



Donor 6631

Genetic Testing Summary

Fairfax Cryobank recommends reviewing this genetic testing summary with your healthcare provider to determine suitability.

Last Updated: 08/09/23

Donor Reported Ancestry: Russian, English Dutch

Jewish Ancestry: Yes

Genetic Test*	Result	Comments/Donor's Residual Risk**
Chromosome analysis (karyotype)	Normal male karyotype	No evidence of clinically significant chromosome abnormalities
Hemoglobin evaluation	Normal hemoglobin fractionation and MCV/MCH results	Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies
Expanded Genetic Disease Carrier Screening Panel attached- 514 diseases by gene sequencing.	<p>Carrier: ABCA4-related conditions (ABCA4)</p> <p>Carrier: Alpha-thalassemia (HBA1/HBA2) aa/a-</p> <p>Carrier: CFTR-related conditions (CFTR)</p> <p>Carrier: Methylmalonic acidemia (MMAB-related)</p> <p>Carrier: Nonsyndromic deafness (MYO15A-related)</p> <p>Carrier: Smith-Lemli-Opitz syndrome (DHCR7)</p> <p>Negative for other genes sequenced.</p>	<p>Partner testing recommended before using this donor.</p> <p>Residual risks for negative results can be seen here:</p> <p>https://www.invitae.com/carrier-residual-risks/</p>

*No single test can screen for all genetic disorders. A negative screening result significantly reduces, but cannot eliminate, the risk for these conditions in a pregnancy.

**Donor residual risk is the chance the donor is still a carrier after testing negative.

Patient name: Donor 6631	Sample type: Blood	Report date: 17-FEB-2023
DOB: [REDACTED]	Sample collection date: 31-JAN-2023	Invitae #: [REDACTED]
Sex assigned at birth: Male	Sample accession date: 02-FEB-2023	Clinical team: [REDACTED]
Gender:		[REDACTED]
Patient ID (MRN):		[REDACTED]

Reason for testing

Gamete donor

Test performed

Invitae Comprehensive Carrier Screen without X-linked Disorders

- Primary Panel (CF, SMA)
- Add-on Comprehensive Carrier Screen without X-linked Disorders genes

[REDACTED]


RESULT: POSITIVE

This carrier test evaluated 514 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: ABCA4-related conditions	ABCA4	c.769-784C>T (Intronic) c.5882G>A (p.Gly1961Glu) §	Autosomal recessive	Yes
Carrier: Alpha-thalassemia	HBA1/ HBA2	HBA1: Deletion (Entire coding sequence)	Autosomal recessive	Yes
Carrier: CFTR-related conditions	CFTR	c.1210-34TG[12]T[5] (Intronic)	Autosomal recessive	Yes
Carrier: Methylmalonic acidemia (MMAB-related)	MMAB	c.660_661del (p.Phe221Hisfs*21)	Autosomal recessive	Yes
Carrier: Nonsyndromic deafness (MYO15A-related)	MYO15A	c.8183G>A (p.Arg2728His)	Autosomal recessive	Yes
Carrier: Smith-Lemli-Opitz syndrome	DHCR7	c.964-1G>C (Splice acceptor)	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 Carrier detection rates and residual risks document.
- 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

ABCA4-related conditions

Two variants, c.769-784C>T (Intronic), Pathogenic, and c.5882G>A (p.Gly1961Glu), Pathogenic (low penetrance), were identified in ABCA4. It is not possible to determine from this test whether the two ABCA4 changes in this individual are located in the same copy of the gene or in different copies of the gene. Therefore, this individual is at least a carrier of, and may be affected with, a ABCA4-related condition.

What are ABCA4-related conditions?

ABCA4-related conditions are a spectrum of inherited retinal disorders that cause impaired vision.

Cone-rod dystrophy (CRD) typically presents during childhood or adolescence and symptoms become more severe over time. Symptoms include reduced visual acuity (farsightedness or nearsightedness), loss of color perception, increased sensitivity to light (photophobia), and difficulty seeing in low light settings (night blindness). Some affected individuals develop involuntary eye movements (nystagmus), and many are legally blind by mid-adulthood.

Stargardt disease typically presents during childhood to early adulthood, although the severity and progression are highly variable. Affected individuals experience symptoms including a dark spot appearing in the center of their vision, having difficulty reading, driving or recognizing faces, difficulty transitioning from an area of light to dark, and photophobia. Individuals can also develop problems with night or color vision over time. Upon retinal exam, there is a characteristic build up of an orange-yellow fatty substance called lipofuscin at the macula at the back of the eye, which is the part of the eye that is responsible for central vision.

Retinitis pigmentosa (RP) typically presents with night blindness, which usually occurs during childhood or adolescence. Vision loss continues over years or decades and typically progresses to a loss of side (peripheral) vision, causing tunnel vision. Ultimately, central vision loss occurs. Many individuals with RP are legally blind by adulthood, though the severity of symptoms and age of onset varies by individual.

Not everyone with a genetic change in ABCA4 will present the same; symptoms and severity can vary, even between family members with the same genetic change. 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.

Clinical evaluation for symptoms of ABCA4-related conditions may be warranted.

Additional family testing may be considered to determine whether these changes are in the same copy of the ABCA4 gene or in different copies.

If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the ABCA4 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. When one individual has genetic changes in each copy of their ABCA4 gene and the partner is a carrier, there is a 50% chance for each of their children 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 ABCA4-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.



Patient name: Donor 6631

DOB: [REDACTED]

Invitae #: [REDACTED]

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
ABCA4-related conditions (AR) NM_000350.2	ABCA4	Pan-ethnic	1 in 45	1 in 441


RESULT: CARRIER

Alpha-thalassemia

A single Pathogenic variant, HBA1: Deletion (Entire coding sequence), was identified. This individual is expected to be a “silent” carrier of alpha-thalassemia (aa/a-).

What is alpha-thalassemia?

Alpha-thalassemia is a blood condition in which the body does not produce enough hemoglobin, a protein in red blood cells that carries oxygen throughout the body. Individuals with one copy (aa/a-, also called “silent” carrier) or two copies (a-/a- or aa/--, also called alpha-thalassemia trait) of certain changes in the HBA1 or HBA2 gene(s) typically have few or no health problems, though some may have mild symptoms such as a reduced number of red blood cells (anemia) and fatigue.

Another form of alpha-thalassemia, HbH disease (a/--), occurs in individuals who have three copies of certain changes in the HBA1 or HBA2 genes. HbH disease typically causes mild to moderate anemia, an enlarged liver and spleen (hepatosplenomegaly), and yellowing of the skin and whites of the eyes (jaundice). Some individuals affected with HbH disease also have bone changes such as overgrowth of the upper jaw or an unusually prominent forehead. HbH disease usually presents in early childhood, and with treatment, affected individuals typically live into adulthood. A more severe form, HbH/Constant Spring, can present with similar features, however, life threatening anemia can occur during fevers.

Hb Bart syndrome (--/--) is the most severe form of alpha-thalassemia, and occurs in individuals who have certain changes in both of their HBA1 genes and both of their HBA2 genes. In Hb Bart, excess fluid builds up in the body of affected fetuses before birth (fetal hydrops, also called hydrops fetalis); newborns have severe symptoms, including anemia, hepatosplenomegaly, heart defects, and abnormalities of the urinary system or genitalia. Most babies with Hb Bart are stillborn or die soon after birth. Treatment for individuals with HbH disease is supportive and focused on managing the individual's symptoms, and may include blood transfusions. Due to the severity of Hb Bart, medical management is directed by the level of parental desire for life-support measures and comfort care in newborns. However, fetal blood transfusions have been shown to increase chances of survival.

Next steps

Carrier testing for the reproductive partner is recommended.

+ If your partner tests positive:

Alpha-thalassemia inheritance involves both the HBA1 and HBA2 genes. Individuals typically have two copies of each of these genes, for a total of four copies of HBA1 and HBA2. Individuals who are carriers for alpha-thalassemia have certain changes in either one copy (“silent” carrier) or two copies (alpha-thalassemia trait) of their HBA1 or HBA2 genes, and are at increased risk for having a child with forms of alpha-thalassemia known as HbH disease (3 copies of certain HBA1 and HBA2 changes) or Hb Bart syndrome (4 copies of certain HBA1 and HBA2 changes). The chance of having a child with either of these conditions is dependent upon the carrier status of the individual's partner, and which combination of HBA1 and HBA2 changes each individual carries.

- 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 alpha-thalassemia. 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
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


RESULT: CARRIER

CFTR-related conditions

A single Pathogenic variant, c.1210-34TG[12]T[5] (Intronic), was identified in CFTR. This variant has unique interpretation considerations. See "What are CFTR-related conditions?" and Variant details for additional information.

What are CFTR-related conditions?

The c.1210-34TG[12]T[5] cystic fibrosis (CF) variant was identified in this individual. There are multiple forms of the 5T variant, which are classified by the number of TG repeats. Each form of the 5T variant is associated with a different degree of risk for CFTR-related symptoms when inherited in combination with a pathogenic variant from the other parent, ranging from a healthy individual to congenital absence of the vas deferens (CAVD) in males to an individual with mild/atypical CF. The combination of the c.1210-34TG[12]T[5] variant with a severe pathogenic CFTR variant from the other parent is associated with symptoms in the majority of individuals; however, most individuals who are homozygous for the c.1210-34TG[12]T[5] variant are asymptomatic (see Variant details section).

R117H is another change which can occur within CFTR as part of a complex allele with a 5T variant. If present, the R117H variant would be reported as a Result to Note.

CFTR-related conditions encompass a spectrum of disorders that typically impact the respiratory and/or digestive systems, and cause male infertility. Cystic fibrosis (CF) is typically a childhood-onset disease in which abnormally thick mucus production can cause a variety of symptoms including recurrent respiratory infections and progressive lung disease, as well as nutritional deficiencies and poor growth due to deficiency of enzymes produced by the pancreas to digest food (pancreatic insufficiency). Symptoms range from mild to severe. Prognosis depends on the severity of symptoms as well as response to treatments; many affected individuals live well into adulthood. Milder forms of CFTR-related conditions include CAVD associated with male infertility, variable respiratory manifestations, and hereditary pancreatitis. Life span is not typically impacted with less severe CFTR-related conditions. Intellect is not affected with the various CFTR-related conditions. The combination of variants identified in an affected individual impacts the observed clinical features and severity of the symptoms. Additional genetic and environmental factors are believed to play a role in determining the risk of developing these complex CFTR-related conditions.

Additionally, individuals with a single disease-causing CFTR variant (heterozygous carriers) may have an approximately 4-10 fold increased risk for chronic pancreatitis, although the absolute risk of pancreatitis remains low (less than 1 in 100). Hereditary pancreatitis is characterized by recurrent episodes of acute inflammation of the pancreas (pancreatitis) beginning in childhood or adolescence, leading to chronic pancreatitis. Chronic pancreatitis is a risk factor for pancreatic cancer. Due to this potential increased risk for chronic pancreatitis, heterozygous carriers may consider follow-up with a medical provider.

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

Next steps

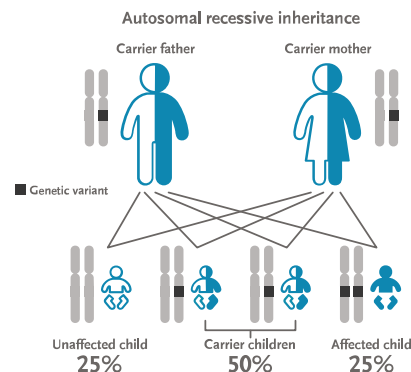
Carrier testing for the reproductive partner is recommended.

+ If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the CFTR 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




Patient name: Donor 6631 **DOB:** ██████████

Invitae #: ██████████

residual risk after testing negative for CFTR-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
CFTR-related conditions (AR) NM_000492.3	CFTR *	Pan-ethnic - classic CF	1 in 45	1 in 4400
		Pan-ethnic - classic CF and CFTR-related disorders	1 in 9	1 in 800


RESULT: CARRIER

Methylmalonic acidemia (MMAB-related)

A single Pathogenic variant, c.660_661del (p.Phe221Hisfs*21), was identified in MMAB.

What is methylmalonic acidemia (MMAB-related)?

Methylmalonic acidemia (MMA) is a condition in which the body is unable to properly process certain building blocks of proteins (amino acids) and fats (lipids). There are multiple forms of MMA, which are caused by changes in different genes. MMA caused by changes in the MMAB gene is also called cobalamin B type MMA. Symptoms of cobalamin B type MMA (MMACblB) are variable in severity and may manifest anytime from infancy through adulthood. Affected infants typically have vomiting, poor growth (failure to thrive), low muscle tone (hypotonia), lack of energy (lethargy), an enlarged liver (hepatomegaly), brain dysfunction (encephalopathy), and developmental delay. In some infants, these symptoms can be fatal. Affected individuals who survive infancy may experience periods of relative health followed by periods of potentially life-threatening illness (decompensation), often brought on by infections or stressors, such as injuries or surgery. Long-term complications can include intellectual disability, impaired growth, movement disorders, kidney disease, and inflammation of the pancreas (pancreatitis). Prognosis and life expectancy depend on the severity of symptoms. Dietary restriction of certain amino acids and supplementation with vitamin B12 (hydroxycobalamin) and folate can help improve symptoms in some affected individuals. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

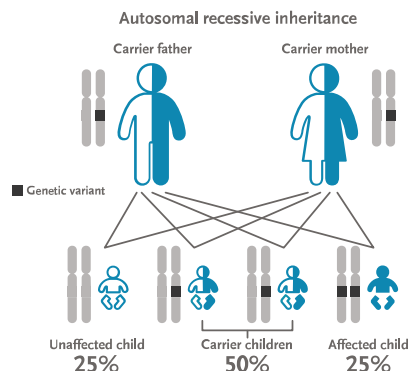
Carrier testing for the reproductive partner is recommended.


If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the MMAB 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 methylmalonic acidemia (MMAB-related). 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
Methylmalonic acidemia (MMAB-related) (AR) NM_052845.3	MMAB	Pan-ethnic	1 in 456	1 in 22750


RESULT: CARRIER

Nonsyndromic deafness (MYO15A-related)

A single Pathogenic variant, c.8183G>A (p.Arg2728His), was identified in MYO15A.

What is nonsyndromic deafness (MYO15A-related)?

Nonsyndromic deafness is a condition that affects an individual's ability to hear. It can be caused by changes in several different genes. Nonsyndromic deafness does not affect any other part of the body. Affected individuals are born with mild to profound deafness that typically does not worsen over time. Severity of deafness may vary, even among members of the same family. Intellect and life span are not impacted. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

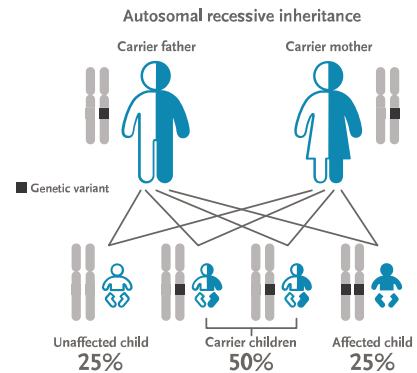
Carrier testing for the reproductive partner is recommended.


If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the MYO15A 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 nonsyndromic deafness (MYO15A-related). 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
Nonsyndromic deafness (MYO15A-related) (AR) NM_016239.3	MYO15A	Pan-ethnic	≤1 in 500	Reduced


RESULT: CARRIER

Smith-Lemli-Opitz syndrome

A single Pathogenic variant, c.964-TG>C (Splice acceptor), was identified in DHCR7.

What is Smith-Lemli-Opitz syndrome?

Smith-Lemli-Opitz syndrome (SLOS) is a condition in which an enzyme deficiency causes the body to have difficulty making cholesterol. SLOS affects several body systems. Symptoms and severity of SLOS can vary, even between family members with the same genetic change. Infants with severe SLOS typically have low muscle tone (hypotonia), feeding difficulties, and slow growth. Other symptoms may include a small head (microcephaly), distinctive facial features, cleft palate, abnormalities of the toes and fingers, short stature, developmental delay, behavioral problems, autism, and intellectual disability. Abnormalities of the heart, lungs, kidneys, and gastrointestinal tract, as well as underdeveloped genitalia in males, are also common. Individuals with milder forms of SLOS may have only hypotonia and subtle facial or toe characteristics, and may have mild intellectual disability or normal intellect. Life expectancy is dependent on the severity of symptoms. It has been reported that approximately 25% of individuals with SLOS die during infancy while others live to adulthood. Treatment may include supplementation with cholesterol and medications. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

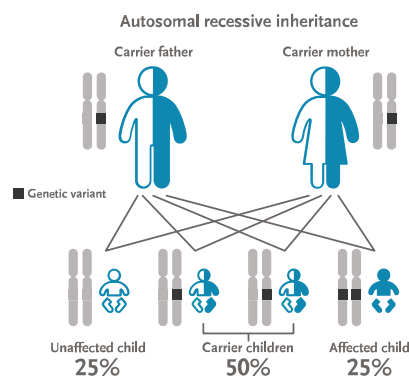
Carrier testing for the reproductive partner is recommended.


If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the DHCR7 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 Smith-Lemli-Opitz syndrome. 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
Smith-Lemli-Opitz syndrome (AR) NM_001360.2	DHCR7	Pan-ethnic	1 in 71	1 in 7000

Results to note

SMN1

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

Pseudodeficiency allele(s)

- 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

ABCA4, Intron 6, c.769-784C>T (Intronic), heterozygous, PATHOGENIC

- This sequence change falls in intron 6 of the ABCA4 gene. It does not directly change the encoded amino acid sequence of the ABCA4 protein.
- This variant is present in population databases (rs144695319, gnomAD 0.4%), and has an allele count higher than expected for a pathogenic variant.
- This variant has been observed in individual(s) with late-onset, foveal-sparing Stargardt disease (PMID: 30643219, 31618761). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant.
- Studies have shown that this variant is associated with altered splicing resulting in introduction of a 162 nuc. pseudoexon (PMID: 30643219).
- For these reasons, this variant has been classified as Pathogenic.

ABCA4, Exon 42, c.5882G>A (p.Gly1961Glu), heterozygous, Pathogenic (low penetrance)

- This sequence change replaces glycine, which is neutral and non-polar, with glutamic acid, which is acidic and polar, at codon 1961 of the ABCA4 protein (p.Gly1961Glu).
- This variant is present in population databases (rs1800553, gnomAD 2.3%), including at least one homozygous and/or hemizygous individual.
- This variant has been observed in many individuals with autosomal recessive Stargardt disease, and has been found in trans (on the opposite chromosome) from many different pathogenic variants (PMID: 28559085, 28181551, 30060493, 19074458, 29555955). This variant appears to be significantly enriched in individuals with Stargardt compared to the general population (PMID: 28327576). In addition, in a large meta-analysis, this variant conferred a 3.2-fold increased risk (95% CI: 1.74–5.95) for age-related macular degeneration (PMID: 25921964). This variant appears to be associated with milder and/or later onset disease (PMID: 28327576, 28446513).
- ClinVar contains an entry for this variant (Variation ID: 7888).
- 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 ABCA4 protein function.
- Experimental studies have shown that this missense change affects ABCA4 function (PMID: 11017087, 29847635).
- In summary, this variant is reported to cause disease. However, because this variant is associated with a milder form of disease than other pathogenic alleles in the ABCA4 gene, and because it is found in homozygosity in healthy individuals, it has been classified as Pathogenic (low penetrance).

CFTR, Intron 9, c.1210-34TG[12]T[5] (Intronic), heterozygous, PATHOGENIC

- This sequence change, also referred to as 5T;TG12 or TG12-5T in the literature, consists of 12 TG and 5 T sequence repeats on the same chromosome, and is located in intron 9 of the CFTR gene. It does not directly change the encoded amino acid sequence of the CFTR protein.
- The frequency data for this variant in the population databases is considered unreliable, as metrics indicate poor data quality at this position in the gnomAD database.
- The TG[12]T[5] allele has been observed in males with congenital bilateral absence of the vas deferens (CBAVD) and in both males and females with cystic fibrosis (CF) when present on the opposite chromosome (in trans) from a severe pathogenic CFTR variant (PMID: 14685937). When this allele is observed in trans with a severe pathogenic CFTR variant, the penetrance of CFTR-related conditions (CBAVD and/or non-classic CF) is expected to be high (>90%); however, the penetrance of classic CF is low (<20%) (PMID: 14685937, 27447098). Individuals who are homozygous for this variant, or who have this variant in combination with TG[11]T[5], are likely to be asymptomatic (PMID: 34196078).
- Algorithms developed to predict the effect of variants on protein structure and function are not available or were not evaluated for this variant.
- Experimental studies demonstrate that the 5T allele leads to exclusion of exon 10 (referred to as exon 9 in some publications) from the mRNA, which ultimately results in a non-functional CFTR protein (PMID: 7691356, 7684641, 10556281, 14685937, 21658649). Importantly, the number of TG repeats (11, 12 or 13) modifies the extent of exon 10 skipping when in cis with the 5T allele (PMID: 14685937, 10556281, 9435322). In a mini-gene assay, the percentage of CFTR mRNA without exon 10 was 54% for TG[11]T[5], 72% for TG[12]T[5] and 100% for TG[13]T[5] (PMID: 10556281).
- Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant is not likely to affect RNA splicing.
- For these reasons, this variant has been classified as Pathogenic.

DHCR7, Intron 8, c.964-TG>C (Splice acceptor), heterozygous, PATHOGENIC

- This sequence change affects an acceptor splice site in intron 8 of the DHCR7 gene. RNA analysis indicates that disruption of this splice site induces altered splicing and likely disrupts the C-terminus of the protein.
- This variant is present in population databases (rs138659167, gnomAD 1.2%), and has an allele count higher than expected for a pathogenic variant.
- Disruption of this splice site has been observed in individual(s) with Smith-Lemli-Opitz syndrome (PMID: 10814720, 10995508, 11427181, 23042628). 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: 93725).
- Variants that disrupt the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Studies have shown that disruption of this splice site results in activation of a cryptic splice site and introduces a new termination codon (PMID: 9653161). However the mRNA is not expected to undergo nonsense-mediated decay.
- For these reasons, this variant has been classified as Pathogenic.

HBA1, Deletion (Entire coding sequence), heterozygous, PATHOGENIC

- A gross deletion of the genomic region encompassing the full coding sequence of the HBA1 gene has been identified. Loss-of-function variants in HBA1 are known to be pathogenic (PMID: 12393486, 27199182).
- Although HBA1 is associated with autosomal recessive disease, a closely related gene called HBA2, when present, can compensate for the loss of HBA1. Disruption of 1 or 2 of the 4 copies of the HBA1 and HBA2 genes is typically associated with no symptoms or very mild symptoms, while disruption of at least 3 of the 4 copies is associated with overt disease (PMID: 19618088, 21381239). Consistent with this, single gene deletions of HBA1 have been observed on the opposite chromosome (in trans) from deletions encompassing both HBA1 and HBA2 in individuals with HbH disease (PMID: 16370493, 1951330, 24826793). Deletions encompassing both HBA1 and HBA2, sometimes along with other nearby genes, have been reported in many individuals affected with alpha-thalassemia and related diseases (PMID: 1520607, 7734346, 12393486, 27492767).
- For these reasons, this variant has been classified as Pathogenic.

MMAB, Exon 9, c.660_661del (p.Phe221Hisfs*21), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Phe221Hisfs*21) in the MMAB gene. While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 30 amino acid(s) of the MMAB protein.
- This variant is present in population databases (no rsID available, gnomAD 0.007%).
- This variant has not been reported in the literature in individuals affected with MMAB-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 553302).



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- This variant disrupts a region of the MMAB protein in which other variant(s) (p.Gln234*) have been determined to be pathogenic (PMID: 16410054, 21604717). This suggests that this is a clinically significant region of the protein, and that variants that disrupt it are likely to be disease-causing.
- For these reasons, this variant has been classified as Pathogenic.

MYO15A, Exon 45, c.8183G>A (p.Arg2728His), heterozygous, PATHOGENIC

- This sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 2728 of the MYO15A protein (p.Arg2728His).
- This variant is present in population databases (rs184435771, gnomAD 0.06%).
- This missense change has been observed in individuals with deafness (PMID: 21917145, 30622556, 31827275, 32747562, 33398081). It has also been observed to segregate with disease in related individuals.
- ClinVar contains an entry for this variant (Variation ID: 228276).
- 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) has been performed at Invitae for this missense variant, however the output from this modeling did not meet the statistical confidence thresholds required to predict the impact of this variant on MYO15A protein function.
- For these reasons, this variant has been classified as Pathogenic.

Residual risk

No carrier test can detect 100% of carriers. There still remains a small risk of being a carrier after a negative test (residual risk). Residual risk values assume a negative family history and are inferred from published carrier frequencies and estimated detection rates based on testing technologies used at Invitae. You can view Invitae's complete Carrier detection rates and residual risks document (containing all carrier genes) online at <https://www.invitae.com/carrier-residual-risks/>. Additionally, the order-specific information for this report is available to download in the portal (under this order's documents) or can be requested by contacting Invitae Client Services. The complete Carrier detection rates and residual risks document will not be applicable for any genes with specimen-specific limitations in sequencing and/or deletion/duplication coverage. Please see the final bullet point in the Limitations section of this report to view if this specimen had any gene-specific coverage gaps.

Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details. Results are negative, unless otherwise indicated in the report.

GENE	TRANSCRIPT	GENE	TRANSCRIPT	GENE	TRANSCRIPT
AAAS	NM_015665.5	AP1S1	NM_001283.3	CBS	NM_000071.2
ABCA12	NM_173076.2	AQP2	NM_000486.5	CC2D1A	NM_017721.5
ABCA3	NM_001089.2	ARG1	NM_000045.3	CC2D2A	NM_001080522.2
ABCA4	NM_000350.2	ARL6	NM_177976.2	CCDC103	NM_213607.2
ABCB11	NM_003742.2	ARSA	NM_000487.5	CCDC39	NM_181426.1
ABCB4	NM_000443.3	ARSB	NM_000046.3	CCDC88C	NM_001080414.3
ABCC2*	NM_000392.4	ASL	NM_000048.3	CD3D	NM_000732.4
ABCC8	NM_000352.4	ASNS	NM_133436.3	CD3E	NM_000733.3
ACAD9	NM_014049.4	ASPA	NM_000049.2	CD40	NM_001250.5
ACADM	NM_000016.5	ASS1	NM_000050.4	CD59	NM_203330.2
ACADVL	NM_000018.3	ATM*	NM_000051.3	CDH23	NM_022124.5
ACAT1	NM_000019.3	ATP6V1B1	NM_001692.3	CEP152	NM_014985.3
ACOX1	NM_004035.6	ATP7B	NM_000053.3	CEP290	NM_025114.3
ACSF3	NM_174917.4	ATP8B1*	NM_005603.4	CERKL	NM_001030311.2
ADA	NM_000022.2	BBS1	NM_024649.4	CFTR*	NM_000492.3
ADAMTS2	NM_014244.4	BBS10	NM_024685.3	CHAT	NM_020549.4
ADAMTSL4	NM_019032.5	BBS12	NM_152618.2	CHRNE	NM_000080.3
ADGRG1	NM_005682.6	BBS2	NM_031885.3	CHRNA3	NM_005199.4
ADGRV1	NM_032119.3	BBS4	NM_033028.4	CIITA	NM_000246.3
AGA	NM_000027.3	BBS5	NM_152384.2	CLCN1	NM_000083.2
AGL	NM_000642.2	BBS7	NM_176824.2	CLN3	NM_001042432.1
AGPS	NM_003659.3	BBS9*	NM_198428.2	CLN5	NM_006493.2
AGXT	NM_000030.2	BCKDHA	NM_000709.3	CLN6	NM_017882.2
AHI1	NM_017651.4	BCKDHB	NM_183050.2	CLN8	NM_018941.3
AIPL1*	NM_014336.4	BCS1L	NM_004328.4	CLRN1	NM_174878.2
AIRE	NM_000383.3	BLM	NM_000057.3	CNGB3	NM_019098.4
ALDH3A2	NM_000382.2	BLOC1S3	NM_212550.4	COL11A2*	NM_080680.2
ALDH7A1	NM_001182.4	BLOC1S6	NM_012388.3	COL17A1	NM_000494.3
ALDOB	NM_000035.3	BMP1	NM_006129.4;NM_001199.3	COL27A1	NM_032888.3
ALG1	NM_019109.4	BRIP1	NM_032043.2	COL4A3	NM_000091.4
ALG6	NM_013339.3	BSND	NM_057176.2	COL4A4	NM_000092.4
ALMS1	NM_015120.4	BTD	NM_000060.3	COL7A1	NM_000094.3
ALPL	NM_000478.5	CAD	NM_004341.4	COX15	NM_004376.6
AMN*	NM_030943.3	CANT1	NM_138793.3	CPS1	NM_001875.4
AMT	NM_000481.3	CAPN3	NM_000070.2	CPT1A	NM_001876.3
ANO10*	NM_018075.3	CASQ2	NM_001232.3	CPT2	NM_000098.2



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GENE	TRANSCRIPT
CRB1	NM_201253.2
CRTAP	NM_006371.4
CTNS	NM_004937.2
CTSA	NM_000308.3
CTSC	NM_001814.5
CTSD	NM_001909.4
CTSK	NM_000396.3
CYBA	NM_000101.3
CYP11A1	NM_000781.2
CYP11B1	NM_000497.3
CYP11B2	NM_000498.3
CYP17A1	NM_000102.3
CYP19A1	NM_031226.2
CYP1B1	NM_000104.3
CYP21A2*	NM_000500.7
CYP27A1	NM_000784.3
CYP27B1	NM_000785.3
CYP7B1	NM_004820.3
DBT	NM_001918.3
DCAF17	NM_025000.3
DCLRE1C	NM_001033855.2
DDX11*	NM_030653.3
DFNB59	NM_001042702.3
DGAT1	NM_012079.5
DGUOK	NM_080916.2
DHCR7	NM_001360.2
DHDDS	NM_024887.3
DLD	NM_000108.4
DLL3	NM_016941.3
DNAH11	NM_001277115.1
DNAH5	NM_001369.2
DNAI1	NM_012144.3
DNAI2	NM_023036.4
DNMT3B	NM_006892.3
DOK7	NM_173660.4
DUOX2*	NM_014080.4
DYNC2H1	NM_001080463.1
DYSF	NM_003494.3
EIF2AK3	NM_004836.6

GENE	TRANSCRIPT
EIF2B1	NM_001414.3
EIF2B2	NM_014239.3
EIF2B3	NM_020365.4
EIF2B4	NM_015636.3
EIF2B5	NM_003907.2
ELP1	NM_003640.3
EPG5	NM_020964.2
ERCC2	NM_000400.3
ERCC6	NM_000124.3
ERCC8	NM_000082.3
ESCO2	NM_001017420.2
ETFA	NM_000126.3
ETFB	NM_001985.2
ETFDH	NM_004453.3
ETHE1	NM_014297.3
EVC	NM_153717.2
EVC2	NM_147127.4
EXOSC3	NM_016042.3
EYS*	NM_001142800.1
FAH*	NM_000137.2
FAM161A	NM_001201543.1
FANCA	NM_000135.2
FANCC	NM_000136.2
FANCD2*	NM_033084.3
FANCE	NM_021922.2
FANCG	NM_004629.1
FANCI	NM_001113378.1
FANCL*	NM_018062.3
FBP1	NM_000507.3
FBXO7	NM_012179.3
FH*	NM_000143.3
FKBP10	NM_021939.3
FKRP	NM_024301.4
FKTN	NM_001079802.1
FMO3	NM_006894.6
FOXN1	NM_003593.2
FOXRED1	NM_017547.3
FRAS1	NM_025074.6
FREM2	NM_207361.5

GENE	TRANSCRIPT
FUCA1	NM_000147.4
G6PC	NM_000151.3
G6PC3	NM_138387.3
GAA	NM_000152.3
GALC*	NM_000153.3
GALE*	NM_000403.3
GALK1	NM_000154.1
GALNS	NM_000512.4
GALNT3	NM_004482.3
GALT	NM_000155.3
GAMT	NM_000156.5
GATM	NM_001482.2
GBA*	NM_001005741.2
GBE1	NM_000158.3
GCDH	NM_000159.3
GCH1	NM_000161.2
GDF5	NM_000557.4
GFM1	NM_024996.5
GHR*	NM_000163.4
GJB2	NM_004004.5
GLB1	NM_000404.2
GLDC	NM_000170.2
GLE1	NM_001003722.1
GNB3*	NM_001128227.2
GNPAT	NM_014236.3
GNPTAB	NM_024312.4
GNPTG	NM_032520.4
GNS	NM_002076.3
GORAB	NM_152281.2
GRHPR	NM_012203.1
GRIP1	NM_021150.3
GSS	NM_000178.2
GUCY2D	NM_000180.3
GUSB	NM_000181.3
HADH	NM_005327.4
HADHA	NM_000182.4
HADHB	NM_000183.2
HAMP	NM_021175.2
HAX1	NM_006118.3



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GENE	TRANSCRIPT
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
HMOX1	NM_002133.2
HOGA1	NM_138413.3
HPD	NM_002150.2
HPS1	NM_000195.4
HPS3	NM_032383.4
HPS4	NM_022081.5
HPS5	NM_181507.1
HPS6	NM_024747.5
HSD17B3	NM_000197.1
HSD17B4	NM_000414.3
HSD3B2	NM_000198.3
HYAL1	NM_153281.1
HYLS1	NM_145014.2
IDUA	NM_000203.4
IGHMBP2	NM_002180.2
IKKBK	NM_001556.2
IL7R	NM_002185.3
INVS	NM_014425.3
ITGA6	NM_000210.3
ITGB3	NM_000212.2
ITGB4	NM_001005731.2
IVD	NM_002225.3
JAK3	NM_000215.3
KCNJ1	NM_000220.4
KCNJ11	NM_000525.3
LAMA2	NM_000426.3
LAMA3	NM_000227.4
LAMB3	NM_000228.2
LAMC2	NM_005562.2
LARGE1	NM_004737.4

GENE	TRANSCRIPT
LCA5	NM_181714.3
LDLR	NM_000527.4
LDLRAP1	NM_015627.2
LHX3	NM_014564.4
LIFR*	NM_002310.5
LIG4	NM_002312.3
LIPA	NM_000235.3
LMBRD1	NM_018368.3
LOXHD1	NM_144612.6
LPL	NM_000237.2
LRAT	NM_004744.4
LRP2	NM_004525.2
LRPPRC	NM_133259.3
LYST	NM_000081.3
MAK	NM_001242957.2
MAN2B1	NM_000528.3
MANBA	NM_005908.3
MCEE	NM_032601.3
MCOLN1	NM_020533.2
MCPH1	NM_024596.4
MECR	NM_016011.3
MED17	NM_004268.4
MESP2	NM_001039958.1
MFSD8	NM_152778.2
MKKS	NM_018848.3
MKS1	NM_017777.3
MLC1*	NM_015166.3
MLYCD	NM_012213.2
MMAA	NM_172250.2
MMAB	NM_052845.3
MMACHC	NM_015506.2
MMADHC	NM_015702.2
MOCS1	NM_001358530.2
MOCS2A	NM_176806.3
MOCS2B	NM_004531.4
MPI	NM_002435.2
MPL	NM_005373.2
MPV17	NM_002437.4
MRE11	NM_005591.3

GENE	TRANSCRIPT
MTHFR*	NM_005957.4
MTR	NM_000254.2
MTRR	NM_002454.2
MTTP	NM_000253.3
MUSK	NM_005592.3
MUT	NM_000255.3
MVK	NM_000431.3
MYO15A	NM_016239.3
MYO7A	NM_000260.3
NAGA	NM_000262.2
NAGLU	NM_000263.3
NAGS	NM_153006.2
NBN	NM_002485.4
NCF2	NM_000433.3
NDRG1	NM_006096.3
NDUFAF2	NM_174889.4
NDUFAF5	NM_024120.4
NDUFS4	NM_002495.3
NDUFS6	NM_004553.4
NDUFS7	NM_024407.4
NDUFV1	NM_007103.3
NEB*	NM_001271208.1
NEU1	NM_000434.3
NGLY1	NM_018297.3
NPC1	NM_000271.4
NPC2	NM_006432.3
NPHP1	NM_000272.3
NPHS1	NM_004646.3
NPHS2	NM_014625.3
NR2E3	NM_014249.3
NSMCE3	NM_138704.3
NTRK1	NM_001012331.1
OAT*	NM_000274.3
OCA2	NM_000275.2
OPA3	NM_025136.3
OSTM1	NM_014028.3
OTOA*	NM_144672.3
OTOF	NM_194248.2;NM_194323.2
P3H1	NM_022356.3


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GENE	TRANSCRIPT
PAH	NM_000277.1
PANK2	NM_153638.2
PC	NM_000920.3
PCBD1	NM_000281.3
PCCA	NM_000282.3
PCCB	NM_000532.4
PCDH15	NM_033056.3
PCNT	NM_006031.5
PDHB	NM_000925.3
PEPD	NM_000285.3
PET100	NM_001171155.1
PEX1*	NM_000466.2
PEX10	NM_153818.1
PEX12	NM_000286.2
PEX13	NM_002618.3
PEX16	NM_004813.2
PEX2	NM_000318.2
PEX26	NM_017929.5
PEX5	NM_001131025.1
PEX6	NM_000287.3
PEX7	NM_000288.3
PFKM	NM_000289.5
PGM3	NM_001199917.1
PHGDH	NM_006623.3
PHKB	NM_000293.2;NM_00103183 5.2
PHKG2	NM_000294.2
PHYH	NM_006214.3
PIGN	NM_176787.4
PKHD1*	NM_138694.3
PLA2G6	NM_003560.2
PLEKHG5	NM_020631.4
PLOD1	NM_000302.3
PMM2	NM_000303.2
PNPO	NM_018129.3
POLG	NM_002693.2
POLH	NM_006502.2
POMGNT1	NM_017739.3
POMT1	NM_007171.3
POMT2	NM_013382.5

GENE	TRANSCRIPT
POR	NM_000941.2
POU1F1	NM_000306.3
PPT1	NM_000310.3
PRCD	NM_001077620.2
PRDM5	NM_018699.3
PRF1	NM_001083116.1
PROP1	NM_006261.4
PSAP	NM_002778.3
PTPRC*	NM_002838.4
PTS	NM_000317.2
PUS1	NM_025215.5
PYGM	NM_005609.3
QDPR	NM_000320.2
RAB23	NM_183227.2
RAG1	NM_000448.2
RAG2	NM_000536.3
RAPSN	NM_005055.4
RARS2	NM_020320.3
RDH12	NM_152443.2
RLBP1	NM_000326.4
RMRP	NR_003051.3
RNASEH2A	NM_006397.2
RNASEH2B	NM_024570.3
RNASEH2C	NM_032193.3
RPE65	NM_000329.2
RPGRIP1L	NM_015272.2
RTEL1	NM_001283009.1
RXYLT1	NM_014254.2
RYR1	NM_000540.2
SACS	NM_014363.5
SAMD9	NM_017654.3
SAMHD1	NM_015474.3
SCO2	NM_005138.2
SEC23B	NM_006363.4
SEPSECS	NM_016955.3
SGCA	NM_000023.2
SGCB	NM_000232.4
SGCD	NM_000337.5
SGCG	NM_000231.2

GENE	TRANSCRIPT
SGSH	NM_000199.3
SKIV2L	NM_006929.4
SLC12A1	NM_000338.2
SLC12A3	NM_000339.2
SLC12A6	NM_133647.1
SLC17A5	NM_012434.4
SLC19A2	NM_006996.2
SLC19A3	NM_025243.3
SLC1A4	NM_003038.4
SLC22A5	NM_003060.3
SLC25A13	NM_014251.2
SLC25A15	NM_014252.3
SLC25A20	NM_000387.5
SLC26A2	NM_000112.3
SLC26A3	NM_000111.2
SLC26A4	NM_000441.1
SLC27A4	NM_005094.3
SLC35A3	NM_012243.2
SLC37A4	NM_001164277.1
SLC38A8	NM_001080442.2
SLC39A4	NM_130849.3
SLC45A2	NM_016180.4
SLC4A11	NM_032034.3
SLC5A5	NM_000453.2
SLC7A7	NM_001126106.2
SMARCA11	NM_014140.3
SMN1*	NM_000344.3
SMPD1	NM_000543.4
SNAP29	NM_004782.3
SPG11	NM_025137.3
SPR	NM_003124.4
SRD5A2	NM_000348.3
ST3GAL5	NM_003896.3
STAR	NM_000349.2
STX11	NM_003764.3
STXBP2	NM_006949.3
SUMF1	NM_182760.3
SUOX	NM_000456.2
SURF1	NM_003172.3


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GENE	TRANSCRIPT
SYNE4	NM_001039876.2
TANGO2	NM_152906.6
TAT	NM_000353.2
TBCD	NM_005993.4
TBCE*	NM_003193.4
TCIRG1	NM_006019.3
TCN2	NM_000355.3
TECPR2	NM_014844.3
TERT	NM_198253.2
TF	NM_001063.3
TFR2	NM_003227.3
TG*	NM_003235.4
TGM1	NM_000359.2
TH	NM_199292.2
TK2	NM_004614.4
TMC1	NM_138691.2
TMEM216	NM_001173990.2
TMEM67	NM_153704.5
TMPRSS3	NM_024022.2
TPO	NM_000547.5
TPP1	NM_000391.3
TREX1	NM_033629.4
TRIM32	NM_012210.3
TRIM37	NM_015294.4
TRMU	NM_018006.4
TSEN54	NM_207346.2
TSFM*	NM_001172696.1
TSHB	NM_000549.4
TSHR	NM_000369.2
TTC37	NM_014639.3
TTPA	NM_000370.3
TULP1	NM_003322.4
TYMP	NM_001953.4
TYR*	NM_000372.4
TYRP1	NM_000550.2
UBR1	NM_174916.2
UNC13D	NM_199242.2
USH1C*	NM_005709.3
USH2A	NM_206933.2

GENE	TRANSCRIPT
VDR	NM_001017535.1
VLDLR	NM_003383.4
VPS11	NM_021729.5
VPS13A*	NM_033305.2
VPS13B	NM_017890.4
VPS45	NM_007259.4
VPS53*	NM_001128159.2
VRK1	NM_003384.2
VSX2	NM_182894.2
WISP3	NM_003880.3
WNT10A	NM_025216.2
WRN*	NM_000553.4
XPA	NM_000380.3
XPC	NM_004628.4
ZBTB24	NM_014797.2
ZFYVE26	NM_015346.3
ZNF469	NM_001127464.2

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 $\geq 50\times$ 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 in the Genes analyzed section. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. 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 GJB2, the reportable range includes large upstream deletions overlapping GJB6. 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 $-\alpha 3.7$ subtypes, and all $-\alpha 3.7$ 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).
- 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>), gnomAD (<http://gnomad.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.
- TBCE: Sequencing analysis for exons 2 includes only cds +/- 10 bp. BBS9: Deletion/duplication analysis is not offered for exon 4. 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. AMN: Deletion/duplication analysis is not offered for exon 1. MLC1: Sequencing analysis for exons 11 includes only cds +/- 10 bp. CFTR: Sequencing analysis for exons 7 includes only cds +/- 10 bp. PTPRC: Sequencing analysis is not offered for exons 3, 15. DUOX2: Deletion/duplication and sequencing analysis is not offered for exons 6-7. USH1C: Deletion/duplication analysis is not offered for exons 5-6. VPS53: Sequencing analysis for exons 14 includes only cds +/- 5 bp. FANCD2: Deletion/duplication analysis is not offered for exons 14-17, 22 and sequencing analysis is not offered for exons 15-17. Sequencing analysis for exons 6, 14, 18, 20, 23, 25, 34 includes only cds +/- 10 bp. COL11A2: Deletion/duplication analysis is not offered for exon 36. 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. GNE: Sequencing analysis for exons 8 includes only cds +/- 10 bp. LIFR: Sequencing analysis for exons 3 includes only cds +/- 5 bp. OAT: Deletion/duplication analysis is not offered for exon 2. PEX1: Sequencing analysis for exons 16 includes only cds +/- 0 bp. PKHD1: Deletion/duplication analysis is not offered for exon 13. EYS: Sequencing analysis for exons 30 includes only cds +/- 0 bp. GALE: Sequencing analysis for exons 10 includes only cds +/- 5 bp. FANCL: Sequencing analysis for exons 4, 10 includes only cds +/- 10 bp. TYR: Deletion/duplication and sequencing analysis is not offered for exon 5. ANO10: Sequencing analysis for exons 8 includes only cds +/- 0 bp. GHR: Deletion/duplication and sequencing analysis is not offered for exon 3. FAH: Deletion/duplication analysis is not offered for exon 14. FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp. TSFM: Sequencing analysis is not offered for exon 5. WRN: Deletion/duplication analysis is not offered for exons 10-11. Sequencing analysis for exons 8, 10-11 includes only cds +/- 10 bp. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. 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. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28. ABCC2: Deletion/duplication analysis is not offered for exons 24-25. OTOA: Deletion/duplication and sequencing analysis is not offered for exons 20-28. DDX11: NM_030653.3:c.1763-1G>C variant only. TG: Deletion/duplication analysis is not offered for exon 18. Sequencing analysis for exons 44 includes only cds +/- 0 bp. ATP8B1: Sequencing analysis for exons 19 includes only cds +/- 10 bp. AIPL1: Sequencing analysis for exons 2 includes only cds +/- 10 bp. GALT: Deletion/duplication analysis is not offered for exon 6. 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". 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,




Patient name: Donor 6631

DOB: [REDACTED]

Invitae #: [REDACTED]

Constant Spring (NM_000517.4:c.427T>C), can be identified by this assay. 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.

This report has been reviewed and approved by:

Mei Zhu, Ph.D., FACMG
Clinical Molecular Geneticist

