INVITAE

INVITAE CARRIER SCREEN RESULTS

Patient name:	[redacted]	**Sample type:**	Saliva	**Report date:**	05/11/2021
[redacted]	[redacted]	**Sample collection date:**	04/19/2021	**Invitae #:**	RQ2224940
Sex:	Male	**Sample accession date:**	04/22/2021	**Clinical team:**	Karen Carey
MRN:					

Reason for testing

Carrier screening

Test performed

Invitae Carrier Screen

- Invitae primary panel (CF, SMA)
- Add-on genes

RESULT: POSITIVE

This carrier test evaluated 283 gene(s) for genetic changes (variants) that are associated with an increased risk of having a child with a genetic condition. Knowledge of carrier status for one of these conditions may provide information that can be used to assist with family planning and/or preparation.

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

RESULTS	GENE	VARIANT(S)	INHERITANCE	PARTNER TESTING RECOMMENDED
Carrier: Carbamoyl phosphate synthetase I deficiency	CPS1	c.2446del (p.Cys816Alafs*5)	Autosomal recessive	Yes
Carrier: Spinal muscular atrophy	SMN1	Deletion (Entire coding sequence)	Autosomal recessive	Yes
Carrier: WNT10A-related conditions	WNT10A	c.682T>A (p.Phe228Ile) §	Autosomal recessive	Yes

§ This variant is known to have low penetrance. See Clinical summary and/or Variant details on following pages for more information.

Next steps

- See the table above for recommendations regarding testing of this individual's reproductive partner.
- Even for genes that have a negative test result, there is always a small risk that an individual could still be a carrier. This is called "residual risk." See the table below for residual risks, which presumes a negative family history of the conditions listed.
- Genetic counseling is recommended to further explain the implications of this test result and assess family health history, which may point to health information that merits additional consideration.
- All patients, regardless of result, may wish to consider additional screening for hemoglobinopathies by complete blood count (CBC) and hemoglobin electrophoresis, if this has not already been completed.
- Individuals can register their tests at https://www.invitae.com/patients/ to access online results, educational resources, and next steps.

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Clinical summary

RESULT: CARRIER

Carbamoyl phosphate synthetase I deficiency

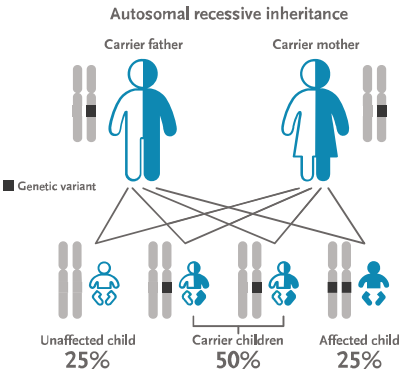
A single Pathogenic variant, c.2446del (p.Cys816Alafs*5), was identified in CPS1.

What is carbamoyl phosphate synthetase I deficiency?

Carbamoyl phosphate synthetase I (CPS1) deficiency is a condition in which ammonia builds up in the bloodstream, damaging the nervous system. Severity of symptoms and age of onset of CPS1 deficiency can vary. In the neonatal form, symptoms present during the newborn period and may include brain dysfunction (encephalopathy), vomiting, sleeping for unusually long periods (somnolence), dangerously low body temperature (hypothermia), seizures, coma, and death. Affected individuals are at risk of recurrent episodes of dangerous ammonia buildup (hyperammonemic episodes). In the late onset form, symptoms present after the newborn period and are often milder than those observed in the neonatal onset form. Early initiation of treatment, including dietary management, may delay onset and/or reduce the severity of symptoms. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

Carrier testing for the reproductive partner is recommended.



If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the CPS1 gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.

If your partner tests negative:

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

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Carbamoyl phosphate synthetase I deficiency (AR) NM_001875.4	CPS1	Pan-ethnic	≤1 in 500	Reduced

RESULT: CARRIER

Spinal muscular atrophy

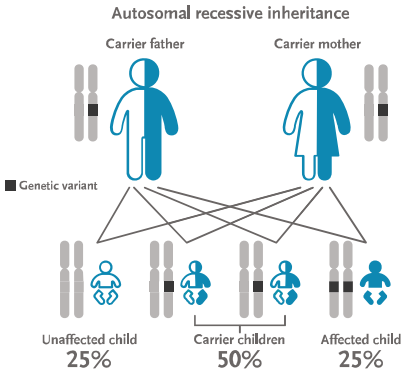
A single Pathogenic variant, Deletion (Entire coding sequence), was identified in SMN1.

What is spinal muscular atrophy?

Spinal muscular atrophy (SMA) is a condition that affects the neuromuscular system. SMA is characterized by loss of the nerves within the spinal cord that control voluntary muscle movement (motor neurons), resulting in progressive muscle weakness and wasting (atrophy). This leads to difficulty with activities such as crawling, sitting up, and walking. Other features of SMA may include involuntary muscle twitching (fasciculations), tremor, swallowing problems leading to feeding difficulties and poor weight gain, sleeping difficulties, respiratory problems due to weakness of the muscles used for breathing, pneumonia, side-to-side curvature of the spine (scoliosis), joint deformities that restrict movement (contractures), and congenital heart disease. Four clinical SMA subtypes have been distinguished: severe infantile acute SMA type I (also referred to as Werdnig-Hoffman disease), infantile chronic SMA type II, juvenile SMA type III (also referred to as Kugelberg-Welander disease), and adult-onset SMA type IV. Prognosis depends on the severity of symptoms, and life expectancy is often reduced in the severe subtypes of the condition. However, age of onset, symptoms, severity, and life expectancy are highly variable, both between and within families, as well as between and within subtypes. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

Carrier testing for the reproductive partner is recommended.



If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the SMN1 gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.

If your partner tests negative:

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

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Spinal muscular atrophy (AR) NM_000344.3	SMN1 *	African-American	1 in 59	1 in 342
		Ashkenazi Jewish	1 in 62	1 in 1017
		Asian	1 in 50	1 in 701
		Caucasian	1 in 45	1 in 880
		Hispanic	1 in 48	1 in 784
		Pan-ethnic	1 in 49	1 in 800

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RESULT: CARRIER

WNT10A-related conditions

A single Pathogenic (low penetrance) variant, c.682T>A (p.Phe228Ile), was identified in WNT10A. See "What are WNT10A-related conditions?" and Variant details for additional information.

What are WNT10A-related conditions?

WNT10A-related conditions include autosomal recessive odonto-onycho-dermal dysplasia (OODD) and Schöpf-Schulz-Passarge syndrome (SSPS) and autosomal dominant isolated tooth agenesis. Individuals with a clinically significant variant in this gene are carriers for the autosomal recessive conditions and may be at risk to develop the autosomal dominant condition associated with this gene.

Autosomal recessive WNT10A-related conditions, OODD and SSPS, refer to a spectrum of features associated with ectodermal dysplasia (ED), which causes abnormal development of the skin, hair, nails, teeth, and sweat glands. OODD is characterized by dental abnormalities including either fewer teeth than normal (hypodontia) or in more severe cases, the absence of six or more teeth (oligodontia), as well as a smooth tongue, malformed nails (onychodysplasia), clusters of enlarged blood vessels on the face (facial telangiectasias), and thickened skin (hyperkeratosis) with excessive sweating (hyperhidrosis) of the palms of the hands and soles of the feet. SSPS shares the same features as OODD, and is also associated with an increased risk of skin tumors which may be benign (non-cancerous) or malignant, and multiple eyelid cysts. Symptoms and severity of autosomal recessive WNT10A-related conditions are variable. Intellect and life span are not impacted.

Isolated tooth agenesis is a condition that affects the development of the teeth. It can be caused by changes in different genes. Isolated tooth agenesis is the congenital absence of one or more teeth, most commonly the permanent (secondary) teeth. Additional dental abnormalities may include small and/or irregular shaped teeth. Some individuals with WNT10A-related tooth agenesis have also been reported to have mild symptoms of ectodermal dysplasia (ED), which is a condition associated with abnormal development of the skin, hair, nails, teeth, and sweat glands. The severity of WNT10A-related tooth agenesis is variable, and some affected individuals may not have obvious symptoms (incomplete penetrance). Intellect and life span are not impacted.

Please note, the c.682T>A (p.Phe228Ile) variant identified in this individual is known to have low penetrance for both the associated autosomal recessive and autosomal dominant conditions. This means that not all individuals with this genetic change will show signs or symptoms of the condition.

Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

Carrier testing for the reproductive partner is recommended.

Due to the potential for personal health risk for this individual associated with this result, follow-up with a medical provider may be warranted.

If your partner tests positive:

The WNT10A gene is associated with conditions that are inherited in both an autosomal recessive and autosomal dominant fashion. In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the WNT10A gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms of the autosomal recessive condition. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition. In autosomal dominant inheritance, an individual with a disease-causing change in one copy of the WNT10A gene is at risk to be affected with autosomal dominant isolated tooth agenesis. When one parent has a change in the WNT10A gene, there is a 50% chance for each child to inherit the change and be at risk to be affected with the autosomal dominant condition.

If your partner tests negative:

[redacted]

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for WNT10A-related conditions. These values are provided only as a guide, are based on the detection rate for the condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the numbers provided apply to the recessive condition(s) associated with the gene.

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
WNT10A-related conditions (AR) NM_025216.2	WNT10A	Pan-ethnic	1 in 305	1 in 30400

Results to note

Pseudodeficiency allele

Benign change, c.1685T>C (p.Ile562Thr), known to be a pseudodeficiency allele, identified in the GALC gene. Pseudodeficiency alleles are not known to be associated with disease, including Krabbe disease.

The presence of a pseudodeficiency allele does not impact this individual's risk to be a carrier. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, including newborn screening; however, pseudodeficiency alleles are not known to cause disease, including Krabbe disease. Carrier testing for the reproductive partner is not indicated.

Variant details

CPS1, Exon 20, c.2446del (p.Cys816Alafs*5), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Cys816Alafs*5) in the CPS1 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in CPS1 are known to be pathogenic (PMID: 21120950).
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with CPS1-related conditions.
- For these reasons, this variant has been classified as Pathogenic.

SMN1, Deletion (Entire coding sequence), heterozygous, 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.

WNT10A, Exon 3, c.682T>A (p.Phe228Ile), heterozygous, Pathogenic (low penetrance)

- This sequence change replaces phenylalanine with isoleucine at codon 228 of the WNT10A protein (p.Phe228Ile). The phenylalanine residue is highly conserved and there is a small physicochemical difference between phenylalanine and isoleucine.
- This variant is present in population databases (rs121908120, ExAC 3.5%), including many homozygous individuals, and has an allele count higher than expected for a pathogenic variant (PMID: 28166811).
- This variant has been observed in many individuals with autosomal recessive forms of ectodermal dysplasia, and has been found in trans (on the opposite chromosome) from many different pathogenic variants (PMID: 19559398, 28976000, 30974434, Invitae). Based on an internal analysis, this variant is associated with reduced penetrance for autosomal recessive disease (15% when in homozygosity and 30-60% when present with another pathogenic variant) compared to other pathogenic or likely pathogenic variants, which have a penetrance of 70-80% (Invitae). In addition, in a large meta-analysis, this variant conferred a 2.25-3.42-fold increased risk (95% CI: 1.39-4.10) for isolated tooth agenesis, the autosomal dominant condition associated with WNT10A (PMID: 29364747). ClinVar contains an entry for this variant (Variation ID: 4462).
- 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, this variant is reported to cause disease. However, because this variant is associated with a lower penetrance form of disease than other pathogenic alleles in the WNT10A gene, and because it is found in homozygosity in healthy individuals, it has been classified as Pathogenic (low penetrance).

Residual risk

This table displays residual risks after a negative result for each of the genes and corresponding disorders. The values provided assume a negative family history and the absence of symptoms for each disorder. For genes associated with both dominant and recessive inheritance, the numbers in this table apply to the recessive condition(s) associated with the gene. Residual risk values are provided for disorders when carrier frequency is greater than 1 in 500. For disorders with carrier frequency equal to, or less than, 1 in 500, residual risk is considered to be reduced substantially. When provided, residual risk values are inferred from published carrier frequencies, and estimated detection rates are based on testing technologies used at Invitae. Residual risks are provided only as a guide for assessing approximate risk given a negative result; values will vary based on the ethnic background of an individual. For individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. For any genes marked with an asterisk*, refer to the Limitations section below for detailed coverage information. In the case of a sample-specific limitation, "N/A" indicates that a residual risk value could not be calculated. AR = autosomal recessive, XL = X-linked, AD = autosomal dominant.

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
3-hydroxy-3-methylglutaryl-CoA lyase deficiency (AR) NM_000191.2	HMGCL	Pan-ethnic	≤1 in 500	Reduced
		Portuguese	1 in 160	1 in 15900
3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency (MCCC1-related) (AR) NM_020166.4	MCCC1	Pan-ethnic	1 in 134	1 in 13300
3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency (MCCC2-related) (AR) NM_022132.4	MCCC2	Pan-ethnic	1 in 134	1 in 13300
ABCB11-related conditions (AR) NM_003742.2	ABCB11	Pan-ethnic	1 in 100	1 in 9900
ABCC8-related conditions (AR) NM_000352.4 When the mother is a noncarrier, but the father is a carrier, there is a residual risk for focal disease (1 in 540 for the Ashkenazi Jewish population; undetermined in other ethnic groups)	ABCC8	Ashkenazi Jewish	1 in 52	1 in 5100
		Finnish	1 in 100	1 in 9900
		Pan-ethnic	1 in 177	1 in 17600
Abetalipoproteinemia (AR) NM_000253.3	MTTP	Ashkenazi Jewish	1 in 131	1 in 13000
		Pan-ethnic	≤1 in 500	Reduced
Achromatopsia (CNGB3-related) (AR) NM_019098.4	CNGB3	Pan-ethnic	1 in 93	1 in 9200
ACOX1-related conditions (AR) NM_004035.6	ACOX1	Pan-ethnic	≤1 in 500	Reduced
Acrodermatitis enteropathica (AR) NM_130849.3	SLC39A4	Pan-ethnic	1 in 354	1 in 35300
Adenosine deaminase deficiency (AR) NM_000022.2	ADA	Pan-ethnic	1 in 224	1 in 2788
Aicardi-Goutieres syndrome 5 (AR) NM_015474.3	SAMHD1	Pan-ethnic	≤1 in 500	Reduced
Aldosterone synthase deficiency (AR) NM_000498.3	CYP11B2	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Iranian)	1 in 30	1 in 2900
Alpha-mannosidosis (AR) NM_000528.3	MAN2B1	Pan-ethnic	1 in 354	1 in 35300
Alpha-thalassemia (AR) NM_000558.4, NM_000517.4	HBA1/ HBA2 *	African-American	1 in 30	1 in 291
		Asian	1 in 20	1 in 191
		Caucasian	≤1 in 500	Reduced
		Pan-ethnic	1 in 25	1 in 241
Alpha-thalassemia X-linked intellectual disability syndrome (XL) NM_000489.4	ATRX	Pan-ethnic	≤1 in 500	Reduced
Alport syndrome (COL4A3-related) (AR) NM_000091.4	COL4A3	Ashkenazi Jewish	1 in 192	1 in 19100
		Caucasian	1 in 284	1 in 28300
		Pan-ethnic	1 in 354	1 in 35300
Alport syndrome (COL4A4-related) (AR) NM_000092.4	COL4A4	Pan-ethnic	1 in 353	1 in 35200

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Alport syndrome (COL4A5-related) (XL) NM_000495.4	COL4A5 *	Pan-ethnic	≤1 in 500	Reduced
Alström syndrome (AR) NM_015120.4	ALMS1	Pan-ethnic	≤1 in 500	Reduced
Argininosuccinate lyase deficiency (AR) NM_000048.3	ASL	Pan-ethnic	1 in 133	1 in 1321
Aromatase deficiency (AR) NM_031226.2	CYP19A1	Pan-ethnic	≤1 in 500	Reduced
Asparagine synthetase deficiency (AR) NM_133436.3	ASNS	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Iranian)	1 in 80	1 in 7900
Aspartylglucosaminuria (AR) NM_000027.3	AGA	Finnish	1 in 69	1 in 6800
		Pan-ethnic	≤1 in 500	Reduced
Ataxia with vitamin E deficiency (AR) NM_000370.3	TTPA	Italian	1 in 274	1 in 2731
		Pan-ethnic	≤1 in 500	Reduced
ATM-related conditions (AR) NM_000051.3	ATM	Pan-ethnic	1 in 100	1 in 9900
		Sephardic Jewish	1 in 69	1 in 6800
ATP7A-related conditions (XL) NM_000052.6	ATP7A	Pan-ethnic	≤1 in 500	Reduced
Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (AR) NM_000383.3	AIRE	Finnish	1 in 79	1 in 7800
		Pan-ethnic	1 in 150	1 in 14900
		Sardinian	1 in 60	1 in 5900
		Sephardic Jewish (Iranian)	1 in 48	1 in 4700
Autosomal recessive congenital ichthyosis (TGM1-related) (AR) NM_000359.2	TGM1	Norwegian	1 in 151	1 in 3000
		Pan-ethnic	1 in 224	1 in 4460
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (AR) NM_014363.5	SACS	French Canadian (Saguenay-Lac-St-Jean)	1 in 21	1 in 2000
		Pan-ethnic	≤1 in 500	Reduced
Bardet-Biedl syndrome (BBS10-related) (AR) NM_024685.3	BBS10	Pan-ethnic	1 in 354	1 in 35300
Bardet-Biedl syndrome (BBS12-related) (AR) NM_152618.2	BBS12	Pan-ethnic	1 in 708	Reduced
BBS1-related conditions (AR) NM_024649.4	BBS1	Faroese	1 in 30	1 in 2900
		Pan-ethnic	1 in 330	1 in 32900
BBS2-related conditions (AR) NM_031885.3	BBS2	Ashkenazi Jewish	1 in 140	1 in 13900
		Pan-ethnic	1 in 560	Reduced
BCS1L-related conditions (AR) NM_004328.4	BCS1L	Caucasian	1 in 407	1 in 40600
		Finnish	1 in 108	1 in 10700
		Pan-ethnic	≤1 in 500	Reduced
Bernard-Soulier syndrome (GP9-related) (AR) NM_000174.4	GP9	Pan-ethnic	≤1 in 500	Reduced
Beta-ketothiolase deficiency (AR) NM_000019.3	ACAT1	Caucasian	1 in 354	1 in 35300
		Pan-ethnic	≤1 in 500	Reduced
Biopterin-deficient hyperphenylalaninemia (PTS-related) (AR) NM_000317.2	PTS	Chinese	1 in 122	1 in 12100
		Pan-ethnic	1 in 433	1 in 43200
Biotinidase deficiency (AR) NM_000060.3	BTD	Pan-ethnic	1 in 125	1 in 12400
Bloom syndrome (AR) NM_000057.3	BLM	Ashkenazi Jewish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
BSND-related conditions (AR) NM_057176.2	BSND	Pan-ethnic	≤1 in 500	Reduced
Canavan disease (AR) NM_000049.2	ASPA	Ashkenazi Jewish	1 in 57	1 in 5600
		Pan-ethnic	1 in 159	1 in 15800
Carnitine palmitoyltransferase I deficiency (AR) NM_001876.3	CPT1A	Hutterite	1 in 16	1 in 1500
		Pan-ethnic	≤1 in 500	Reduced
Carnitine palmitoyltransferase II deficiency (AR) NM_000098.2	CPT2	Ashkenazi Jewish	1 in 45	1 in 4400
		Pan-ethnic	1 in 182	1 in 18100

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Carpenter syndrome (RAB23-related) (AR) NM_183227.2	RAB23	Pan-ethnic	≤1 in 500	Reduced
Cartilage-hair hypoplasia-anauxetic dysplasia spectrum disorders (AR) NR_003051.3	RMRP	Amish	1 in 10	1 in 900
		Finnish	1 in 76	1 in 7500
		Pan-ethnic	≤1 in 500	Reduced
CDH23-related conditions (AR) NM_022124.5	CDH23	Pan-ethnic	1 in 202	1 in 4020
CEP290-related conditions (AR) NM_025114.3	CEP290	Pan-ethnic	1 in 185	1 in 18400
Cerebrotendinous xanthomatosis (AR) NM_000784.3	CYP27A1	Pan-ethnic	1 in 112	1 in 5550
		Sephardic Jewish	1 in 76	1 in 3750
CERKL-related conditions (AR) NM_001030311.2	CERKL	Pan-ethnic	1 in 137	1 in 13600
		Sephardic Jewish	1 in 24	1 in 2300
CFTR-related conditions (AR) NM_000492.3	CFTR	African-American - classic CF	1 in 61	1 in 6000
		Ashkenazi Jewish - classic CF	1 in 29	1 in 2800
		Asian - classic CF	1 in 88	1 in 8700
		Caucasian - classic CF	1 in 28	1 in 2700
		Pan-ethnic - classic CF	1 in 45	1 in 4400
		Pan-ethnic - classic CF and CFTR-related disorders	1 in 9	1 in 800
Charcot-Marie-Tooth disease type 1X (XL) NM_000166.5	GJB1	Pan-ethnic	≤1 in 500	Reduced
Charcot-Marie-Tooth disease type 4D (AR) NM_006096.3	NDRG1	Pan-ethnic	≤1 in 500	Reduced
		Roma	1 in 22	1 in 2100
Chorea-acanthocytosis (AR) NM_033305.2	VPS13A *	Pan-ethnic	≤1 in 500	Reduced
Choroideremia (XL) NM_000390.2	CHM	Pan-ethnic	≤1 in 500	Reduced
Chronic granulomatous disease (CYBA-related) (AR) NM_000101.3	CYBA	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Moroccan)	1 in 13	1 in 1200
Chronic granulomatous disease (CYBB-related) (XL) NM_000397.3	CYBB	Pan-ethnic	≤1 in 500	Reduced
Citrin deficiency (AR) NM_014251.2	SLC25A13	Chinese	1 in 65	1 in 6400
		Japanese	1 in 65	1 in 6400
		Korean	1 in 112	1 in 11100
		Pan-ethnic	1 in 313	1 in 31200
		Southern Chinese and Taiwanese	1 in 48	1 in 4700
Citrullinemia type 1 (AR) NM_000050.4	ASS1	Pan-ethnic	1 in 120	1 in 2975
CLN3-related conditions (AR) NM_001042432.1	CLN3	Pan-ethnic	1 in 230	1 in 22900
CLRN1-related conditions (AR) NM_174878.2	CLRN1	Ashkenazi Jewish	1 in 120	1 in 11900
		Pan-ethnic	1 in 533	Reduced
Cobalamin C deficiency (AR) NM_015506.2	MMACHC	Pan-ethnic	1 in 123	1 in 12200
Cobalamin D deficiency (AR) NM_015702.2	MMADHC *	Pan-ethnic	≤1 in 500	Reduced
Cohen syndrome (AR) NM_017890.4	VPS13B	Amish (Ohio)	1 in 12	1 in 1100
		Pan-ethnic	≤1 in 500	Reduced
Combined malonic and methylmalonic aciduria (AR) NM_174917.4	ACSF3	Pan-ethnic	1 in 87	1 in 8600
Combined oxidative phosphorylation deficiency 1 (AR) NM_024996.5	GFM1	Pan-ethnic	≤1 in 500	Reduced
Combined oxidative phosphorylation deficiency 3 (AR) NM_001172696.1	TSFM *	Finnish	1 in 80	1 in 1129
		Pan-ethnic	≤1 in 500	Reduced
Combined pituitary hormone deficiency (LHX3-related) (AR) NM_014564.4	LHX3	Pan-ethnic	≤1 in 500	Reduced

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Combined pituitary hormone deficiency (PROP1-related) (AR) NM_006261.4	PROP1	Pan-ethnic	1 in 45	1 in 2200
Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase deficiency (AR) NM_000198.3	HSD3B2	Pan-ethnic	≤1 in 500	Reduced
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (AR) NM_000500.7	CYP21A2 *	Pan-ethnic	1 in 61	1 in 751
Congenital disorder of glycosylation (SLC35A3-related) (AR) NM_012243.2	SLC35A3	Ashkenazi Jewish	1 in 469	1 in 46800
		Pan-ethnic	≤1 in 500	Reduced
Congenital disorder of glycosylation type Ia (AR) NM_000303.2	PMM2	Ashkenazi Jewish	1 in 61	1 in 6000
		Caucasian	1 in 60	1 in 5900
		Pan-ethnic	1 in 190	1 in 18900
Congenital disorder of glycosylation type Ib (AR) NM_002435.2	MPI	Pan-ethnic	≤1 in 500	Reduced
Congenital disorder of glycosylation type Ic (AR) NM_013339.3	ALG6 *	Pan-ethnic	≤1 in 500	Reduced
Congenital insensitivity to pain with anhidrosis (AR) NM_001012331.1	NTRK1	Pan-ethnic	≤1 in 500	Reduced
Congenital myasthenic syndrome (CHRNE-related) (AR) NM_000080.3	CHRNE	European Roma	1 in 25	1 in 2400
		Pan-ethnic	1 in 200	1 in 19900
Congenital nephrotic syndrome type 1 (AR) NM_004646.3	NPHS1	Finnish	1 in 46	1 in 4500
		Old Order Mennonite	1 in 12	1 in 1100
		Pan-ethnic	≤1 in 500	Reduced
Congenital nephrotic syndrome type 2 (AR) NM_014625.3	NPHS2	Pan-ethnic	≤1 in 500	Reduced
Corneal dystrophy and perceptive deafness (AR) NM_032034.3	SLC4A11	Pan-ethnic	≤1 in 500	Reduced
CRB1-related conditions (AR) NM_201253.2	CRB1	Pan-ethnic	1 in 112	1 in 11100
CYP17A1-related conditions (AR) NM_000102.3	CYP17A1	Pan-ethnic	≤1 in 500	Reduced
Cystinosis (AR) NM_004937.2	CTNS	French Canadian (Saguenay-Lac-St-Jean)	1 in 39	1 in 3800
		Pan-ethnic	1 in 158	1 in 15700
		Sephardic Jewish (Moroccan)	1 in 100	1 in 9900
DHDDS-related conditions (AR) NM_024887.3	DHDDS	Ashkenazi Jewish	1 in 117	1 in 11600
		Pan-ethnic	≤1 in 500	Reduced
Dihydrolipoamide dehydrogenase deficiency (AR) NM_000108.4	DLD	Ashkenazi Jewish	1 in 107	1 in 5300
		Pan-ethnic	≤1 in 500	Reduced
Distal renal tubular acidosis with deafness (ATP6V1B1-related) (AR) NM_001692.3	ATP6V1B1	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 140	1 in 13900
DMD-related conditions (XL) NM_004006.2	DMD	Pan-ethnic	1 in 667	Reduced
DYSF-related conditions (AR) NM_003494.3	DYSF	Pan-ethnic	1 in 311	1 in 31000
		Sephardic Jewish (Libyan)	1 in 10	1 in 900
Dyskeratosis congenita spectrum disorders (RTEL1-related) (AR) NM_001283009.1	RTEL1	Ashkenazi Jewish	1 in 222	1 in 22100
		Pan-ethnic	≤1 in 500	Reduced
Dystrophic epidermolysis bullosa (AR) NM_000094.3	COL7A1	Pan-ethnic	1 in 370	1 in 12300
EDA-related conditions (XL) NM_001399.4	EDA	Pan-ethnic	≤1 in 500	Reduced
Ehlers-Danlos syndrome, dermatosparaxis type (AR) NM_014244.4	ADAMTS2	Ashkenazi Jewish	1 in 187	1 in 18600
		Pan-ethnic	≤1 in 500	Reduced
Ellis-van Creveld syndrome (EVC-related) (AR) NM_153717.2	EVC	Amish	1 in 8	1 in 700
		Pan-ethnic	1 in 220	1 in 21900

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Emery-Dreifuss muscular dystrophy (EMD-related) (XL) NM_000117.2	EMD	Pan-ethnic	≤1 in 500	Reduced
Ethylmalonic encephalopathy (AR) NM_014297.3	ETHE1	Pan-ethnic	≤1 in 500	Reduced
Fabry disease (XL) NM_000169.2	GLA	Pan-ethnic	≤1 in 500	Reduced
Factor IX deficiency (hemophilia B) (XL) NM_000133.3	F9	Pan-ethnic	≤1 in 500	Reduced
Factor XI deficiency (hemophilia C) (AR) NM_000128.3	F11	Ashkenazi Jewish	1 in 11	1 in 1000
		Pan-ethnic	≤1 in 500	Reduced
Familial chylomicronemia syndrome (AR) NM_000237.2	LPL	French Canadian (Saguenay-Lac-St-Jean)	1 in 46	1 in 4500
		Pan-ethnic	≤1 in 500	Reduced
Familial dysautonomia (AR) NM_003640.3	ELP1	Ashkenazi Jewish	1 in 36	1 in 3500
		Pan-ethnic	≤1 in 500	Reduced
Familial hypercholesterolemia (LDLR-related) (AD) NM_000527.4	LDLR	Afrikaner	1 in 72	1 in 7100
		Ashkenazi Jewish	1 in 69	1 in 6800
		French Canadian	1 in 270	1 in 26900
		Pan-ethnic	1 in 250	1 in 24900
Familial hypercholesterolemia (LDLRAP1-related) (AR) NM_015627.2	LDLRAP1	Pan-ethnic	≤1 in 500	Reduced
		Sardinian	1 in 143	1 in 14200
Familial Mediterranean fever (AR) NM_000243.2	MEFV	Armenian	1 in 8	1 in 71
		Ashkenazi Jewish	1 in 13	1 in 121
		Pan-ethnic	1 in 64	1 in 631
		Sephardic Jewish	1 in 14	1 in 131
		Turkish	1 in 8	1 in 71
Fanconi anemia type A (AR) NM_000135.2	FANCA	Afrikaner	1 in 83	1 in 8200
		Pan-ethnic	1 in 345	1 in 34400
		Sephardic Jewish	1 in 133	1 in 13200
		Spanish Roma	1 in 64	1 in 6300
Fanconi anemia type C (AR) NM_000136.2	FANCC	Ashkenazi Jewish	1 in 89	1 in 8800
		Pan-ethnic	1 in 417	1 in 41600
Fanconi anemia type G (AR) NM_004629.1	FANCG	African-American	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
FH-related conditions (AR) NM_000143.3	FH	Pan-ethnic	≤1 in 500	Reduced
FMR1-related conditions including fragile X syndrome (XL) NM_002024.5 CGG repeats observed: 20	FMR1 *	Ashkenazi Jewish	1 in 58	1 in 5700
		Asian	≤1 in 500	Reduced
		Caucasian	1 in 187	1 in 18600
		Hispanic	≤1 in 500	Reduced
		Pan-ethnic	1 in 259	1 in 25800
Galactokinase deficiency galactosemia (AR) NM_000154.1	GALK1	Pan-ethnic	1 in 122	1 in 12100
		Roma	1 in 47	1 in 4600
Galactosemia (GALT-related) (AR) NM_000155.3	GALT	African-American	1 in 87	1 in 8600
		Ashkenazi Jewish	1 in 156	1 in 15500
		Irish Traveller	1 in 11	1 in 1000
		Pan-ethnic	1 in 100	1 in 9900
GBA-related conditions including Gaucher disease (AR) NM_001005741.2	GBA *	Ashkenazi Jewish	1 in 15	1 in 234
		Pan-ethnic	1 in 158	1 in 561
GBE1-related conditions (AR) NM_000158.3	GBE1	Ashkenazi Jewish	1 in 68	1 in 6700
		Pan-ethnic	1 in 387	1 in 38600
Gitelman syndrome (AR) NM_000339.2	SLC12A3	Pan-ethnic	1 in 100	1 in 9900
GJB2-related conditions (AR) NM_004004.5	GJB2	Ashkenazi Jewish	1 in 13	1 in 1200
		Pan-ethnic	1 in 50	1 in 4900
		Thai	1 in 9	1 in 800

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
GLB1-related conditions (AR) NM_000404.2	GLB1	Pan-ethnic	1 in 158	1 in 15700
		Roma	1 in 50	1 in 4900
		South Brazilian	1 in 58	1 in 5700
GLE1-related conditions (AR) NM_001003722.1	GLE1	Finnish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
Glutaric acidemia type I (AR) NM_000159.3	GCDH	Amish	1 in 9	1 in 800
		Oji-Cree First Nations	1 in 9	1 in 800
		Pan-ethnic	1 in 87	1 in 8600
Glutaric acidemia type IIA (AR) NM_000126.3	ETFA	Pan-ethnic	≤1 in 500	Reduced
Glutaric acidemia type IIC (AR) NM_004453.3	ETFDH	Asian	1 in 87	1 in 8600
		Pan-ethnic	1 in 250	1 in 24900
Glycine encephalopathy (AMT-related) (AR) NM_000481.3	AMT	Finnish	1 in 142	1 in 14100
		Pan-ethnic	1 in 325	1 in 32400
Glycine encephalopathy (GLDC-related) (AR) NM_000170.2	GLDC	Caucasian	1 in 141	1 in 14000
		Pan-ethnic	1 in 165	1 in 16400
Glycogen storage disease type Ia (AR) NM_000151.3	G6PC	Ashkenazi Jewish	1 in 71	1 in 1400
		Pan-ethnic	1 in 177	1 in 3520
Glycogen storage disease type Ib (AR) NM_001164277.1	SLC37A4	Pan-ethnic	1 in 354	1 in 7060
Glycogen storage disease type II (Pompe disease) (AR) NM_000152.3	GAA	African-American	1 in 60	1 in 5900
		Ashkenazi Jewish	1 in 58	1 in 5700
		Asian	1 in 112	1 in 11100
		Pan-ethnic	1 in 100	1 in 9900
Glycogen storage disease type III (AR) NM_000642.2	AGL	Faroese	1 in 28	1 in 540
		Pan-ethnic	1 in 159	1 in 3160
		Sephardic Jewish (Moroccan)	1 in 34	1 in 660
Glycogen storage disease type V (AR) NM_005609.3	PYGM	Caucasian	1 in 158	1 in 15700
		Pan-ethnic	1 in 171	1 in 17000
		Sephardic Jewish (Kurdish)	1 in 84	1 in 8300
Glycogen storage disease type VII (AR) NM_000289.5	PFKM	Ashkenazi Jewish	1 in 250	1 in 24900
		Pan-ethnic	≤1 in 500	Reduced
GNE-related conditions (AR) NM_001128227.2	GNE	Pan-ethnic	1 in 179	1 in 17800
		Sephardic Jewish (Iranian)	1 in 10	1 in 900
GNPTAB-related conditions (AR) NM_024312.4	GNPTAB	Irish Traveller	1 in 15	1 in 1400
		Pan-ethnic	1 in 200	1 in 19900
GP1BA-related conditions (AR) NM_000173.6	GP1BA *	Pan-ethnic	≤1 in 500	Reduced
Guanidinoacetate methyltransferase deficiency (AR) NM_000156.5	GAMT	Pan-ethnic	≤1 in 500	Reduced
		Portuguese	1 in 125	1 in 12400
Gyrate atrophy of the choroid and retina (AR) NM_000274.3	OAT *	Finnish	1 in 126	1 in 12500
		Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 177	1 in 17600
HADHA-related conditions (AR) NM_000182.4	HADHA	Caucasian	1 in 250	1 in 24900
		Finnish	1 in 125	1 in 12400
		Pan-ethnic	1 in 350	1 in 34900
HBB-related hemoglobinopathies (AR) NM_000518.4	HBB	African-American	1 in 8	1 in 700
		Asian	1 in 54	1 in 5300
		Caucasian	1 in 373	1 in 37200
		Hispanic	1 in 17	1 in 1600
		Mediterranean	1 in 28	1 in 2700
		Pan-ethnic	1 in 49	1 in 4800
Hereditary fructose intolerance (AR) NM_000035.3	ALDOB	African-American	1 in 226	1 in 22500
		Middle Eastern	1 in 97	1 in 9600
		Pan-ethnic	1 in 122	1 in 12100

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Hereditary hemochromatosis type 2 (HJV-related) (AR) NM_213653.3	HJV	Pan-ethnic	≤1 in 500	Reduced
Hereditary hemochromatosis type 3 (AR) NM_003227.3	TFR2	Pan-ethnic	≤1 in 500	Reduced
Hermansky-Pudlak syndrome type 1 (AR) NM_000195.4	HPS1	Pan-ethnic	≤1 in 500	Reduced
		Puerto Rican (Northwestern)	1 in 21	1 in 2000
Hermansky-Pudlak syndrome type 3 (AR) NM_032383.4	HPS3	Ashkenazi Jewish	1 in 235	1 in 23400
		Pan-ethnic	≤1 in 500	Reduced
		Puerto Rican (Central)	1 in 63	1 in 6200
HGSNAT-related conditions (AR) NM_152419.2	HGSNAT	Pan-ethnic	≤1 in 500	Reduced
Holocarboxylase synthetase deficiency (AR) NM_000411.6	HLCS	Faroese	1 in 20	1 in 1900
		Japanese	1 in 158	1 in 15700
		Pan-ethnic	1 in 224	1 in 22300
Homocystinuria due to cobalamin E deficiency (AR) NM_002454.2	MTRR	Pan-ethnic	≤1 in 500	Reduced
Homocystinuria due to cystathionine beta-synthase deficiency (AR) NM_000071.2	CBS	Norwegian	1 in 40	1 in 3900
		Pan-ethnic	1 in 224	1 in 22300
		Qatari	1 in 21	1 in 2000
Homocystinuria due to MTHFR deficiency (AR) NM_005957.4	MTHFR *	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Bukharian)	1 in 39	1 in 3800
HSD17B4-related conditions (AR) NM_000414.3	HSD17B4	Pan-ethnic	1 in 158	1 in 15700
Hydrolethalus syndrome type 1 (AR) NM_145014.2	HYLS1	Finnish	1 in 40	1 in 3900
		Pan-ethnic	≤1 in 500	Reduced
Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (AR) NM_014252.3	SLC25A15	Metis (Saskatchewan)	1 in 19	1 in 1800
		Pan-ethnic	≤1 in 500	Reduced
Hypophosphatasia (AR) NM_000478.5	ALPL	Mennonite	1 in 25	1 in 480
		Pan-ethnic	1 in 150	1 in 2980
Isovaleric acidemia (AR) NM_002225.3	IVD	Pan-ethnic	1 in 250	1 in 24900
Joubert syndrome and related disorders (MKS1-related) (AR) NM_017777.3	MKS1	Finnish	1 in 47	1 in 920
		Pan-ethnic	1 in 260	1 in 5180
Joubert syndrome and related disorders (RPGRIP1L-related) (AR) NM_015272.2	RPGRIP1L *	Pan-ethnic	1 in 259	1 in 5160
Joubert syndrome and related disorders (TMEM216-related) (AR) NM_001173990.2	TMEM216	Ashkenazi Jewish	1 in 92	1 in 9100
		Pan-ethnic	≤1 in 500	Reduced
Junctional epidermolysis bullosa (LAMC2-related) (AR) NM_005562.2	LAMC2	Pan-ethnic	≤1 in 500	Reduced
KCNJ11-related conditions (AR) NM_000525.3	KCNJ11	Pan-ethnic	≤1 in 500	Reduced
Krabbe disease (AR) NM_000153.3	GALC *	Druze	1 in 6	1 in 500
		Pan-ethnic	1 in 158	1 in 15700
LAMA3-related conditions (AR) NM_000227.4	LAMA3	Pan-ethnic	≤1 in 500	Reduced
LAMB3-related conditions (AR) NM_000228.2	LAMB3	Pan-ethnic	1 in 317	1 in 31600
Leber congenital amaurosis 5 (AR) NM_181714.3	LCA5	Pan-ethnic	1 in 645	Reduced
Leber congenital amaurosis 13 (AR) NM_152443.2	RDH12	Pan-ethnic	1 in 460	1 in 45900
Leukoencephalopathy with vanishing white matter (EIF2B5-related) (AR) NM_003907.2	EIF2B5	Pan-ethnic	≤1 in 500	Reduced
Limb-girdle muscular dystrophy (CAPN3-related) (AR) NM_000070.2	CAPN3	Pan-ethnic	1 in 134	1 in 13300

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Limb-girdle muscular dystrophy type 2C (AR) NM_000231.2	SGCG	Caucasian	1 in 571	Reduced
		Japanese	1 in 374	1 in 37300
		Moroccan	1 in 250	1 in 24900
		Pan-ethnic	≤1 in 500	Reduced
		Roma	1 in 59	1 in 5800
Limb-girdle muscular dystrophy type 2D (AR) NM_000023.2	SGCA	Caucasian	1 in 286	1 in 28500
		Finnish	1 in 150	1 in 14900
		Pan-ethnic	≤1 in 500	Reduced
Limb-girdle muscular dystrophy type 2E (AR) NM_000232.4	SGCB	Caucasian	1 in 404	1 in 5038
		Pan-ethnic	≤1 in 500	Reduced
Lipoid congenital adrenal hyperplasia (AR) NM_000349.2	STAR	Korean	1 in 170	1 in 16900
		Pan-ethnic	≤1 in 500	Reduced
Lysinuric protein intolerance (AR) NM_001126106.2	SLC7A7	Finnish	1 in 120	1 in 2380
		Japanese	1 in 120	1 in 2380
		Pan-ethnic	≤1 in 500	Reduced
Lysosomal acid lipase deficiency (AR) NM_000235.3	LIPA	Caucasian	1 in 112	1 in 1850
		Pan-ethnic	1 in 359	1 in 5967
		Sephardic Jewish (Iranian)	1 in 33	1 in 534
Major histocompatibility complex class II deficiency (CIITA-related) (AR) NM_000246.3	CIITA	Pan-ethnic	≤1 in 500	Reduced
Maple syrup urine disease type 1A (AR) NM_000709.3	BCKDHA	Mennonite	1 in 10	1 in 900
		Pan-ethnic	1 in 373	1 in 37200
Maple syrup urine disease type 1B (AR) NM_183050.2	BCKDHB	Ashkenazi Jewish	1 in 97	1 in 9600
		Pan-ethnic	1 in 346	1 in 34500
Medium-chain acyl-CoA dehydrogenase deficiency (AR) NM_000016.5	ACADM	Northern European	1 in 40	1 in 3900
		Pan-ethnic	1 in 66	1 in 6500
Megalencephalic leukoencephalopathy with subcortical cysts 1 (AR) NM_015166.3	MLC1	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Libyan)	1 in 40	1 in 3900
Metachromatic leukodystrophy (ARSA-related) (AR) NM_000487.5	ARSA	Navajo	1 in 40	1 in 780
		Pan-ethnic	1 in 100	1 in 1980
		Sephardic Jewish	1 in 46	1 in 900
Methylmalonic acidemia (MMAA-related) (AR) NM_172250.2	MMAA	Pan-ethnic	1 in 316	1 in 10500
Methylmalonic acidemia (MMAB-related) (AR) NM_052845.3	MMAB	Pan-ethnic	1 in 456	1 in 22750
Methylmalonic acidemia (MUT-related) (AR) NM_000255.3	MUT	Pan-ethnic	1 in 204	1 in 5075
MFSD8-related conditions (AR) NM_152778.2	MFSD8	Pan-ethnic	≤1 in 500	Reduced
Microcephaly, postnatal progressive, with seizures and brain atrophy (AR) NM_004268.4	MED17	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 20	1 in 1900
Mitochondrial complex I deficiency 9 (AR) NM_004553.4	NDUFS6	Ashkenazi Jewish	1 in 290	1 in 28900
		Caucasus Jewish	1 in 24	1 in 2300
		Pan-ethnic	≤1 in 500	Reduced
Mitochondrial complex I deficiency 16 (AR) NM_024120.4	NDUFAF5	Ashkenazi Jewish	1 in 290	1 in 28900
		Pan-ethnic	≤1 in 500	Reduced
Mitochondrial complex I deficiency 20/ACAD9 deficiency (AR) NM_014049.4	ACAD9	Pan-ethnic	≤1 in 500	Reduced
Mitochondrial complex IV deficiency / Leigh syndrome, French Canadian type (AR) NM_133259.3	LRPPRC	French Canadian (Saguenay-Lac-St-Jean)	1 in 23	1 in 2200
		Pan-ethnic	≤1 in 500	Reduced
Mitochondrial DNA depletion syndrome-6 (AR) NM_002437.4	MPV17	Navajo	1 in 20	1 in 475
		Pan-ethnic	≤1 in 500	Reduced

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Mitochondrial neurogastrointestinal encephalomyopathy (AR) NM_001953.4	TYMP	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 158	1 in 15700
MPL-related conditions (AR) NM_005373.2	MPL	Ashkenazi Jewish	1 in 57	1 in 5600
		Pan-ethnic	≤1 in 500	Reduced
Mucolipidosis type III gamma (AR) NM_032520.4	GNPTG	Pan-ethnic	≤1 in 500	Reduced
Mucolipidosis type IV (AR) NM_020533.2	MCOLN1	Ashkenazi Jewish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type I (AR) NM_000203.4	IDUA	Pan-ethnic	1 in 148	1 in 4900
Mucopolysaccharidosis type II (XL) NM_000202.6	IDS *	Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type IIIA (AR) NM_000199.3	SGSH	Northern European	1 in 173	1 in 17200
		Pan-ethnic	1 in 215	1 in 21400
		Taiwanese	≤1 in 500	Reduced
Mucopolysaccharidosis type IIIB (AR) NM_000263.3	NAGLU	Pan-ethnic	1 in 224	1 in 22300
Mucopolysaccharidosis type IIID (AR) NM_002076.3	GNS	Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type IX (AR) NM_153281.1	HYAL1	Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type VI (AR) NM_000046.3	ARSB	Pan-ethnic	1 in 250	1 in 24900
Multiple sulfatase deficiency (AR) NM_182760.3	SUMF1	Pan-ethnic	≤1 in 500	Reduced
Muscular dystrophy-dystroglycanopathy (FKRP-related) (AR) NM_024301.4	FKRP	Norwegian	1 in 116	1 in 11500
		Pan-ethnic	1 in 158	1 in 15700
Muscular dystrophy-dystroglycanopathy (FKTN-related) (AR) NM_001079802.1	FKTN	Ashkenazi Jewish	1 in 80	1 in 7900
		Japanese	1 in 188	1 in 18700
		Pan-ethnic	≤1 in 500	Reduced
MYO7A-related conditions (AR) NM_000260.3	MYO7A	Pan-ethnic	1 in 200	1 in 3980
Myopathy, lactic acidosis, and sideroblastic anemia 1 (AR) NM_025215.5	PUS1	Pan-ethnic	≤1 in 500	Reduced
N-acetylglutamate synthase deficiency (AR) NM_153006.2	NAGS	Pan-ethnic	≤1 in 500	Reduced
NBN-related conditions (AR) NM_002485.4	NBN *	Eastern European	1 in 155	1 in 15400
		Pan-ethnic	≤1 in 500	Reduced
Nemaline myopathy 2 (AR) NM_001271208.1	NEB *	Ashkenazi Jewish	1 in 108	1 in 10700
		Pan-ethnic	1 in 158	1 in 3140
Nephrogenic diabetes insipidus (AQP2-related) (AR) NM_000486.5	AQP2	Pan-ethnic	1 in 1118	Reduced
Neuronal ceroid lipofuscinosis type 1 (AR) NM_000310.3	PPT1	Finnish	1 in 70	1 in 3450
		Pan-ethnic	1 in 199	1 in 9900
Neuronal ceroid lipofuscinosis type 2 (AR) NM_000391.3	TPP1	Newfoundland	1 in 53	1 in 1734
		Pan-ethnic	1 in 250	1 in 8300
Neuronal ceroid lipofuscinosis type 5 (AR) NM_006493.2	CLN5	Finnish	1 in 115	1 in 11400
		Pan-ethnic	≤1 in 500	Reduced
Neuronal ceroid lipofuscinosis type 6 (AR) NM_017882.2	CLN6	Pan-ethnic	≤1 in 500	Reduced
Neuronal ceroid lipofuscinosis type 8 (AR) NM_018941.3	CLN8	Finnish	1 in 135	1 in 13400
		Pan-ethnic	≤1 in 500	Reduced
Niemann-Pick disease type C (NPC1-related) (AR) NM_000271.4	NPC1	Pan-ethnic	1 in 183	1 in 18200
Niemann-Pick disease type C (NPC2-related) (AR) NM_006432.3	NPC2	Pan-ethnic	1 in 871	Reduced

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Niemann-Pick disease types A and B (AR) NM_000543.4	SMPD1	Ashkenazi Jewish	1 in 90	1 in 1780
		Pan-ethnic	1 in 250	1 in 4980
Nonsyndromic deafness 77 (AR) NM_144612.6	LOXHD1	Ashkenazi Jewish	1 in 180	1 in 17900
		Pan-ethnic	≤1 in 500	Reduced
NR2E3-related conditions (AR) NM_014249.3	NR2E3	Pan-ethnic	≤1 in 500	Reduced
OPA3-related conditions (AR) NM_025136.3	OPA3	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Iraqi)	1 in 10	1 in 900
Ornithine transcarbamylase deficiency (XL) NM_000531.5	OTC	Pan-ethnic	≤1 in 500	Reduced
Osteopetrosis (TCIRG1-related) (AR) NM_006019.3	TCIRG1	Ashkenazi Jewish	1 in 350	1 in 34900
		Chuvash	1 in 30	1 in 2900
		Pan-ethnic	1 in 317	1 in 31600
PCDH15-related conditions (AR) NM_033056.3	PCDH15	Ashkenazi Jewish	1 in 78	1 in 7700
		Pan-ethnic	1 in 400	1 in 39900
PEX7-related conditions (AR) NM_000288.3	PEX7	Pan-ethnic	1 in 157	1 in 15600
Phenylalanine hydroxylase deficiency (AR) NM_000277.1	PAH	African-American	1 in 111	1 in 11000
		Ashkenazi Jewish	1 in 225	1 in 22400
		East Asian	1 in 50	1 in 1225
		Finnish	1 in 225	1 in 22400
		Irish	1 in 33	1 in 3200
		Japanese	1 in 200	1 in 19900
		Pan-ethnic	1 in 58	1 in 5700
		Turkish	1 in 26	1 in 2500
Phosphoglycerate dehydrogenase deficiency (AR) NM_006623.3	PHGDH	Ashkenazi Jewish	1 in 400	1 in 39900
		Pan-ethnic	≤1 in 500	Reduced
Polycystic kidney disease (PKHD1-related) (AR) NM_138694.3	PKHD1	Pan-ethnic	1 in 70	1 in 6900
Polymicrogyria (ADGRG1-related) (AR) NM_005682.6	ADGRG1	Pan-ethnic	≤1 in 500	Reduced
POMGNT1-related conditions (AR) NM_017739.3	POMGNT1	Finnish	1 in 111	1 in 11000
		Pan-ethnic	≤1 in 500	Reduced
Pontocerebellar hypoplasia type 2D (AR) NM_016955.3	SEPSECS	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Moroccan and Iraqi)	1 in 43	1 in 4200
Pontocerebellar hypoplasia type 6 (AR) NM_020320.3	RARS2	Pan-ethnic	≤1 in 500	Reduced
Primary carnitine deficiency (AR) NM_003060.3	SLC22A5	Faroese	1 in 9	1 in 800
		Japanese	1 in 100	1 in 9900
		Pan-ethnic	1 in 71	1 in 7000
Primary ciliary dyskinesia (DNAH5-related) (AR) NM_001369.2	DNAH5	Pan-ethnic	1 in 109	1 in 10800
Primary ciliary dyskinesia (DNAI1-related) (AR) NM_012144.3	DNAI1	Pan-ethnic	1 in 250	1 in 24900
Primary ciliary dyskinesia (DNAI2-related) (AR) NM_023036.4	DNAI2	Ashkenazi Jewish	1 in 200	1 in 19900
		Pan-ethnic	1 in 354	1 in 35300
Primary hyperoxaluria type 1 (AR) NM_000030.2	AGXT	Pan-ethnic	1 in 135	1 in 13400
Primary hyperoxaluria type 2 (AR) NM_012203.1	GRHPR	Pan-ethnic	≤1 in 500	Reduced
Primary hyperoxaluria type 3 (AR) NM_138413.3	HOGA1	Pan-ethnic	1 in 354	1 in 35300
Propionic acidemia (PCCA-related) (AR) NM_000282.3	PCCA	Arab	1 in 100	1 in 2475
		Pan-ethnic	1 in 224	1 in 5575
Propionic acidemia (PCCB-related) (AR) NM_000532.4	PCCB	Arab	1 in 100	1 in 9900
		Greenlandic Inuit	1 in 20	1 in 1900
		Pan-ethnic	1 in 224	1 in 22300

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
PRPS1-related conditions (XL) NM_002764.3	PRPS1	Pan-ethnic	≤1 in 500	Reduced
PSAP-related conditions (AR) NM_002778.3	PSAP	Pan-ethnic	≤1 in 500	Reduced
Pycnodysostosis (AR) NM_000396.3	CTSK	Pan-ethnic	1 in 438	1 in 43700
Pyruvate dehydrogenase complex deficiency (PDHA1-related) (XL) NM_000284.3	PDHA1	Pan-ethnic	≤1 in 500	Reduced
Pyruvate dehydrogenase complex deficiency (PDHB-related) (AR) NM_000925.3	PDHB	Pan-ethnic	≤1 in 500	Reduced
RAPSN-related conditions (AR) NM_005055.4	RAPSN	Pan-ethnic	1 in 283	1 in 28200
Retinitis pigmentosa 25 (AR) NM_001142800.1	EYS	Pan-ethnic	1 in 129	1 in 12800
		Sephardic Jewish	1 in 42	1 in 4100
Retinitis pigmentosa 28 (AR) NM_001201543.1	FAM161A	Ashkenazi Jewish	1 in 214	1 in 21300
		Pan-ethnic	1 in 289	1 in 28800
		Sephardic Jewish	1 in 41	1 in 4000
Rhizomelic chondrodysplasia punctata type 3 (AR) NM_003659.3	AGPS	Pan-ethnic	≤1 in 500	Reduced
Roberts syndrome (AR) NM_001017420.2	ESCO2	Pan-ethnic	≤1 in 500	Reduced
RPE65-related conditions (AR) NM_000329.2	RPE65	Pan-ethnic	1 in 228	1 in 22700
		Sephardic Jewish	1 in 90	1 in 8900
Sandhoff disease (AR) NM_000521.3	HEXB	Metis (Saskatchewan)	1 in 15	1 in 1400
		Pan-ethnic	1 in 180	1 in 17900
Schimke immuno-osseous dysplasia (AR) NM_014140.3	SMARCAL1	Pan-ethnic	≤1 in 500	Reduced
Severe combined immunodeficiency due to DCLRE1C (Artemis) deficiency (AR) NM_001033855.2	DCLRE1C	Navajo and Apache	1 in 10	1 in 900
		Pan-ethnic	≤1 in 500	Reduced
Severe combined immunodeficiency due to RAG2 deficiency (AR) NM_000536.3	RAG2	Pan-ethnic	≤1 in 500	Reduced
Severe congenital neutropenia due to HAX1 deficiency (AR) NM_006118.3	HAX1	Pan-ethnic	≤1 in 500	Reduced
Severe congenital neutropenia due to VPS45 deficiency (AR) NM_007259.4	VPS45	Pan-ethnic	≤1 in 500	Reduced
Sialic acid storage diseases (AR) NM_012434.4	SLC17A5	Finnish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
Sjögren-Larsson syndrome (AR) NM_000382.2	ALDH3A2	Pan-ethnic	≤1 in 500	Reduced
		Swedish	1 in 250	1 in 24900
SLC12A6-related conditions (AR) NM_133647.1	SLC12A6	French Canadian (Saguenay-Lac-St-Jean)	1 in 23	1 in 2200
		Pan-ethnic	≤1 in 500	Reduced
SLC26A2-related conditions (AR) NM_000112.3	SLC26A2	Finnish	1 in 75	1 in 1480
		Pan-ethnic	1 in 158	1 in 3140
SLC26A4-related conditions (AR) NM_000441.1	SLC26A4	Asian	1 in 74	1 in 7300
		Pan-ethnic	1 in 80	1 in 7900
Smith-Lemli-Opitz syndrome (AR) NM_001360.2	DHCR7	African-American	1 in 339	1 in 33800
		Ashkenazi Jewish	1 in 41	1 in 4000
		Hispanic	1 in 135	1 in 13400
		Northern European	1 in 50	1 in 4900
		Pan-ethnic	1 in 71	1 in 7000
		Sephardic Jewish	1 in 68	1 in 6700
		Southern European	1 in 83	1 in 8200

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Spastic paraplegia type 49 (AR) NM_014844.3	TECPR2	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish - Bukharian	1 in 38	1 in 3700
Spondylocostal dysostosis (AR) NM_001039958.1	MESP2	Pan-ethnic	1 in 224	1 in 22300
		Puerto Rican	1 in 55	1 in 5400
Steel syndrome (AR) NM_032888.3	COL27A1 *	Pan-ethnic	≤1 in 500	Reduced
		Puerto Rican	1 in 51	1 in 5000
Stüve-Wiedemann syndrome (AR) NM_002310.5	LIFR	Pan-ethnic	≤1 in 500	Reduced
Tay-Sachs disease (AR) NM_000520.4	HEXA	Ashkenazi Jewish	1 in 27	1 in 2600
		Asian	1 in 126	1 in 12500
		Caucasian	1 in 182	1 in 18100
		French Canadian	1 in 27	1 in 2600
		Irish	1 in 41	1 in 4000
		Pan-ethnic	1 in 250	1 in 24900
		Sephardic Jewish	1 in 125	1 in 12400
Transient infantile liver failure (AR) NM_018006.4	TRMU	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Yemenite)	1 in 34	1 in 3300
Tyrosine hydroxylase deficiency (AR) NM_199292.2	TH	Caucasian	1 in 224	1 in 22300
		Pan-ethnic	≤1 in 500	Reduced
Tyrosinemia type I (AR) NM_000137.2	FAH *	Ashkenazi Jewish	1 in 143	1 in 2840
		French Canadian	1 in 66	1 in 1300
		French Canadian (Saguenay-Lac-St-Jean)	1 in 16	1 in 300
		Pan-ethnic	1 in 125	1 in 2480
USH1C-related conditions (AR) NM_005709.3	USH1C *	French Canadian/Acadian	1 in 227	1 in 22600
		Pan-ethnic	1 in 353	1 in 3521
		Sephardic Jewish	1 in 125	1 in 1241
USH2A-related conditions (AR) NM_206933.2	USH2A	Caucasian	1 in 70	1 in 6900
		Pan-ethnic	1 in 112	1 in 11100
		Sephardic Jewish	1 in 36	1 in 3500
Very long-chain acyl-CoA dehydrogenase deficiency (AR) NM_000018.3	ACADVL	Pan-ethnic	1 in 100	1 in 9900
VRK1-related conditions (AR) NM_003384.2	VRK1	Ashkenazi Jewish	1 in 225	1 in 22400
		Pan-ethnic	≤1 in 500	Reduced
VSX2-related conditions (AR) NM_182894.2	VSX2	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 145	1 in 14400
Wilson disease (AR) NM_000053.3	ATP7B	Ashkenazi Jewish	1 in 67	1 in 3300
		Canary Islander	1 in 25	1 in 1200
		Pan-ethnic	1 in 90	1 in 4450
		Sardinian	1 in 50	1 in 2450
		Sephardic Jewish	1 in 65	1 in 3200
X-linked adrenoleukodystrophy (XL) NM_000033.3	ABCD1	Pan-ethnic	1 in 16800	Reduced
		Sephardic Jewish	≤1 in 500	Reduced
X-linked creatine transporter deficiency (XL) NM_005629.3	SLC6A8	Pan-ethnic	≤1 in 500	Reduced
X-linked juvenile retinoschisis (XL) NM_000330.3	RS1	Pan-ethnic	≤1 in 500	Reduced
X-linked myotubular myopathy (XL) NM_000252.2	MTM1	Pan-ethnic	≤1 in 500	Reduced
X-linked severe combined immunodeficiency (XL) NM_000206.2	IL2RG	Pan-ethnic	≤1 in 500	Reduced
Zellweger spectrum disorder (PEX1-related) (AR) NM_000466.2	PEX1	Pan-ethnic	1 in 144	1 in 14300
Zellweger spectrum disorder (PEX2-related) (AR) NM_000318.2	PEX2	Ashkenazi Jewish	1 in 227	1 in 22600
		Pan-ethnic	≤1 in 500	Reduced
Zellweger spectrum disorder (PEX6-related) (AR) NM_000287.3	PEX6	French Canadian	1 in 55	1 in 5400
		Pan-ethnic	1 in 294	1 in 29300

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
		Sephardic Jewish	1 in 18	1 in 1700
Zellweger spectrum disorder (PEX10-related) (AR) NM_153818.1	PEX10	Pan-ethnic	1 in 606	Reduced

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 10bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Invitae utilizes a classification methodology to identify next-generation sequencing (NGS)-detected variants that require orthogonal confirmation (Lincoln, et al. J Mol Diagn. 2019 Mar;21(2):318-329.). Pathogenic and Likely Pathogenic variants that do not meet the validated quality thresholds are confirmed. Confirmation technologies may 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 GBA and CYP21A2, the reference genome has been modified to mask the sites of polymorphic paralog sequence variants (PSVs) in both the gene and pseudogene. If one or more reportable variants is identified (see Limitations), the gene is amplified by long-range PCR; PacBio sequencing of the long-range amplicons is used to confirm the variant. Gene conversion and fusion events are flagged by our NGS pipeline and reportable pseudogene-derived variants are identified by long-range PCR followed by PacBio sequencing of the long-range amplicons. In some cases, it may not be possible to disambiguate between the gene and pseudogene. For HBA1/2, the reference genome has been modified to force some sequencing reads derived from HBA1 to align to HBA2, and variant calling algorithms are modified to support an expectation of 4 alleles in these regions. HBA1/2 copy number calling is performed by a custom hypothesis testing algorithm which generates diplotype calls. If sequence data for a sample does not support a unique high confidence match from among hypotheses tested, that sample is flagged for manual review. Copy number variation is only reported for coding sequence of HBA1 and HBA2 and the HS-40 region. This assay does not distinguish among the -α3.7 subtypes, and all -α3.7 variants are called as HBA1 deletions. This assay may not detect overlapping copy gain and copy loss events when the breakpoints of those events are similar. For FMR1, triplet repeats are detected by PCR with fluorescently labeled primers followed by capillary electrophoresis. Reference ranges: Normal: <45 CGG repeats, intermediate: 45-54 CGG repeats, premutation: 55-200 CGG repeats, full mutation: >200 CGG repeats. For alleles with 55-90 triplet repeats, the region surrounding the FMR1 repeat is amplified by PCR. The PCR amplicons are then processed through PacBio SMRTBell library prep and sequenced using PacBio long read technology. The number of AGG interruptions within the 55-90 triplet repeat is read directly from the resulting DNA sequences. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).
- The following transcripts were used in this analysis. 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: ABCB11 (NM_003742.2), ABCC8 (NM_000352.4), ABCD1 (NM_000033.3), ACAD9 (NM_014049.4), ACADM (NM_000016.5), ACADVL (NM_000018.3), ACAT1 (NM_000019.3), ACOX1 (NM_004035.6), ACSF3 (NM_174917.4), ADA (NM_000022.2), ADAMTS2 (NM_014244.4), ADGRG1 (NM_005682.6), AGA (NM_000027.3), AGL (NM_000642.2), AGPS (NM_003659.3), AGXT (NM_000030.2), AIRE (NM_000383.3), ALDH3A2 (NM_000382.2), ALDOB (NM_000035.3), ALG6 (NM_013339.3), ALMS1 (NM_015120.4), ALPL (NM_000478.5), AMT (NM_000481.3), AQP2 (NM_000486.5), ARSA (NM_000487.5), ARSB (NM_000046.3), ASL (NM_000048.3), ASNS (NM_133436.3), ASPA (NM_000049.2), ASS1 (NM_000050.4), ATM (NM_000051.3), ATP6V1B1 (NM_001692.3), ATP7A (NM_000052.6), ATP7B (NM_000053.3), ATRX (NM_000489.4), BBS1 (NM_024649.4), BBS10 (NM_024685.3), BBS12 (NM_152618.2), BBS2 (NM_031885.3), BCKDHA (NM_000709.3), BCKDHB (NM_183050.2), BCS1L (NM_004328.4), BLM (NM_000057.3), BSND (NM_057176.2), BTD (NM_000060.3), CAPN3 (NM_000070.2), CBS (NM_000071.2), CDH23 (NM_022124.5), CEP290 (NM_025114.3), CERKL (NM_001030311.2), CFTR (NM_000492.3), CHM (NM_000390.2), CHRNE (NM_000080.3), CIITA (NM_000246.3), CLN3 (NM_001042432.1), CLN5 (NM_006493.2), CLN6 (NM_017882.2), CLN8 (NM_018941.3), CLRN1 (NM_174878.2), CNGB3 (NM_019098.4), COL27A1 (NM_032888.3), COL4A3 (NM_000091.4), COL4A4 (NM_000092.4), COL4A5 (NM_000495.4), COL7A1 (NM_000094.3), CPS1 (NM_001875.4),

CPT1A (NM_001876.3), CPT2 (NM_000098.2), CRB1 (NM_201253.2), CTNS (NM_004937.2), CTSK (NM_000396.3), CYBA (NM_000101.3), CYBB (NM_000397.3), CYP11B2 (NM_000498.3), CYP17A1 (NM_000102.3), CYP19A1 (NM_031226.2), CYP21A2 (NM_000500.7), CYP27A1 (NM_000784.3), DCLRE1C (NM_001033855.2), DHCR7 (NM_001360.2), DHDDS (NM_024887.3), DLD (NM_000108.4), DMD (NM_004006.2), DNAH5 (NM_001369.2), DNAI1 (NM_012144.3), DNAI2 (NM_023036.4), DYSF (NM_003494.3), EDA (NM_001399.4), EIF2B5 (NM_003907.2), ELP1 (NM_003640.3), EMD (NM_000117.2), ESCO2 (NM_001017420.2), ETFA (NM_000126.3), ETFDH (NM_004453.3), ETHE1 (NM_014297.3), EVC (NM_153717.2), EYS (NM_001142800.1), F11 (NM_000128.3), F9 (NM_000133.3), FAH (NM_000137.2), FAM161A (NM_001201543.1), FANCA (NM_000135.2), FANCC (NM_000136.2), FANCG (NM_004629.1), FH (NM_000143.3), FKRP (NM_024301.4), FKTN (NM_001079802.1), FMR1 (NM_002024.5), G6PC (NM_000151.3), GAA (NM_000152.3), GALC (NM_000153.3), GALK1 (NM_000154.1), GALT (NM_000155.3), GAMT (NM_000156.5), GBA (NM_001005741.2), GBE1 (NM_000158.3), GCDH (NM_000159.3), GFM1 (NM_024996.5), GJB1 (NM_000166.5), GJB2 (NM_004004.5), GLA (NM_000169.2), GLB1 (NM_000404.2), GLDC (NM_000170.2), GLE1 (NM_001003722.1), GNE (NM_001128227.2), GNPTAB (NM_024312.4), GNPTG (NM_032520.4), GNS (NM_002076.3), GP1BA (NM_000173.6), GP9 (NM_000174.4), GRHPR (NM_012203.1), HADHA (NM_000182.4), HAX1 (NM_006118.3), HBA1 (NM_000558.4), HBA2 (NM_000517.4), HBB (NM_000518.4), HEXA (NM_000520.4), HEXB (NM_000521.3), HGSNAT (NM_152419.2), HJV (NM_213653.3), HLCS (NM_000411.6), HMGCL (NM_000191.2), HOGA1 (NM_138413.3), HPS1 (NM_000195.4), HPS3 (NM_032383.4), HSD17B4 (NM_000414.3), HSD3B2 (NM_000198.3), HYAL1 (NM_153281.1), HYLS1 (NM_145014.2), IDS (NM_000202.6), IDUA (NM_000203.4), IL2RG (NM_000206.2), IVD (NM_002225.3), KCNJ11 (NM_000525.3), LAMA3 (NM_000227.4), LAMB3 (NM_000228.2), LAMC2 (NM_005562.2), LCA5 (NM_181714.3), LDLR (NM_000527.4), LDLRAP1 (NM_015627.2), LHX3 (NM_014564.4), LIFR (NM_002310.5), LIPA (NM_000235.3), LOXHD1 (NM_144612.6), LPL (NM_000237.2), LRPPRC (NM_133259.3), MAN2B1 (NM_000528.3), MCCC1 (NM_020166.4), MCCC2 (NM_022132.4), MCOLN1 (NM_020533.2), MED17 (NM_004268.4), MEFV (NM_000243.2), MESP2 (NM_001039958.1), MFSD8 (NM_152778.2), MKS1 (NM_017777.3), MLC1 (NM_015166.3), MMAA (NM_172250.2), MMAB (NM_052845.3), MMACHC (NM_015506.2), MMADHC (NM_015702.2), MPI (NM_002435.2), MPL (NM_005373.2), MPV17 (NM_002437.4), MTHFR (NM_005957.4), MTM1 (NM_000252.2), MTRR (NM_002454.2), MTTP (NM_000253.3), MUT (NM_000255.3), MYO7A (NM_000260.3), NAGLU (NM_000263.3), NAGS (NM_153006.2), NBN (NM_002485.4), NDRG1 (NM_006096.3), NDUFAF5 (NM_024120.4), NDUFS6 (NM_004553.4), NEB (NM_001271208.1), NPC1 (NM_000271.4), NPC2 (NM_006432.3), NPHS1 (NM_004646.3), NPHS2 (NM_014625.3), NR2E3 (NM_014249.3), NTRK1 (NM_001012331.1), OAT (NM_000274.3), OPA3 (NM_025136.3), OTC (NM_000531.5), PAH (NM_000277.1), PCCA (NM_000282.3), PCCB (NM_000532.4), PCDH15 (NM_033056.3), PDHA1 (NM_000284.3), PDHB (NM_000925.3), PEX1 (NM_000466.2), PEX10 (NM_153818.1), PEX2 (NM_000318.2), PEX6 (NM_000287.3), PEX7 (NM_000288.3), PFKM (NM_000289.5), PHGDH (NM_006623.3), PKHD1 (NM_138694.3), PMM2 (NM_000303.2), POMGNT1 (NM_017739.3), PPT1 (NM_000310.3), PROP1 (NM_006261.4), PRPS1 (NM_002764.3), PSAP (NM_002778.3), PTS (NM_000317.2), PUS1 (NM_025215.5), PYGM (NM_005609.3), RAB23 (NM_183227.2), RAG2 (NM_000536.3), RAPSN (NM_005055.4), RARS2 (NM_020320.3), RDH12 (NM_152443.2), RMRP (NR_003051.3), RPE65 (NM_000329.2), RPGRIP1L (NM_015272.2), RS1 (NM_000330.3), RTEL1 (NM_001283009.1), SACS (NM_014363.5), SAMHD1 (NM_015474.3), SEPSECS (NM_016955.3), SGCA (NM_000023.2), SGCB (NM_000232.4), SGCG (NM_000231.2), SGSH (NM_000199.3), SLC12A3 (NM_000339.2), SLC12A6 (NM_133647.1), SLC17A5 (NM_012434.4), SLC22A5 (NM_003060.3), SLC25A13 (NM_014251.2), SLC25A15 (NM_014252.3), SLC26A2 (NM_000112.3), SLC26A4 (NM_000441.1), SLC35A3 (NM_012243.2), SLC37A4 (NM_001164277.1), SLC39A4 (NM_130849.3), SLC4A11 (NM_032034.3), SLC6A8 (NM_005629.3), SLC7A7 (NM_001126106.2), SMARCAL1 (NM_014140.3), SMN1 (NM_000344.3), SMPD1 (NM_000543.4), STAR (NM_000349.2), SUMF1 (NM_182760.3), TCIRG1 (NM_006019.3), TECPR2 (NM_014844.3), TFR2 (NM_003227.3), TGM1 (NM_000359.2), TH (NM_199292.2), TMEM216 (NM_001173990.2), TPP1 (NM_000391.3), TRMU (NM_018006.4), TSFM (NM_001172696.1), TTPA (NM_000370.3), TYMP (NM_001953.4), USH1C (NM_005709.3), USH2A (NM_206933.2), VPS13A (NM_033305.2), VPS13B (NM_017890.4), VPS45 (NM_007259.4), VRK1 (NM_003384.2), VSX2 (NM_182894.2), WNT10A (NM_025216.2).

- Variants of uncertain significance are not included in this report; however, if additional evidence becomes available to indicate that a previously uncertain variant is clinically significant, Invitae will update this report and provide notification.
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (http://exac.broadinstitute.org) and dbSNP (http://ncbi.nlm.nih.gov/SNP).

Disclaimer

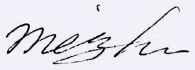
DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan,

but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

Limitations

- Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. 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.
- FMR1: Sizing accuracy is expected to be +/-1 for CGG repeat alleles less than or equal to 90 repeat units and +/-3 for CGG repeat alleles greater than 90 repeat units. If the two CGG repeats listed are the same, this may indicate that both alleles are the same size or that one allele is too small to be detected by this analysis. The number of AGG interruptions is only determined for females with triplet repeat sizes of 55-90. ALG6: Deletion/duplication analysis is not offered for exons 11-12. IDS: Detection of complex rearrangements not offered (PMID: 7633410, 20301451). 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. RPGRIP1L: Sequencing analysis is not offered for exon 23. TSFM: Sequencing analysis is not offered for exon 5. COL4A5: Deletion/duplication analysis is not offered for exons 11-12. MMADHC: Deletion/duplication analysis is not offered for exons 5-6. USH1C: Deletion/duplication analysis is not offered for exons 5-6. CYP21A2: Analysis includes the most common variants (c.92C>T(p.Pro31Leu), c.293-13C>G (intronic), c.332_339delGAGACTAC (p.Gly111Valfs*21), c.518T>A (p.Ile173Asn), c.710T>A (p.Ile237Asn), c.713T>A (p.Val238Glu), c.719T>A (p.Met240Lys), c.844G>T (p.Val282Leu), c.923dupT (p.Leu308Phefs*6), c.955C>T (p.Gln319*), c.1069C>T(p.Arg357Trp), c.1360C>T (p.Pro454Ser) and the 30Kb deletion) as well as select rare HGMD variants only (list available upon request). Full gene duplications are reported only in the presence of a pathogenic variant(s). When a duplication and a pathogenic variant(s) is identified, phase (cis/trans) cannot be determined. Full gene deletion analysis is not offered. Sensitivity to detect these variants, if they result from complex gene conversion/fusion events, may be reduced. GP1BA: c.104delA (p.Lys35Argfs*4), c.165_168delTGAG (p.Ser55Argfs*12), c.376A>G (p.Asn126Asp), c.434T>C (p.Leu145Pro), c.515C>T (p.Ala172Val), c.584_586delTCC (p.Leu195del), c.673T>A (p.Cys225Ser), c.1454dupT (p.Ser486Ilefs*12), c.1480delA (p.Thr494Profs*59), c.1601_1602delAT (p.Tyr534Cysfs*82), c.1620G>A (p.Trp540*) variants only. NBN: Deletion/duplication analysis is not offered for exons 15-16. OAT: Deletion/duplication analysis is not offered for exon 2. GBA: c.84dupG (p.Leu29Alafs*18), c.115+1G>A (Splice donor), c.222_224delTAC (p.Thr75del), c.475C>T (p.Arg159Trp), c.595_596delCT (p.Leu199Aspfs*62), c.680A>G (p.Asn227Ser), c.721G>A (p.Gly241Arg), c.754T>A (p.Phe252Ile), c.1226A>G (p.Asn409Ser), c.1246G>A (p.Gly416Ser), c.1263_1317del (p.Leu422Profs*4), c.1297G>T (p.Val433Leu), c.1342G>C (p.Asp448His), c.1343A>T (p.Asp448Val), c.1448T>C (p.Leu483Pro), c.1504C>T (p.Arg502Cys), c.1505G>A (p.Arg502His), c.1603C>T (p.Arg535Cys), c.1604G>A (p.Arg535His) variants only. Sensitivity to detect these variants if they result from complex gene conversion events may be reduced. HBA2: Sequencing analysis is not offered for exons 1-2. HBA1/2: This assay is designed to detect deletions and duplications of HBA1 and/or HBA2, resulting from the -alpha20.5, --MED, --SEA, --FIL/--THAI, -alpha3.7, -alpha4.2, anti3.7 and anti4.2. Sensitivity to detect other copy number variants may be reduced. Detection of overlapping deletion and duplication events will be limited to combinations of events with significantly differing boundaries. In addition, deletion of the enhancer element HS-40 and the sequence variant, Constant Spring (NM_000517.4:c.427T>C), can be identified by this assay. COL27A1: Deletion/duplication analysis is not offered for exons 46-47. FAH: Deletion/duplication analysis is not offered for exon 14. GALC: Deletion/duplication analysis is not offered for exon 6. 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. SMN1 or SMN2: NM_000344.3:c.*3+80T>G variant only. SMN1: Systematic exon numbering is used for all genes, including SMN1, and for this reason the exon typically referred to as exon 7 in the literature (PMID: 8838816) is referred to as exon 8 in this report. This assay unambiguously detects SMN1 exon 8 copy number. The presence of the g.27134T>G variant (also known as c.*3+80T>G) is reported if SMN1 copy number = 2. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28.

This report has been reviewed and approved by:



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