



Reproductive Technologies, Inc.

THE SPERM BANK OF CALIFORNIA

2115 MILVIA STREET, BERKELEY 94704 PHONE 510.841.1858 www.thespermbankofca.org A 501(c)(3) CORPORATION

Acknowledgement of Positive Carrier Screening Results: Donor 6045

I, the undersigned recipient, understand that this donor has tested **POSITIVE** as a carrier for the following condition(s):

- **COL11A2-related conditions**
- **Congenital insensitivity to pain with anhidrosis (NTRK1)**
- **Pyridoxine-dependent epilepsy (ALDH7A1)**

I intend to use sperm samples from this donor for insemination or other assisted conception procedure(s).

I acknowledge that The Sperm Bank of California (TSBC) has made the donor's genetic testing results available to me and my medical providers, and that I have reviewed these results. I understand that TSBC **strongly recommends** that I review these genetic testing results with a Genetic Counselor and my medical providers. I understand that TSBC can refer me to genetic counseling services if desired.

I understand that recipient testing is strongly recommended when a donor has positive carrier screening results and that such testing can reduce but not eliminate risks.

I acknowledge that I personally assume all risks associated with use of semen samples provided by a donor who has tested **POSITIVE as a carrier for COL11A2-related conditions, Congenital insensitivity to pain with anhidrosis (NTRK1), and Pyridoxine-dependent epilepsy (ALDH7A1).**

On behalf of myself and my spouse, heirs, representatives, I hereby release and forever hold harmless TSBC and its current and former officers, directors, employees, attorneys, insurers, consultants, agents, and representatives (collectively "Releases") from any liability or responsibility whatsoever for any and all outcomes, and hereby release and forever discharge Releases from any and all actions, causes of action, demands, damages, losses, liabilities, suits, expenses, including attorneys' fees and costs, of whatever character, in law or in equity, whether currently known, suspected, unknown or unsuspected, matured or unmatured, arising out of my use of sperm donated by a donor who has tested **POSITIVE as a carrier for COL11A2-related conditions, Congenital insensitivity to pain with anhidrosis (NTRK1), and Pyridoxine-dependent epilepsy (ALDH7A1).**

This release involves the waiver of all rights and benefits that I may have under California Civil Code section 1542, which states: "A general release does not extend to claims that the creditor or releasing party does not know or suspect to exist in his or her favor at the time of executing the release and that, if known by him or her, would have materially affected his or her settlement with the debtor or released party."

Please select one of the following:

- I have been tested for the above named condition(s) and/or I plan to be tested prior to using the samples.
- I understand that TSBC **strongly recommends** that I discuss these results with a Genetic Counselor and my medical providers and consider testing for the above named condition(s). At this time I have **declined** testing and/or **do not anticipate being tested.**

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2115 Milvia Street, Berkeley Ca 94704 Phone 510.841.1858 Fax: 510.841.0332 Email: staff@tsbca.org

I understand that if I transfer my vials (or embryos if applicable) to any other person, including my spouse, that TSBC requires that person (1) register with TSBC and (2) complete an **Acknowledgement of Positive Carrier Screening Results**.

I understand that any and all questions as to the legal interpretation, validity or any other aspect of this agreement shall be determined by the laws of the State of California, regardless of the location or residence of any of the parties.

Recipient's signature

Recipient's printed name

Date

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GENETIC TESTING: POSITIVE CARRIER STATUS

This donor tested **POSITIVE** as a carrier for one or more autosomal recessive conditions as described on the prior page and in the attached genetic testing results.

What does it mean to be a carrier?

All people carry genetic mutations in their DNA. Genetic testing can help to identify some, but not all, of these mutations. While this donor carries a mutation for one or more recessively inherited condition(s), **offspring from this donor are not expected to be at risk of developing these condition(s) unless the recipient (or egg provider if different from the recipient) also carries a genetic mutation for the same condition(s).** For this reason, we strongly encourage you to discuss carrier screening for yourself (or your egg provider) with your physician and a genetic counselor. Genetic testing can reduce but not eliminate risks.

What are my next steps?

1. Download the genetic test results and review with your medical providers

We **strongly recommend** that you discuss this donor's genetic test results with your physician **PRIOR TO SCHEDULING A SHIPMENT OR PICK-UP**, to confirm the donor is suitable for your use. Vials retrieved from the building cannot be exchanged or refunded. The donor's genetic test results are available for free download on the donor's page at <https://www.thespermbankofca.org/donor-catalog>.

2. We recommend scheduling a genetic counseling session.

A genetic counselor can explain the results in detail including the inheritance pattern, potential risks to your children, and the available testing options that you may want to consider for yourself (or your egg provider). Phone or in person consultations are available for a fee with TSBC's Genetic Counselors at San Francisco Genetic Counseling (<https://www.sfggenetics.org/>) or you can locate a genetic counselor at www.findageneticcounselor.com.

3. Complete and return the Acknowledgement of Positive Carrier Screening Results

TSBC requires that all recipients selecting this donor complete this acknowledgement form **PRIOR TO SCHEDULING A SHIPMENT OR PICK-UP**. Completing this form documents that you have been informed about this donor's genetic test results and that you are aware of TSBC's recommendation to discuss the genetic test results with your medical providers as noted above.



Reproductive Technologies, Inc.

THE SPERM BANK OF CALIFORNIA

EXPANDED CARRIER SCREENING RESULTS DONOR 6045

Expanded carrier screening for 268 autosomal recessive conditions was completed by Invitae and reported on 01/24/2023.

The results were **POSITIVE** for **COL11A2-related conditions, Congenital insensitivity to pain with anhidrosis (NTRK1), and Pyridoxine-dependent epilepsy (ALDH7A1)**. Donor 6045 is a carrier for these conditions.

It is strongly recommended that recipients who use this donor's sperm undergo carrier screening for these specific conditions.

Testing was negative for the remainder of genes screened.

| Disease | Result | Residual risk to be a carrier (based on Peruvian, Spanish and French ancestry) |
|---|---|--|
| COL11A2-related conditions | POSITIVE | n/a |
| Congenital insensitivity to pain with anhidrosis (NTRK1) | POSITIVE | n/a |
| Pyridoxine-dependent epilepsy (ALDH7A1) | POSITIVE | n/a |
| Cystic Fibrosis | Negative | 1 in 4400 |
| Spinal Muscular Atrophy | Negative: 2 copies exon 7 c.*3+80T>G variant not detected | 1 in 784 |
| HBB Hemoglobinopathies & Thalassemia | Negative | 1 in 4800 |
| Alpha Thalassemia | Negative | Reduced |

Genetic screening tests can significantly reduce, but never completely eliminate, the chance that a person is a carrier for a particular disorder.

Please refer to the donor's Invitae expanded carrier test report for more information on the testing completed and the donor's results.

Please also see the Health Problems List for a summary of the information that this donor has provided to us regarding personal and family medical history.

Sincerely,

Janine Mash
LCGC Certified Genetic Counselor
San Francisco Genetic Counseling

| | | |
|------------------------------------|--|--|
| Patient name: 6045 DONOR | Sample type: Saliva | Report date: 24-JAN-2023 |
| Sex assigned at birth: Male | Sample collection date: 17-JAN-2023 | Invitae #: RQ4395789 |
| Gender: | Sample accession date: 18-JAN-2023 | Clinical team: Janine Mash Lorraine Bonner, MD |
| Patient ID (MRN): | | |

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


RESULT: POSITIVE

This carrier test evaluated 525 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: COL11A2-related conditions | COL11A2 | c.1119+1G>A (Splice donor) | Autosomal recessive | Yes |
| Carrier: Congenital insensitivity to pain with anhidrosis | NTRK1 | c.2041_2068del (p.Thr681Profs*124) | Autosomal recessive | Yes |
| Carrier: Pyridoxine-dependent epilepsy (ALDH7A1-related) | ALDH7A1 | c.589C>T (p.Pro197Ser) | Autosomal recessive | Yes |



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

COL11A2-related conditions

A single Likely Pathogenic variant, c.1119+1G>A (Splice donor), was identified in COL11A2.

What are COL11A2-related conditions?

The COL11A2 gene is associated with multiple conditions that can have both distinct and overlapping symptoms, as well as different inheritance patterns. COL11A2-related conditions include autosomal recessive and autosomal dominant nonsyndromic deafness and otospondylomegaepiphyseal dysplasia, as well as autosomal recessive fibrochondrogenesis and autosomal dominant Stickler syndrome type III. 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 COL11A2 variant identified in this individual is expected to be associated with autosomal recessive COL11A2-related conditions.

COL11A2-related conditions are a spectrum of conditions that typically affect hearing with variable involvement of the skeletal system.

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. 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.

Otospondylomegaepiphyseal dysplasia (OSMED) is characterized by deafness caused by damage to structures in the inner ear (sensorineural deafness), short limbs, enlarged joints, joint pain/stiffness, distinct flattened facial appearance, and an opening in the roof of the mouth (cleft palate). Symptoms become apparent during infancy. Intelligence is not typically affected.

The typical skeletal features of fibrochondrogenesis include short long bones that are wide at the ends (noted as dumbbell-shaped), short and wide ribs, and flattened bones of the spine (platyspondyly) that appear pinched. A narrow chest (thorax) prevents the lungs from developing normally, which results in respiratory failure shortly after birth. Other features include distinct facial appearance and cleft palate. Individuals who survive into childhood have developmental delay, short limbs with joint deformities (contractures), nearsightedness (myopia), clouding of the lens of the eye (cataracts), and sensorineural deafness. Life expectancy is generally reduced, but the prognosis depends on the severity of symptoms.

For all COL11A2-associated conditions, the severity and types of symptoms can vary widely, even within the same family. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

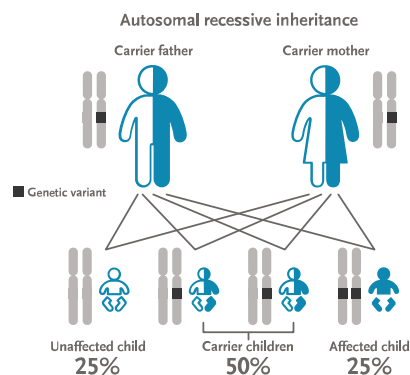
Carrier testing for the reproductive partner is recommended.

If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the COL11A2 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: 6045 DONOR

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residual risk after testing negative for COL11A2-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 |
|--|-----------|------------|------------------------------------|---|
| COL11A2-related conditions (AR) NM_080680.2 | COL11A2 * | Pan-ethnic | ≤1 in 500 | Reduced |


RESULT: CARRIER

Congenital insensitivity to pain with anhidrosis

A single Pathogenic variant, c.2041_2068del (p.Thr681Profs*124), was identified in NTRK1.

What is congenital insensitivity to pain with anhidrosis?

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type 4 (HSAN4), is a condition which affects the nervous system. CIPA is characterized by pain and temperature insensitivity, inability to sweat (anhidrosis), and intellectual disability. The inability to sense all types of pain results in repeated injuries, including biting of the tongue and fingertips (self-mutilation), bone fractures that may not heal properly, joint dislocations and deformations, and skin infections. The inability to sweat can lead to dangerously high fevers, which may be life-threatening. Other neurologic functions are spared, including sense of touch, vibration, and position. Symptoms typically present in infancy or childhood, but age of onset can vary, even between people with the same genetic change. Some people with CIPA have low muscle tone (hypotonia) when they are young, but muscle strength and tone improve and may become normal as they get older. With careful medical attention, affected individuals can live into adulthood. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

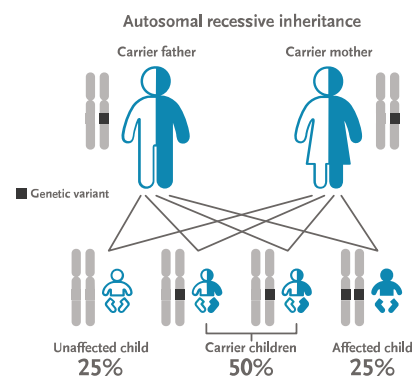
Carrier testing for the reproductive partner is recommended.

+ If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the NTRK1 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 congenital insensitivity to pain with anhidrosis. 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 |
|---|-------|------------|------------------------------------|---|
| Congenital insensitivity to pain with anhidrosis (AR) NM_001012331.1 | NTRK1 | Pan-ethnic | ≤1 in 500 | Reduced |


RESULT: CARRIER

Pyridoxine-dependent epilepsy (ALDH7A1-related)

A single Pathogenic variant, c.589C>T (p.Pro197Ser), was identified in ALDH7A1.

What is pyridoxine-dependent epilepsy (ALDH7A1-related)?

Pyridoxine-dependent epilepsy is a condition that involves seizures. The condition can be caused by changes in different genes. Seizures may be observed at birth or later in infancy and can vary in type, including seizures that affect only one area of the brain and do not affect consciousness (partial), seizures that affect both halves of the brain at the same time (generalized), seizures with muscle jerks (myoclonic), seizures with sudden loss of muscle strength (atonic), seizures in babies that cause arm and leg stiffness and bending of the body (infantile spasms), and seizures with activity that lasts five minutes, or occur within a five-minute time period (status epilepticus). Treatment with vitamin B6 (pyridoxine) has been successfully used to reduce or eliminate the seizures. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

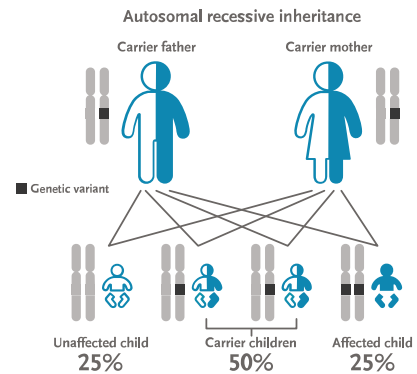
Carrier testing for the reproductive partner is recommended.

+ If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the ALDH7A1 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 pyridoxine-dependent epilepsy (ALDH7A1-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 |
|---|---------|------------|------------------------------------|---|
| Pyridoxine-dependent epilepsy (ALDH7A1-related) (AR) NM_001182.4 | ALDH7A1 | Pan-ethnic | 1 in 127 | 1 in 12600 |

Results to note

SMN1

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

Pseudodeficiency allele(s)

- Benign changes, c.1685T>C (p.Ile562Thr), known to be pseudodeficiency alleles, 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

ALDH7A1, Exon 6, c.589C>T (p.Pro197Ser), heterozygous, PATHOGENIC

- This sequence change replaces proline, which is neutral and non-polar, with serine, which is neutral and polar, at codon 197 of the ALDH7A1 protein (p.Pro197Ser).
- This variant is present in population databases (rs779652673, gnomAD 0.003%).
- This missense change has been observed in individual(s) with pyridoxine-dependent epilepsy (PMID: 20554659). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant.
- This variant is also known as c.505C>T, p.Pro169Ser.
- ClinVar contains an entry for this variant (Variation ID: 426363).
- 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 ALDH7A1 protein function.
- For these reasons, this variant has been classified as Pathogenic.

COL11A2, Intron 8, c.1119+1G>A (Splice donor), heterozygous, Likely Pathogenic

- This sequence change affects a donor splice site in intron 8 of the COL11A2 gene. It is expected to disrupt RNA splicing. Variants that disrupt the donor or acceptor splice site typically lead to a loss of protein function (PMID: 16199547), and loss-of-function variants in COL11A2 are known to be pathogenic (PMID: 10677296, 21204229).
- This variant is present in population databases (rs367706373, gnomAD 0.005%).
- This variant has not been reported in the literature in individuals affected with COL11A2-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1510558).
- Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.
- In summary, the currently available evidence indicates that the variant is pathogenic, but additional data are needed to prove that conclusively. Therefore, this variant has been classified as Likely Pathogenic.

NTRK1, Exon 15, c.2041_2068del (p.Thr681Profs*124), heterozygous, PATHOGENIC

- This sequence change results in a frameshift in the NTRK1 gene (p.Thr681Profs*124). While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 110 amino acid(s) of the NTRK1 protein and extend the protein by 13 additional amino acid residues.
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with NTRK1-related conditions.



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- This variant disrupts a region of the NTRK1 protein in which other variant(s) (p.Pro762Leu) have been determined to be pathogenic (PMID: 15534759, 22032467, 23112235). 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.

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 |



Patient name: 6045 DONOR

Invitae #: RQ4395789

| 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 |
| F11 | NM_000128.3 |
| F2 | NM_000506.3 |
| F5 | NM_000130.4 |
| 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 |

| GENE | TRANSCRIPT |
|---------|----------------|
| FOXRED1 | NM_017547.3 |
| FRAS1 | NM_025074.6 |
| FREM2 | NM_207361.5 |
| 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 |
| GNE* | NM_001128227.2 |
| GNPAT | NM_014236.3 |
| GNPTAB | NM_024312.4 |
| GNPTG | NM_032520.4 |
| GNS | NM_002076.3 |
| GORAB | NM_152281.2 |
| GP1BA* | NM_000173.6 |
| GP9 | NM_000174.4 |
| GRHPR | NM_012203.1 |
| GRIP1 | NM_021150.3 |
| GSS | NM_000178.2 |
| GUCY2D | NM_000180.3 |
| GUSB | NM_000181.3 |

| GENE | TRANSCRIPT |
|---------|----------------|
| HADH | NM_005327.4 |
| HADHA | NM_000182.4 |
| HADHB | NM_000183.2 |
| HAMP | NM_021175.2 |
| HAX1 | NM_006118.3 |
| HBA1* | NM_000558.4 |
| HBA2 | NM_000517.4 |
| HBB* | NM_000518.4 |
| HEXA | NM_000520.4 |
| HEXB | NM_000521.3 |
| HFE | NM_000410.3 |
| HGD | NM_000187.3 |
| 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 |
| IKKB | 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 |

| GENE | TRANSCRIPT |
|---------|----------------|
| 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 |
| 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 |
| MCCC1 | NM_020166.4 |
| MCCC2 | NM_022132.4 |
| MCEE | NM_032601.3 |
| MCOLN1 | NM_020533.2 |
| MCPH1 | NM_024596.4 |
| MECR | NM_016011.3 |
| MED17 | NM_004268.4 |
| MEFV | NM_000243.2 |
| 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 |

| GENE | TRANSCRIPT |
|---------|----------------|
| 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 |
| 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 |

| GENE | TRANSCRIPT |
|--------|--------------------------------|
| 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 |
| 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 |

| GENE | TRANSCRIPT |
|----------|----------------|
| 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 |
| 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 |

| GENE | TRANSCRIPT |
|----------|----------------|
| SACS | NM_014363.5 |
| SAMD9 | NM_017654.3 |
| SAMHD1 | NM_015474.3 |
| SCO2 | NM_005138.2 |
| SEC23B | NM_006363.4 |
| SEPSECS | NM_016955.3 |
| SERPINA1 | NM_000295.4 |
| SGCA | NM_000023.2 |
| SGCB | NM_000232.4 |
| SGCD | NM_000337.5 |
| SGCG | NM_000231.2 |
| 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 |
| SMARCAL1 | NM_014140.3 |
| SMN1* | NM_000344.3 |
| SMPD1 | NM_000543.4 |

| GENE | TRANSCRIPT |
|---------|----------------|
| 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 |
| 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 |
| TC* | 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 |

| GENE | TRANSCRIPT |
|---------|----------------|
| 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 |
| 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. CFTR: Sequencing analysis for exons 7 includes only cds +/- 10 bp. 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. GP1BA: c.104delA (p.Lys35Argfs*4), c.165_168delTGAG (p.Ser55Argfs*12), c.376A>G (p.Asn126Asp), c.434T>C (p.Leu145Pro), c.515C>T (p.Ala172Val), c.584_586delTCC (p.Leu195del), c.673T>A (p.Cys225Ser), c.1454dupT (p.Ser486Ilefs*12), c.1480delA (p.Thr494Profs*59), c.1601_1602delAT (p.Tyr534Cysfs*82), c.1620G>A (p.Trp540*) variants only. MLC1: Sequencing analysis for exons 11 includes only cds +/- 10 bp. BBS9: Deletion/duplication analysis is not offered for exon 4. COL11A2: Deletion/duplication analysis is not offered for exon 36. 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. EYS: Sequencing analysis for exons 30 includes only cds +/- 0 bp. GNE: Sequencing analysis for exons 8 includes only cds +/- 10 bp. HBB: Sequencing analysis is not offered for exons 2-3. 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. 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. PTPRC: Sequencing analysis is not offered for exons 3, 15. DUOX2: Deletion/duplication and sequencing analysis is not offered for exons 6-7. TSFM: Sequencing analysis is not offered for exon 5. GALE: Sequencing analysis for exons 10 includes only cds +/- 5 bp. TYR: Deletion/duplication and sequencing analysis is not offered for exon 5. ANO10: Sequencing analysis for exons 8 includes only cds +/- 0 bp. FANCL: Sequencing analysis for exons 4, 10 includes only cds +/- 10 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. WRN: Deletion/duplication analysis is not offered for exons 10-11. Sequencing analysis for exons 8, 10-11 includes only cds +/- 10 bp. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28. 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. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. 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. GALC: Deletion/duplication analysis is not offered for exon 6. GBA: c.84dupG (p.Leu29A1afs*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.



Patient name: 6045 DONOR

Invitae #: RQ4395789

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. 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. ABCC2: Deletion/duplication analysis is not offered for exons 24-25. OTOA: Deletion/duplication and sequencing analysis is not offered for exons 20-28. ATP8B1: Sequencing analysis for exons 19 includes only cds +/- 10 bp. AIPL1: Sequencing analysis for exons 2 includes only cds +/- 10 bp.

This report has been reviewed and approved by:



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