST3GAL3	NM_006279.3
ST3GAL5	NM_003896.3
STAG2	NM_001042749.2
STAMBP	NM_006463.4
STAT1	NM_007315.3
STN1	NM_024928.4
STRADA	NM_001003787.2
STX11	NM_003764.3
STX1B	NM_052874.4
STXBP1	NM_003165.3
STXBP2	NM_006949.3
SUCLA2	NM_003850.2
SUCLG1	NM_003849.3
SUMF1	NM_182760.3
SUOX	NM_000456.2
SURF1	NM_003172.3
SYN1	NM_133499.2

GENE	TRANSCRIPT
SYNE1	NM_033071.3
SYNGAP1	NM_006772.2
SYNJ1	NM_003895.3
SZT2	NM_015284.3
TACO1	NM_016360.3
TAF2*	NM_003184.3
TANGO2	NM_152906.6
TARS2	NM_025150.4
TBC1D24	NM_001199107.1
TBCD	NM_005993.4
TBCK	NM_001163435.2
TBL1XR1	NM_024665.4
TCF4	NM_001083962.1
TGIF1	NM_173208.2
TH	NM_199292.2
TIMM50	NM_001001563.3
TK2	NM_004614.4
TM4SF20*	NM_024795.4
TMEM106B	NM_018374.3
TMEM126B	NM_018480.4
TMEM165	NM_018475.4
TMEM67	NM_153704.5
TMEM70	NM_017866.5
TMTC3	NM_181783.3
TPI1	NM_000365.5
TPK1	NM_022445.3
TPP1	NM_000391.3
TRAPPC11	NM_021942.5
TRAPPC9	NM_031466.7
TREM2	NM_018965.3;NM_001271821.1
TREX1	NM_033629.4
TRMT10A	NM_152292.4
TRMT5	NM_020810.3
TSC1	NM_000368.4
TSC2	NM_000548.3
TSEN54	NM_207346.2
TSFM*	NM_001172696.1
TTC19	NM_017775.3
TTPA	NM_000370.3

GENE	TRANSCRIPT
TUBA1A	NM_006009.3
TUBA8	NM_018943.2
TUBB2A*	NM_001069.2
TUBB4A	NM_006087.3
TUFM	NM_003321.4
TWNK	NM_021830.4
TYMP	NM_001953.4
TYROBP	NM_003332.3
UBA5	NM_024818.4
UBE2A	NM_003336.3
UBE3A	NM_130838.1
UFM1	NM_001286704.1
UGT1A1	NM_000463.2
UNC13D	NM_199242.2
UNC80	NM_032504.1
UPB1	NM_016327.2
VARS2	NM_001167734.1
VCP	NM_007126.3
VPS11	NM_021729.5
VPS33A	NM_022916.4
WARS2	NM_015836.3
WDR45	NM_007075.3
WDR62	NM_001083961.1
WHSC1	NM_133330.2
WWOX	NM_016373.3
YWHAG	NM_012479.3
ZDHHC9	NM_016032.3
ZEB2	NM_014795.3
ZFYVE26	NM_015346.3
ZIC1	NM_003412.3
ZIC2	NM_007129.3
ZNF335	NM_022095.3
ZSWIM6	NM_020928.1

Methods

- Complete list of tests performed: Invitae Epilepsy Panel, Add-on FLNA Gene, Add-on PTEN Gene, Invitae Leukodystrophy and Genetic Leukoencephalopathy Panel, Invitae Cerebral Palsy Spectrum Disorders 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.

CSTB: Dodecamer repeat numbers in the 5' UTR are not determined. ARX: Analysis is validated to detect polyalanine expansions but sensitivity may be reduced. PRNP: Octapeptide repeat numbers are not determined. PSPH: Deletion/duplication and sequencing analysis is not offered for exons 4-5. HTT: Deletion/duplication and sequencing analysis is not offered for exon 1. Trinucleotide repeat expansions are not determined on this assay. DDC: Deletion/duplication analysis is not offered for exons 10-11. TAF2: Sequencing analysis is not offered for exon 2. TUBB2A: Deletion/duplication and sequencing analysis is not offered for exon 2. KCNC3: Sequencing analysis is not offered for exon 4. PTEN: Sequencing analysis for exons 8 includes only cds +/- 10 bp. RANBP2: Deletion/duplication and sequencing analysis is not offered for exons 1-11, 15-29. SIK1: Deletion/duplication analysis is not offered for exons 13-14. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. GALC: Deletion/duplication analysis is not offered for exon 6. CTDP1: c.863+389C>T variant only. COL4A2: Deletion/duplication and sequencing analysis is not offered for exon 21. RNF216: Deletion/duplication and sequencing analysis is not offered for exons 2, 6. KMT2C: Deletion/duplication and sequencing analysis is not offered for exons 15, 19, 21, 24. SDHA: Deletion/duplication analysis is not offered for this gene. Sequencing analysis for exons 6-8, 14 includes only cds +/- 10 bp. KANSL1: Deletion/duplication analysis is not offered for exons 2-3. COX10: Deletion/duplication and sequencing analysis is not offered for exon 6. TM4SF20: Deletion/duplication analysis is not offered for exon 1. RNF13: Sequencing analysis is not offered for exon 4. IDS: Detection of complex rearrangements not offered (PMID: 7633410, 20301451). PACS1: c.607C>T variant only. DDX3X: Sequencing analysis is not offered for exon 3. TSFM: Sequencing analysis is not offered for exon 5. 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. FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp. CACNA1A: Trinucleotide repeat expansions are not determined on this assay. RARS: Deletion/duplication analysis is not offered for exon 14.

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.

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