INVITAE

# INVITAE CARRIER SCREEN RESULTS

| | | | | | |
|---|---|---|---|---|---|
| **Patient name:** | [redacted] | **Sample type:** | Blood | **Report date:** | 15-SEP-2022 |
| **DOB:** | [redacted] | **Sample collection date:** | 19-AUG-2022 | **Invitae #:** | [redacted] |
| **Sex assigned at birth:** | Male | **Sample accession date:** | 25-AUG-2022 | **Clinical team:** | Valerie Shaikly |
| **Gender:** | Man | | | | |
| **Patient ID (MRN):** | BFA 0164 | | | | |

**Reason for testing**

Gamete donor

**Test performed**

Invitae Carrier Screen

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

## RESULT: POSITIVE

This carrier test evaluated 175 gene(s) for genetic changes (variants) that are associated with an increased risk of having a child with a genetic condition. Knowledge of carrier status for one of these conditions may provide information that can be used to assist with family planning and/or preparation. Carrier screening is not intended for diagnostic purposes. To identify a potential genetic basis for a condition in the individual being tested, diagnostic testing for the gene(s) of interest is recommended.

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

| RESULTS | GENE | VARIANT(S) | INHERITANCE | PARTNER TESTING RECOMMENDED |
|---|---|---|---|---|
| **Carrier:** Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia | AIRE | c.967_979del (p.Leu323Serfs*51) | Autosomal recessive | Yes |
| **Carrier:** Limb-girdle muscular dystrophy type 2D | SGCA | c.518T>C (p.Leu173Pro) | Autosomal recessive | Yes |

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## Next steps

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

## Clinical summary

### RESULT: CARRIER

# Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia

A single Pathogenic variant, c.967_979del (p.Leu323Serfs*51), was identified in AIRE.

**What is autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia?**

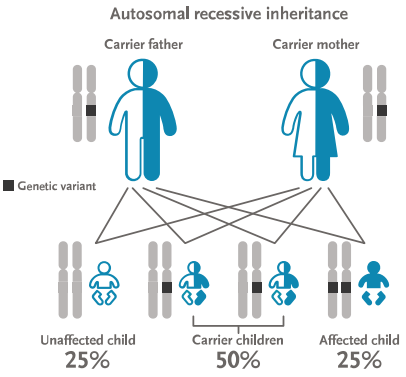
Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (APECED) is a condition that can be inherited in an autosomal recessive or autosomal dominant manner. To understand which condition a genetic change is associated with, a review of the entire report, including the variant details section, is recommended.

Please note that the AIRE variant identified in this individual is expected to be associated with autosomal recessive autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia.

APECED is an autoimmune disease. An autoimmune condition is one in which the immune system attacks the body's own tissues and organs. One characteristic symptom of APECED is chronic fungal infections of the skin and mucous membranes (mucocutaneous candidiasis) which frequently present in infancy. Other characteristic symptoms include decreased secretion or activity of the parathyroid hormone (hypoparathyroidism) and shortage of various adrenal hormones (adrenocortical insufficiency). Both of these often present in childhood. Additional common features include premature ovarian insufficiency, reduced number of red blood cells due to insufficient vitamin B12 (pernicious anemia), loss of skin color in patches (vitiligo), hair loss (alopecia), thin enamel weakening the surface of the teeth (enamel hypoplasia), and inflammation of the cornea of the eye (keratitis). Symptoms and severity of APECED are highly variable. Prognosis depends on the severity of symptoms. Individuals with autosomal dominant APECED, which is caused by a single pathogenic AIRE variant, typically have later onset and milder symptoms or may show no obvious symptoms (reduced penetrance) compared to individuals with autosomal recessive APECED. 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 AIRE 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 autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia. 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 |
|---|---|---|---|---|
| Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (AR)<br>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 |

## RESULT: CARRIER

# Limb-girdle muscular dystrophy type 2D

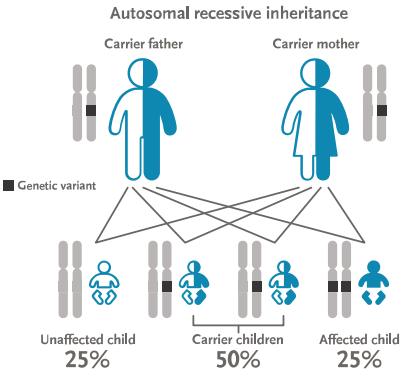
A single Pathogenic variant, c.518T>C (p.Leu173Pro), was identified in SGCA.

### What is limb-girdle muscular dystrophy type 2D?

Limb-girdle muscular dystrophy (LGMD) refers to a group of conditions that cause muscle weakness primarily in the arm and leg muscles that are closest to the body (proximal muscles). LGMDs can be caused by changes in several different genes. Several forms of LMGD type 2, including LGMD2C, 2D, 2E, and 2F (also known as LGMDR5, R3, R4, and R6 respectively), are collectively referred to as sarcoglycanopathies. The sarcoglycanopathies are characterized by proximal muscle weakness and loss of muscle mass (atrophy) that begins in childhood. This results in difficulty walking and frequent falls, enlarged calves (calf hypertrophy), protrusion of the shoulder blades (scapular winging), excess inward curvature of the lower spine (lumbar lordosis), joint deformities (contractures), and elevated serum creatine kinase levels. Affected individuals typically also have breathing difficulties and/or heart problems such as abnormal heart rhythm (arrhythmia) or weakened heart muscles (cardiomyopathy) in later stages of the condition. While the symptoms of sarcoglycanopathies are typically severe and worsen over time, milder cases with only minimal muscle weakness and slower disease progression have been reported. Symptoms and severity can vary, even between family members with the same genetic change. Certain genetic forms of LGMD may be associated with specific muscle biopsy findings. 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 SGCA 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 limb-girdle muscular dystrophy type 2D. 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 |
|---|---|---|---|---|
| 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 |

## Results to note

### FMR1

- Normal triplet repeats observed: 30

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

### SMN1

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

### Pseudodeficiency allele(s)

- Benign change, c.*96A>G (Non-coding), known to be a pseudodeficiency allele, identified in the ARSA gene. Pseudodeficiency alleles are not known to be associated with disease, including metachromatic leukodystrophy (ARSA-related).
- Benign change, c.1021C>T (p.Arg341Trp), known to be a pseudodeficiency allele, identified in the FAH gene. Pseudodeficiency alleles are not known to be associated with disease, including tyrosinemia type I.
- 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, even when there are two copies of the variant (homozygous) or when in combination with another disease-causing variant (compound heterozygous). Carrier testing for the reproductive partner is not indicated based on this result.

## Variant details

AIRE, Exon 8, c.967_979del (p.Leu323Serfs*51), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Leu323Serfs*51) in the AIRE gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in AIRE are known to be pathogenic (PMID: 11524731, 26141571).
- This variant is present in population databases (rs779937061, gnomAD 0.09%).
- This premature translational stop signal has been observed in individual(s) with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) and is the most common variant found in affected individuals of British or Anglo-American ancestry (PMID: 9837820, 11524731, 27588307). It has also been observed to segregate with disease in related individuals.
- This variant is also known as c.964del13, c.967_979del13, p.C322del13, or c.1094_1106del.
- ClinVar contains an entry for this variant (Variation ID: 3309).
- For these reasons, this variant has been classified as Pathogenic.

SGCA, Exon 5, c.518T>C (p.Leu173Pro), heterozygous, PATHOGENIC

- This sequence change replaces leucine, which is neutral and non-polar, with proline, which is neutral and non-polar, at codon 173 of the SGCA protein (p.Leu173Pro).
- This variant is present in population databases (rs143962150, gnomAD 0.1%).
- This missense change has been observed in individual(s) with sarcoglycanopathy (PMID: 9032047, 18285821; Invitae). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant.
- ClinVar contains an entry for this variant (Variation ID: 281027).

- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is expected to disrupt SGCA protein function.
- For these reasons, this variant has been classified as Pathogenic.

## 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, unless otherwise noted. 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)<br>NM_000191.2 | HMGCL | Pan-ethnic | ≤1 in 500 | Reduced |
| | | Portuguese | 1 in 160 | 1 in 15900 |
| ABCC8-related conditions (AR)<br>NM_000352.4<br>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 |
| Adenosine deaminase deficiency (AR)<br>NM_000022.2 | ADA | Pan-ethnic | 1 in 224 | 1 in 2788 |
| Alpha-mannosidosis (AR)<br>NM_000528.3 | MAN2B1 | Pan-ethnic | 1 in 354 | 1 in 35300 |
| Alpha-thalassemia (AR)<br>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 |
| Alport syndrome (COL4A3-related) (AR)<br>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)<br>NM_000092.4 | COL4A4 | Pan-ethnic | 1 in 353 | 1 in 35200 |
| Alport syndrome (COL4A5-related) (XL)<br>NM_000495.4 | COL4A5 * | Pan-ethnic | ≤1 in 500 | Reduced |
| Alström syndrome (AR)<br>NM_015120.4 | ALMS1 | Pan-ethnic | ≤1 in 500 | Reduced |
| Arginase deficiency (AR)<br>NM_000045.3 | ARG1 | Pan-ethnic | 1 in 274 | 1 in 27300 |
| Argininosuccinate lyase deficiency (AR)<br>NM_000048.3 | ASL | Pan-ethnic | 1 in 133 | 1 in 1321 |
| Aspartylglucosaminuria (AR)<br>NM_000027.3 | AGA | Finnish | 1 in 69 | 1 in 6800 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |
| Ataxia with vitamin E deficiency (AR)<br>NM_000370.3 | TTPA | Italian | 1 in 274 | 1 in 2731 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |
| ATM-related conditions (AR)<br>NM_000051.3 | ATM | Pan-ethnic | 1 in 100 | 1 in 9900 |
| | | Sephardic Jewish | 1 in 69 | 1 in 6800 |
| ATP7A-related conditions (XL)<br>NM_000052.6 | ATP7A | Pan-ethnic | ≤1 in 500 | Reduced |
| Autosomal recessive congenital ichthyosis (TGM1-related) (AR)<br>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)<br>NM_014363.5 | SACS | French Canadian (Saguenay-Lac-St-Jean) | 1 in 21 | 1 in 2000 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| 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 |
| 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 |
| Canavan disease (AR) NM_000049.2 | ASPA | Ashkenazi Jewish | 1 in 57 | 1 in 5600 |
| | | Pan-ethnic | 1 in 159 | 1 in 15800 |
| Carbamoyl phosphate synthetase I deficiency (AR) NM_001875.4 | CPS1 | Pan-ethnic | ≤1 in 500 | Reduced |
| 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 |
| 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 |
| Cerebrotendinous xanthomatosis (AR) NM_000784.3 | CYP27A1 | Pan-ethnic | 1 in 112 | 1 in 5550 |
| | | Sephardic Jewish | 1 in 76 | 1 in 3750 |
| 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 |
| Citrullinemia type 1 (AR) NM_000050.4 | ASS1 * | Pan-ethnic | 1 in 120 | N/A |
| 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 |
| Cockayne syndrome A (AR) NM_000082.3 | ERCC8 | Pan-ethnic | 1 in 514 | Reduced |
| Cockayne syndrome B (AR) NM_000124.3 | ERCC6 | Pan-ethnic | 1 in 377 | 1 in 37600 |
| Cohen syndrome (AR) NM_017890.4 | VPS13B | Amish (Ohio) | 1 in 12 | 1 in 1100 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |
| Combined pituitary hormone deficiency (PROP1-related) (AR) NM_006261.4 | PROP1 | Pan-ethnic | 1 in 45 | 1 in 2200 |
| Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (AR) NM_000500.7 | CYP21A2 * | Pan-ethnic | 1 in 61 | 1 in 751 |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| 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 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 |
| CYP11B1-related conditions (AR) NM_000497.3 | CYP11B1 | Pan-ethnic | 1 in 194 | 1 in 19300 |
| | | Sephardic Jewish (Moroccan) | 1 in 40 | 1 in 3900 |
| 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 |
| Dihydrolipoamide dehydrogenase deficiency (AR) NM_000108.4 | DLD | Ashkenazi Jewish | 1 in 107 | 1 in 5300 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |
| 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 |
| 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 |
| EVC2-related conditions (AR) NM_147127.4 | EVC2 | Pan-ethnic | 1 in 199 | 1 in 19800 |
| Fabry disease (XL) NM_000169.2 | GLA | 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 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 |
| FMR1-related conditions including fragile X syndrome (XL) NM_002024.5 | 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 |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| 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 |
| 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 |
| 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 |
| 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 |
| 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 | N/A |
| | | Pan-ethnic | 1 in 165 | N/A |
| 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 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 |
| 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 |
| 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 |
| 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 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 |
| 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 |
| 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 |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| 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 (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 |
| LAMA2-related muscular dystrophy (AR) NM_000426.3 | LAMA2 | Pan-ethnic | 1 in 87 | 1 in 8600 |
| 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 |
| Limb-girdle muscular dystrophy (CAPN3-related) (AR) NM_000070.2 | CAPN3 | Pan-ethnic | 1 in 134 | 1 in 13300 |
| 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 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 |
| 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 |
| 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 |
| Maple syrup urine disease type 2 (AR) NM_001918.3 | DBT | Pan-ethnic | ≤1 in 500 | Reduced |
| 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 |
| 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 |
| 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 |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| Mucopolysaccharidosis type I (AR)<br>NM_000203.4 | IDUA | Pan-ethnic | 1 in 148 | 1 in 4900 |
| Mucopolysaccharidosis type II (XL)<br>NM_000202.6 | IDS * | Pan-ethnic | ≤1 in 500 | Reduced |
| Mucopolysaccharidosis type IIIA (AR)<br>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)<br>NM_000263.3 | NAGLU | Pan-ethnic | 1 in 224 | 1 in 22300 |
| Muscular dystrophy-dystroglycanopathy (FKRP-related) (AR)<br>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)<br>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)<br>NM_000260.3 | MYO7A | Pan-ethnic | 1 in 200 | 1 in 3980 |
| Nemaline myopathy 2 (AR)<br>NM_001271208.1 | NEB * | Ashkenazi Jewish | 1 in 108 | 1 in 10700 |
| | | Pan-ethnic | 1 in 158 | 1 in 3140 |
| Neuronal ceroid lipofuscinosis type 1 (AR)<br>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)<br>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)<br>NM_006493.2 | CLN5 | Finnish | 1 in 115 | 1 in 11400 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |
| Neuronal ceroid lipofuscinosis type 6 (AR)<br>NM_017882.2 | CLN6 | Pan-ethnic | ≤1 in 500 | Reduced |
| Neuronal ceroid lipofuscinosis type 8 (AR)<br>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)<br>NM_000271.4 | NPC1 | Pan-ethnic | 1 in 183 | 1 in 18200 |
| Niemann-Pick disease type C (NPC2-related) (AR)<br>NM_006432.3 | NPC2 | Pan-ethnic | 1 in 871 | Reduced |
| Niemann-Pick disease types A and B (AR)<br>NM_000543.4 | SMPD1 | Ashkenazi Jewish | 1 in 90 | 1 in 1780 |
| | | Pan-ethnic | 1 in 250 | 1 in 4980 |
| Nijmegen breakage syndrome (AR)<br>NM_002485.4 | NBN * | Eastern European | 1 in 155 | 1 in 15400 |
| | | Pan-ethnic | ≤1 in 500 | Reduced |
| OPA3-related conditions (AR)<br>NM_025136.3 | OPA3 | Pan-ethnic | ≤1 in 500 | Reduced |
| | | Sephardic Jewish (Iraqi) | 1 in 10 | 1 in 900 |
| Ornithine transcarbamylase deficiency (XL)<br>NM_000531.5 | OTC | Pan-ethnic | ≤1 in 500 | Reduced |
| Osteopetrosis (TCIRG1-related) (AR)<br>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)<br>NM_033056.3 | PCDH15 | Ashkenazi Jewish | 1 in 78 | 1 in 7700 |
| | | Pan-ethnic | 1 in 400 | 1 in 39900 |
| PEX7-related conditions (AR)<br>NM_000288.3 | PEX7 | Pan-ethnic | 1 in 157 | 1 in 15600 |
| Phenylalanine hydroxylase deficiency (AR)<br>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 |
| Polycystic kidney disease (PKHD1-related) (AR)<br>NM_138694.3 | PKHD1 | Pan-ethnic | 1 in 70 | 1 in 6900 |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| POMGNT1-related conditions (AR) NM_017739.3 | POMGNT1 | Finnish | 1 in 111 | 1 in 11000 |
| | | 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 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 |
| Pycnodysostosis (AR) NM_000396.3 | CTSK | Pan-ethnic | 1 in 438 | 1 in 43700 |
| Pyruvate carboxylase deficiency (AR) NM_000920.3 | PC | Algonquian Indian | 1 in 10 | 1 in 180 |
| | | Pan-ethnic | 1 in 250 | 1 in 4980 |
| Roberts syndrome (AR) NM_001017420.2 | ESCO2 | Pan-ethnic | ≤1 in 500 | Reduced |
| Sandhoff disease (AR) NM_000521.3 | HEXB | Metis (Saskatchewan) | 1 in 15 | 1 in 1400 |
| | | Pan-ethnic | 1 in 180 | 1 in 17900 |
| 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 |
| SLC37A4-related conditions (AR) NM_001164277.1 | SLC37A4 | Pan-ethnic | 1 in 354 | 1 in 7060 |
| 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 |
| Spastic paraplegia type 15 (AR) NM_015346.3 | ZFYVE26 | Pan-ethnic | ≤1 in 500 | Reduced |
| Spinal muscular atrophy (AR) NM_000344.3 Carrier residual risks listed are for 2 copy SMN1 results. Carrier residual risk for >2 copies are 5- to 10-fold lower. | 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 |
| Spondylocostal dysostosis (MESP2-related) (AR) NM_001039958.1 | MESP2 | Pan-ethnic | 1 in 224 | 1 in 22300 |
| | | Puerto Rican | 1 in 55 | 1 in 5400 |
| 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 |

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| | | 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 |
| 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 |
| Tyrosinemia type II (AR) NM_000353.2 | TAT | Pan-ethnic | 1 in 250 | 1 in 24900 |
| 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 |
| 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 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 |
| Xeroderma pigmentosum complementation group A (AR) NM_000380.3 | XPA | Japanese | 1 in 100 | 1 in 9900 |
| | | Pan-ethnic | 1 in 1667 | Reduced |
| Xeroderma pigmentosum complementation group C (AR) NM_004628.4 | XPC | Pan-ethnic | 1 in 763 | Reduced |
| | | Tunisian | 1 in 50 | 1 in 4900 |
| 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 |
| | | Sephardic Jewish | 1 in 18 | 1 in 1700 |
| Zellweger spectrum disorder (PEX10-related) (AR) NM_153818.1 | PEX10 | Pan-ethnic | 1 in 606 | Reduced |
| Zellweger spectrum disorder (PEX12-related) (AR) NM_000286.2 | PEX12 | Pan-ethnic | 1 in 409 | 1 in 40800 |

## 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.). Confirmation of the presence and location of reportable variants is performed based on stringent criteria established by Invitae (1400 16th Street, San Francisco, CA 94103, #05D2040778), as needed, using one of several validated orthogonal approaches (PubMed ID 30610921). The following analyses are performed if relevant to the requisition. For GBA the reference genome has been modified to mask the sites of polymorphic paralog sequence variants (PSVs) in both the gene and pseudogene. For CYP21A2 and GBA, if one or more reportable variants, gene conversion, or fusion event is identified via our NGS pipeline (see Limitations), these variants are confirmed by PacBio sequencing of an amplicon generated by long-range PCR and subsequent short-range PCR. In some cases, it may not be possible to disambiguate between the gene and pseudogene. For 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: ABCC8 (NM_000352.4), ABCD1 (NM_000033.3), ACADM (NM_000016.5), ACADVL (NM_000018.3), ADA (NM_000022.2), AGA (NM_000027.3), AGL (NM_000642.2), 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), ARG1 (NM_000045.3), ARSA (NM_000487.5), ASL (NM_000048.3), ASPA (NM_000049.2), ASS1 (NM_000050.4), ATM (NM_000051.3), ATP7A (NM_000052.6), ATP7B (NM_000053.3), 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), BTD (NM_000060.3), CAPN3 (NM_000070.2), CBS (NM_000071.2), CFTR (NM_000492.3), CLN3 (NM_001042432.1), CLN5 (NM_006493.2), CLN6 (NM_017882.2), CLN8 (NM_018941.3), CLRN1 (NM_174878.2), COL4A3 (NM_000091.4), COL4A4 (NM_000092.4), COL4A5 (NM_000495.4), CPS1 (NM_001875.4), CPT1A (NM_001876.3), CPT2 (NM_000098.2), CTNS (NM_004937.2), CTSK (NM_000396.3), CYP11B1 (NM_000497.3), CYP21A2 (NM_000500.7), CYP27A1 (NM_000784.3), DBT (NM_001918.3), DHCR7 (NM_001360.2), DLD (NM_000108.4), DMD (NM_004006.2), DYSF (NM_003494.3), ELP1 (NM_003640.3), ERCC6 (NM_000124.3), ERCC8 (NM_000082.3), ESCO2 (NM_001017420.2), EVC (NM_153717.2), EVC2 (NM_147127.4), FAH (NM_000137.2), FANCA (NM_000135.2), FANCC (NM_000136.2), 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), GBA (NM_001005741.2), GCDH (NM_000159.3), GJB2 (NM_004004.5), GLA (NM_000169.2), GLB1 (NM_000404.2), GLDC (NM_000170.2), GNE (NM_001128227.2), GNPTAB (NM_024312.4), GNPTG (NM_032520.4), GRHPR (NM_012203.1), HADHA (NM_000182.4), HBA1 (NM_000558.4), HBA2 (NM_000517.4), HBB (NM_000518.4), HEXA (NM_000520.4), HEXB (NM_000521.3), HGSNAT (NM_152419.2), HLCS (NM_000411.6), HMGCL (NM_000191.2), HOGA1 (NM_138413.3), HSD17B4 (NM_000414.3), HYLS1 (NM_145014.2), IDS (NM_000202.6), IDUA (NM_000203.4), IL2RG (NM_000206.2), IVD (NM_002225.3), KCNJ11 (NM_000525.3), LAMA2 (NM_000426.3), LAMA3 (NM_000227.4), LAMB3 (NM_000228.2), LAMC2 (NM_005562.2), LIPA (NM_000235.3), LRPPRC (NM_133259.3), MAN2B1 (NM_000528.3), MCOLN1 (NM_020533.2), MEFV (NM_000243.2), MESP2 (NM_001039958.1), MKS1 (NM_017777.3), MLC1 (NM_015166.3), MMAA (NM_172250.2), MMAB (NM_052845.3), MMACHC (NM_015506.2), MPI (NM_002435.2), MTM1 (NM_000252.2), MUT (NM_000255.3), MYO7A (NM_000260.3), NAGLU (NM_000263.3), NBN (NM_002485.4), NEB (NM_001271208.1), NPC1 (NM_000271.4), NPC2 (NM_006432.3), NPHS1 (NM_004646.3), NPHS2 (NM_014625.3), OPA3 (NM_025136.3), OTC (NM_000531.5), PAH (NM_000277.1), PC (NM_000920.3), PCCA (NM_000282.3), PCCB (NM_000532.4), PCDH15 (NM_033056.3), PEX1 (NM_000466.2), PEX10 (NM_153818.1), PEX12 (NM_000286.2), PEX2 (NM_000318.2), PEX6 (NM_000287.3), PEX7 (NM_000288.3), PKHD1 (NM_138694.3), PMM2 (NM_000303.2), POMGNT1 (NM_017739.3), PPT1 (NM_000310.3), PROP1 (NM_006261.4), PTS (NM_000317.2), RMRP (NR_003051.3), RS1 (NM_000330.3), RTEL1 (NM_001283009.1),

SACS (NM_014363.5), SGCA (NM_000023.2), SGCB (NM_000232.4), SGCG (NM_000231.2), SGSH (NM_000199.3), SLC12A6 (NM_133647.1), SLC17A5 (NM_012434.4), SLC22A5 (NM_003060.3), SLC26A2 (NM_000112.3), SLC26A4 (NM_000441.1), SLC37A4 (NM_001164277.1), SMN1 (NM_000344.3), SMPD1 (NM_000543.4), STAR (NM_000349.2), TAT (NM_000353.2), TCIRG1 (NM_006019.3), TGM1 (NM_000359.2), TH (NM_199292.2), TMEM216 (NM_001173990.2), TPP1 (NM_000391.3), TTPA (NM_000370.3), USH1C (NM_005709.3), USH2A (NM_206933.2), VPS13B (NM_017890.4), XPA (NM_000380.3), XPC (NM_004628.4), ZFYVE26 (NM_015346.3).

- This report only includes variants that have a clinically significant association with the conditions tested as of the report date. Variants of uncertain significance, benign variants, and likely benign variants are not included in this report. However, if additional evidence becomes available to indicate that the clinical significance of a variant has changed, Invitae may update this report and provide notification.
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at **http://www.ncbi.nlm.nih.gov/pubmed**.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (**http://exac.broadinstitute.org**) 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. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination.
- FMR1: 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. GBA: c.84dupG (p.Leu29Alafs*18), c.115+1G>A (Splice donor), c.222_224delTAC (p.Thr75del), c.475C>T (p.Arg159Trp), c.595_596delCT (p.Leu199Aspfs*62), c.680A>G (p.Asn227Ser), c.721G>A (p.Gly241Arg), c.754T>A (p.Phe252Ile), c.1226A>G (p.Asn409Ser), c.1246G>A (p.Gly416Ser), c.1263_1317del (p.Leu422Profs*4), c.1297G>T (p.Val433Leu), c.1342G>C (p.Asp448His), c.1343A>T (p.Asp448Val), c.1448T>C (p.Leu483Pro), c.1504C>T (p.Arg502Cys), c.1505G>A (p.Arg502His), c.1603C>T (p.Arg535Cys), c.1604G>A (p.Arg535His) variants only. Rarely, sensitivity to detect these variants may be reduced. When sensitivity is reduced, zygosity may be reported as "unknown". IDS: Detection of complex rearrangements not offered (PMID: 7633410, 20301451). SMN1: Systematic exon numbering is used for all genes, including SMN1, and for this reason the exon typically referred to as exon 7 in the literature (PMID: 8838816) is referred to as exon 8 in this report. This assay unambiguously detects SMN1 exon 8 copy number. The presence of the g.27134T>G variant (also known as c.*3+80T>G) is reported if SMN1 copy number = 2. SMN1 or

SMN2: NM_000344.3:c.*3+80T>G variant only. 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. COL4A5: Deletion/duplication analysis is not offered for exons 11-12. NBN: Deletion/duplication analysis is not offered for exons 15-16. USH1C: Deletion/duplication analysis is not offered for exons 5-6. FAH: Deletion/duplication analysis is not offered for exon 14. GALC: Deletion/duplication analysis is not offered for exon 6. 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. HBA2: Sequencing analysis is not offered for exons 1-2. 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. ALG6: Deletion/duplication analysis is not offered for exons 11-12.

- Copy number could not be ascertained for the genes and exons noted below. Follow up testing may be indicated: ASS1: Exons 9-10; GLDC: Exons 11-12

## This report has been reviewed and approved by:

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