



Donor 6289

Genetic Testing Summary

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

Last Updated: 09/20/21

Donor Reported Ancestry: Mexican, Spanish (from Spain)

Jewish Ancestry: No

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
Cystic Fibrosis (CF) carrier screening	Negative by gene sequencing in the CFTR gene	1/440
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/894
Expanded Genetic Disease Carrier Screening Panel attached- 283 diseases by gene sequencing	<p>Carrier: Combined SAP Deficiency (PSAP)</p> <p>Carrier: Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (CYP21A2)</p> <p>Carrier: Primary Hyperoxaluria, Type 3 (HOGA1)</p> <p>Negative for other genes sequenced</p>	Partner testing recommended before using this donor.

*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 Information

Name: Donor 6289
 Date of Birth: [REDACTED]
 Sema4 ID: [REDACTED]
 Client ID: [REDACTED]
 Indication: Carrier Testing

Specimen Information

Specimen Type: Blood
 Date Collected: 11/23/2020
 Date Received: 11/24/2020
 Final Report: 12/10/2020

Referring Provider

[REDACTED]
 Fairfax Cryobank, Inc.
 [REDACTED]
 [REDACTED]

Expanded Carrier Screen (283) Minus TSE

Number of genes tested: 283

SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
<p style="text-align: center;">Carrier of Combined SAP Deficiency (AR) Associated gene(s): <i>PSAP</i> Variant(s) Detected: c.650C>T, p.T217I, Pathogenic, Heterozygous (one copy)</p> <p style="text-align: center;">Carrier of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (AR) Associated gene(s): <i>CYP21A2</i> Variant(s) Detected: c.841G>T, p.V281L, Pathogenic, Heterozygous (one copy)</p> <p style="text-align: center;">Carrier of Primary Hyperoxaluria, Type 3 (AR) Associated gene(s): <i>HOGA1</i> Variant(s) Detected: c.700+5G>T, Pathogenic, Heterozygous (one copy)</p>	<p>Negative for all other genes tested To view a full list of genes and diseases tested please see Table 1 in this report</p>

AR=Autosomal recessive; XL=X-linked

Recommendations

- Testing the partner for the above positive disorder(s) and genetic counseling are recommended.
- Please note that for female carriers of X-linked diseases, follow-up testing of a male partner is not indicated.
- CGG repeat analysis of *FMR1* for fragile X syndrome is not performed on males as repeat expansion of premutation alleles is not expected in the male germline.
- Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.
- Consideration of residual risk by ethnicity after a negative carrier screen is recommended for the other diseases on the panel, especially in the case of a positive family history for a specific disorder.

Interpretation of positive results

Combined SAP Deficiency (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.650C>T, p.T217I, was detected in the *PSAP* gene (NM_002778.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for combined SAP deficiency. Therefore, this individual is expected to be at least a carrier for combined SAP deficiency. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Combined SAP Deficiency?

Pathogenic variants in the *PSAP* gene result in a spectrum of pan-ethnic, autosomal recessive neurological diseases, called metachromatic leukodystrophy, combined *PSAP* deficiency, atypical Gaucher disease, and atypical Krabbe disease.

- Metachromatic leukodystrophy results in progressive difficulty walking, deterioration of intelligence, and neuropathy. Eventually, seizures, paralysis, and loss of senses result in an unresponsive state. Age of onset can range from infancy to adulthood; life expectancy depends on the age of onset, but can be as early as childhood for those with early onset disease.
- Combined *PSAP* deficiency is a neurologic disease characterized by changes in brain structures, seizures, and difficulty controlling movements, and is fatal in infancy.
- Atypical Gaucher disease can cause a variety of symptoms, including anemia, organ enlargement, bone deformities, or changes in brain structures. Age of onset can range from infancy to adulthood; life expectancy depends on the age of onset, but can be as early as childhood for those with early onset disease.
- Atypical Krabbe disease involves loss of developmental milestones, irritability, stiffness, and hypersensitivity to stimuli. Subsequently, patients will experience a rapid, severe loss of mental and physical capabilities, until they no longer respond to stimulation. Age of onset can range from infancy to adulthood; life expectancy depends on the age of onset, but can be as early as childhood for those with early onset disease.

It may be possible to predict the phenotype that will develop in some patients, depending on the pathogenic *PSAP* variants identified. However, this may not be possible in all patients.

Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (AR)

Results and Interpretation

CYP21A2 copy number: 2

No pathogenic copy number variants detected

CYP21A2 sequencing: c.841G>T, p.V281L, Pathogenic, Heterozygous (one copy)

Genes analyzed: *CYP21A2* (NM_000500.6)

Inheritance: Autosomal Recessive

A heterozygous (one copy) pathogenic missense variant, c.841G>T, p.V281L, was detected in the *CYP21A2* gene (NM_000500.6). Please note that this variant is typically causative for the non-classic form of congenital adrenal hyperplasia (PMID: 29450859). Variants associated with the non-classic form usually cause non-classic congenital adrenal hyperplasia when found in trans with a pathogenic allele, regardless of whether the second variant is associated with classic or non-classic disease (PMID: 29450859). Therefore, this individual is expected to be at least a carrier for non-classic congenital adrenal hyperplasia. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is congenital adrenal hyperplasia (due to 21-hydroxylase deficiency)?

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency in the enzymes involved in cortisol biosynthesis. The majority (95%) of CAH cases are due to 21-hydroxylase deficiency (21-OHD CAH), which is caused by homozygous or compound heterozygous pathogenic variants in the gene *CYP21A2*. Approximately 20% of mutant alleles have deletions of 30 kb that have been generated by unequal meiotic crossing-over between the two genes. Another 75% of mutant alleles are due to gene conversion events, where an inactivating mutation from the *CYP21A1P* pseudogene is introduced into one copy of the *CYP21A2* gene, thus making the gene non-functional. Three different forms of 21-OHD CAH have been reported: a classic salt wasting form, a classic simple virilizing form, and a non-classic form.

- The classic salt wasting form results from a nonfunctional enzyme and is the most severe. The phenotype includes prenatal onset of virilization and inadequate adrenal aldosterone secretion that can result in fatal salt-wasting crises.
- The classic simple virilizing form results from low levels of functional enzyme and involves prenatal virilization but no salt-wasting.
- The non-classic form, which results from a mild enzyme deficiency, occurs postnatally and involves phenotypes associated with hyperandrogenism, such as hirsutism, delayed menarche, and infertility.

Treatment for the classic forms of the disorder include glucocorticoid and mineralocorticoid replacement therapy, as well as the possibility of feminizing genitoplasty, while patients with the non-classic form usually do not require treatment. The life expectancy for this disorder can be normal with treatment, however the occurrence of salt-wasting crises can be fatal.

Primary Hyperoxaluria, Type 3 (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic intronic variant, c.700+5G>T, was detected in the *HOGA1* gene (NM_138413.3). When this variant is present in trans with a pathogenic variant, it is considered to be causative for primary hyperoxaluria, type 3. Therefore, this individual is expected to be at least a carrier for primary hyperoxaluria, type 3. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Primary Hyperoxaluria, Type 3?

Primary hyperoxaluria, type 3 is an autosomal recessive disease caused by pathogenic variants in the *HOGA1* gene. While it has been diagnosed in patients of various ethnicities, it may be more prevalent in individuals of Ashkenazi Jewish descent due to the presence of a founder mutation. Age of onset is typically in childhood, and the disease is characterized by the accumulation of calcium oxalate in the kidney and urinary tract, leading to kidney stone formation. Some patients have a milder phenotype where they do not develop kidney stones. Life expectancy is not thought to be affected, and no genotype-phenotype correlation has been reported.

Test description

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested, and go.sema4.com/residualrisk for specific detection rates and residual risk by ethnicity. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.



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Genes and diseases tested

For specific detection rates and residual risk by ethnicity, please visit go.sema4.com/residualrisk

Table 1: List of genes and diseases tested with detailed results

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
⊕ Positive				
Combined SAP Deficiency	PSAP	AR	Carrier	c.650C>T, p.T217I, Pathogenic, Heterozygous (one copy)
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	CYP21A2	AR	Carrier	CYP21A2 copy number: 2 No pathogenic copy number variants detected CYP21A2 sequencing: c.841G>T, p.V281L, Pathogenic, Heterozygous (one copy)
Primary Hyperoxaluria, Type 3	HOGA1	AR	Carrier	c.700+5G>T, Pathogenic, Heterozygous (one copy)
⊖ Negative				
3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	HSD3B2	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-Related)	MCCC1	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)	MCCC2	AR	Reduced Risk	
3-Methylglutaconic Aciduria, Type III	OPA3	AR	Reduced Risk	
3-Phosphoglycerate Dehydrogenase Deficiency	PHGDH	AR	Reduced Risk	
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	PTS	AR	Reduced Risk	
Abetalipoproteinemia	MTTP	AR	Reduced Risk	
Achromatopsia (CNGB3-related)	CNGB3	AR	Reduced Risk	
Acrodermatitis Enteropathica	SLC39A4	AR	Reduced Risk	
Acute Infantile Liver Failure	TRMU	AR	Reduced Risk	
Acyl-CoA Oxidase I Deficiency	ACOX1	AR	Reduced Risk	
Adenosine Deaminase Deficiency	ADA	AR	Reduced Risk	
Adrenoleukodystrophy, X-Linked	ABCD1	XL	Reduced Risk	
Aicardi-Goutieres Syndrome (SAMHD1-Related)	SAMHD1	AR	Reduced Risk	
Alpha-Mannosidosis	MAN2B1	AR	Reduced Risk	
Alpha-Thalassemia	HBA1/HBA2	AR	Reduced Risk	HBA1 Copy Number: 2 HBA2 Copy Number: 2 No pathogenic copy number variants detected HBA1/HBA2 Sequencing: Negative
Alpha-Thalassemia Mental Retardation Syndrome	ATRX	XL	Reduced Risk	
Alport Syndrome (COL4A3-Related)	COL4A3	AR	Reduced Risk	
Alport Syndrome (COL4A4-Related)	COL4A4	AR	Reduced Risk	
Alport Syndrome (COL4A5-Related)	COL4A5	XL	Reduced Risk	
Alstrom Syndrome	ALMS1	AR	Reduced Risk	
Andermann Syndrome	SLC12A6	AR	Reduced Risk	
Argininosuccinic Aciduria	ASL	AR	Reduced Risk	
Aromatase Deficiency	CYP19A1	AR	Reduced Risk	
Arthrogryposis, Mental Retardation, and Seizures	SLC35A3	AR	Reduced Risk	
Asparagine Synthetase Deficiency	ASNS	AR	Reduced Risk	
Aspartylglycosaminuria	AGA	AR	Reduced Risk	
Ataxia With Isolated Vitamin E Deficiency	TTPA	AR	Reduced Risk	
Ataxia-Telangiectasia	ATM	AR	Reduced Risk	
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay	SACS	AR	Reduced Risk	
Bardet-Biedl Syndrome (BBS10-Related)	BBS10	AR	Reduced Risk	
Bardet-Biedl Syndrome (BBS12-Related)	BBS12	AR	Reduced Risk	
Bardet-Biedl Syndrome (BBS1-Related)	BBS1	AR	Reduced Risk	

Bardet-Biedl Syndrome (BBS2-Related)	BBS2	AR	Reduced Risk
Bare Lymphocyte Syndrome, Type II	CIITA	AR	Reduced Risk
Bartter Syndrome, Type 4A	BSND	AR	Reduced Risk
Bernard-Soulier Syndrome, Type A1	GP1BA	AR	Reduced Risk
Bernard-Soulier Syndrome, Type C	GP9	AR	Reduced Risk
Beta-Globin-Related Hemoglobinopathies	HBB	AR	Reduced Risk
Beta-Ketothiolase Deficiency	ACAT1	AR	Reduced Risk
Bilateral Frontoparietal Polymicrogyria	GPR56	AR	Reduced Risk
Biotinidase Deficiency	BTD	AR	Reduced Risk
Bloom Syndrome	BLM	AR	Reduced Risk
Canavan Disease	ASPA	AR	Reduced Risk
Carbamoylphosphate Synthetase I Deficiency	CPS1	AR	Reduced Risk
Camitine Palmitoyltransferase IA Deficiency	CPT1A	AR	Reduced Risk
Camitine Palmitoyltransferase II Deficiency	CPT2	AR	Reduced Risk
Carpenter Syndrome	RAB23	AR	Reduced Risk
Cartilage-Hair Hypoplasia	RMRP	AR	Reduced Risk
Cerebral Creatine Deficiency Syndrome 1	SLC6A8	XL	Reduced Risk
Cerebral Creatine Deficiency Syndrome 2	GAMT	AR	Reduced Risk
Cerebrotendinous Xanthomatosis	CYP27A1	AR	Reduced Risk
Charcot-Marie-Tooth Disease, Type 4D	NDRG1	AR	Reduced Risk
Charcot-Marie-Tooth Disease, Type 5 / Arts Syndrome	PRPS1	XL	Reduced Risk
Charcot-Marie-Tooth Disease, X-Linked	GJB1	XL	Reduced Risk
Choreoacanthocytosis	VPS13A	AR	Reduced Risk
Choroideremia	CHM	XL	Reduced Risk
Chronic Granulomatous Disease (CYBA-Related)	CYBA	AR	Reduced Risk
Chronic Granulomatous Disease (CYBB-Related)	CYBB	XL	Reduced Risk
Citrin Deficiency	SLC25A13	AR	Reduced Risk
Citrullinemia, Type 1	ASS1	AR	Reduced Risk
Cohen Syndrome	VPS13B	AR	Reduced Risk
Combined Malonic and Methylmalonic Aciduria	ACSF3	AR	Reduced Risk
Combined Oxidative Phosphorylation Deficiency 1	GFM1	AR	Reduced Risk
Combined Oxidative Phosphorylation Deficiency 3	TSMF	AR	Reduced Risk
Combined Pituitary Hormone Deficiency 2	PROP1	AR	Reduced Risk
Combined Pituitary Hormone Deficiency 3	LHX3	AR	Reduced Risk
Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency	CYP17A1	AR	Reduced Risk
Congenital Amegakaryocytic Thrombocytopenia	MPL	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ia	PMM2	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ib	MPI	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ic	ALG6	AR	Reduced Risk
Congenital Insensitivity to Pain with Anhidrosis	NTRK1	AR	Reduced Risk
Congenital Myasthenic Syndrome (CHRNE-Related)	CHRNE	AR	Reduced Risk
Congenital Myasthenic Syndrome (RAPSN-Related)	RAPSN	AR	Reduced Risk
Congenital Neutropenia (HAX1-Related)	HAX1	AR	Reduced Risk
Congenital Neutropenia (VPS45-Related)	VPS45	AR	Reduced Risk
Corneal Dystrophy and Perceptive Deafness	SLC4A11	AR	Reduced Risk
Corticosterone Methyloxidase Deficiency	CYP11B2	AR	Reduced Risk
Cystic Fibrosis	CFTR	AR	Reduced Risk
Cystinosis	CTNS	AR	Reduced Risk
D-Bifunctional Protein Deficiency	HSD17B4	AR	Reduced Risk
Deafness, Autosomal Recessive 77	LOXHD1	AR	Reduced Risk
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	DMD	XL	Reduced Risk
Dyskeratosis Congenita (RTEL1-Related)	RTEL1	AR	Reduced Risk
Dystrophic Epidermolysis Bullosa	COL7A1	AR	Reduced Risk
Ehlers-Danlos Syndrome, Type VIIC	ADAMTS2	AR	Reduced Risk
Ellis-van Creveld Syndrome (EVC-Related)	EVC	AR	Reduced Risk
Emery-Dreifuss Myopathy 1	EMD	XL	Reduced Risk
Enhanced S-Cone Syndrome	NR2E3	AR	Reduced Risk
Ethylmalonic Encephalopathy	ETHE1	AR	Reduced Risk

Fabry Disease	GLA	XL	Reduced Risk	
Factor IX Deficiency	F9	XL	Reduced Risk	
Factor XI Deficiency	F11	AR	Reduced Risk	
Familial Autosomal Recessive Hypercholesterolemia	LDLRAP1	AR	Reduced Risk	
Familial Dysautonomia	IKBKAP	AR	Reduced Risk	
Familial Hypercholesterolemia	LDLR	AR	Reduced Risk	
Familial Hyperinsulinism (ABCC8-Related)	ABCC8	AR	Reduced Risk	
Familial Hyperinsulinism (KCNJ11-Related)	KCNJ11	AR	Reduced Risk	
Familial Mediterranean Fever	MEFV	AR	Reduced Risk	
Fanconi Anemia, Group A	FANCA	AR	Reduced Risk	
Fanconi Anemia, Group C	FANCC	AR	Reduced Risk	
Fanconi Anemia, Group G	FANCG	AR	Reduced Risk	
Fragile X Syndrome	FMR1	XL	Reduced Risk	FMR1 CGG repeat sizes: Not Performed FMR1 Sequencing: Negative Fragile X CGG triplet repeat expansion testing was not performed at this time, as the patient has either been previously tested or is a male.
Fumarase Deficiency	FH	AR	Reduced Risk	
GRACILE Syndrome and Other BCS1L-Related Disorders	BCS1L	AR	Reduced Risk	
Galactokinase Deficiency	GALK1	AR	Reduced Risk	
Galactosemia	GALT	AR	Reduced Risk	
Gaucher Disease	GBA	AR	Reduced Risk	
Gitelman Syndrome	SLC12A3	AR	Reduced Risk	
Glutaric Acidemia, Type I	GCDH	AR	Reduced Risk	
Glutaric Acidemia, Type IIa	ETFA	AR	Reduced Risk	
Glutaric Acidemia, Type IIc	ETFDH	AR	Reduced Risk	
Glycine Encephalopathy (AMT-Related)	AMT	AR	Reduced Risk	
Glycine Encephalopathy (GLDC-Related)	GLDC	AR	Reduced Risk	
Glycogen Storage Disease, Type II	GAA	AR	Reduced Risk	
Glycogen Storage Disease, Type III	AGL	AR	Reduced Risk	
Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	GBE1	AR	Reduced Risk	
Glycogen Storage Disease, Type Ia	G6PC	AR	Reduced Risk	
Glycogen Storage Disease, Type Ib	SLC37A4	AR	Reduced Risk	
Glycogen Storage Disease, Type V	PYGM	AR	Reduced Risk	
Glycogen Storage Disease, Type VII	PFKM	AR	Reduced Risk	
HMG-CoA Lyase Deficiency	HMGCL	AR	Reduced Risk	
Hemochromatosis, Type 2A	HFE2	AR	Reduced Risk	
Hemochromatosis, Type 3	TFR2	AR	Reduced Risk	
Hereditary Fructose Intolerance	ALDOB	AR	Reduced Risk	
Hereditary Spastic Paraparesis 49	TECP2	AR	Reduced Risk	
Hermansky-Pudlak Syndrome, Type 1	HPS1	AR	Reduced Risk	
Hermansky-Pudlak Syndrome, Type 3	HPS3	AR	Reduced Risk	
Holocarboxylase Synthetase Deficiency	HLCS	AR	Reduced Risk	
Homocystinuria (CBS-Related)	CBS	AR	Reduced Risk	
Homocystinuria due to MTHFR Deficiency	MTHFR	AR	Reduced Risk	
Homocystinuria, cbI E Type	MTRR	AR	Reduced Risk	
Hydrolethalus Syndrome	HYLS1	AR	Reduced Risk	
Hyperomithinemia-Hyperammonemia-Homocitrullinuria Syndrome	SLC25A15	AR	Reduced Risk	
Hypohidrotic Ectodermal Dysplasia 1	EDA	XL	Reduced Risk	
Hypophosphatasia	ALPL	AR	Reduced Risk	
Inclusion Body Myopathy 2	GNE	AR	Reduced Risk	
Infantile Cerebral and Cerebellar Atrophy	MED17	AR	Reduced Risk	
Isovaleric Acidemia	IVD	AR	Reduced Risk	
Joubert Syndrome 2	TMEM216	AR	Reduced Risk	
Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome	RPGRIPL	AR	Reduced Risk	
Junctional Epidermolysis Bullosa (LAMA3-Related)	LAMA3	AR	Reduced Risk	
Junctional Epidermolysis Bullosa (LAMB3-Related)	LAMB3	AR	Reduced Risk	

Junctional Epidermolysis Bullosa (LAMC2-Related)	LAMC2	AR	Reduced Risk
Krabbe Disease	GALC	AR	Reduced Risk
Lamellar Ichthyosis, Type 1	TGM1	AR	Reduced Risk
Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies	CEP290	AR	Reduced Risk
Leber Congenital Amaurosis 13	RDH12	AR	Reduced Risk
Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	RPE65	AR	Reduced Risk
Leber Congenital Amaurosis 5	LCA5	AR	Reduced Risk
Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	CRB1	AR	Reduced Risk
Leigh Syndrome, French-Canadian Type	LRPPRC	AR	Reduced Risk
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogryposis with Anterior Horn Cell Disease	GLE1	AR	Reduced Risk
Leukoencephalopathy with Vanishing White Matter	EIF2B5	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2A	CAPN3	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2B	DYSF	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2C	SGCG	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2D	SGCA	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2E	SGCB	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2I	FKRP	AR	Reduced Risk
Lipoamide Dehydrogenase Deficiency	DLD	AR	Reduced Risk
Lipoid Adrenal Hyperplasia	STAR	AR	Reduced Risk
Lipoprotein Lipase Deficiency	LPL	AR	Reduced Risk
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	HADHA	AR	Reduced Risk
Lysinuric Protein Intolerance	SLC7A7	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1a	BCKDHA	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1b	BCKDHB	AR	Reduced Risk
Meckel 1 / Bardet-Biedl Syndrome 13	MKS1	AR	Reduced Risk
Medium Chain Acyl-CoA Dehydrogenase Deficiency	ACADM	AR	Reduced Risk
Megalencephalic Leukoencephalopathy with Subcortical Cysts	MLC1	AR	Reduced Risk
Menkes Disease	ATP7A	XL	Reduced Risk
Metachromatic Leukodystrophy	ARSA	AR	Reduced Risk
Methylmalonic Acidemia (MMAA-Related)	MMAA	AR	Reduced Risk
Methylmalonic Acidemia (MMAB-Related)	MMAB	AR	Reduced Risk
Methylmalonic Acidemia (MUT-Related)	MUT	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	MMACHC	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	MMADHC	AR	Reduced Risk
Microphthalmia / Anophthalmia	VSX2	AR	Reduced Risk
Mitochondrial Complex I Deficiency (ACAD9-Related)	ACAD9	AR	Reduced Risk
Mitochondrial Complex I Deficiency (NDUFAF5-Related)	NDUFAF5	AR	Reduced Risk
Mitochondrial Complex I Deficiency (NDUFS6-Related)	NDUFS6	AR	Reduced Risk
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	MPV17	AR	Reduced Risk
Mitochondrial Myopathy and Sideroblastic Anemia 1	PUS1	AR	Reduced Risk
Mucopolidosis II / IIIA	GNPTAB	AR	Reduced Risk
Mucopolidosis III Gamma	GNPTG	AR	Reduced Risk
Mucopolidosis IV	MCOLN1	AR	Reduced Risk
Mucopolysaccharidosis Type I	IDUA	AR	Reduced Risk
Mucopolysaccharidosis Type II	IDS	XL	Reduced Risk
Mucopolysaccharidosis Type IIIA	SGSH	AR	Reduced Risk
Mucopolysaccharidosis Type IIIB	NAGLU	AR	Reduced Risk
Mucopolysaccharidosis Type IIIC	HGSNAT	AR	Reduced Risk
Mucopolysaccharidosis Type IIID	GNS	AR	Reduced Risk
Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	GLB1	AR	Reduced Risk

Mucopolysaccharidosis type IX	<i>HYAL1</i>	AR	Reduced Risk
Mucopolysaccharidosis type VI	<i>ARSB</i>	AR	Reduced Risk
Multiple Sulfatase Deficiency	<i>SUMF1</i>	AR	Reduced Risk
Muscle-Eye-Brain Disease and Other <i>POMGNT1</i> -Related Congenital Muscular Dystrophy-Dystroglycanopathies	<i>POMGNT1</i>	AR	Reduced Risk
Myoneurogastrointestinal Encephalopathy	<i>TYMP</i>	AR	Reduced Risk
Myotubular Myopathy 1	<i>MTM1</i>	XL	Reduced Risk
N-Acetylglutamate Synthase Deficiency	<i>NAGS</i>	AR	Reduced Risk
Nemaline Myopathy 2	<i>NEB</i>	AR	Reduced Risk
Nephrogenic Diabetes Insipidus, Type II	<i>AQP2</i>	AR	Reduced Risk
Nephrotic Syndrome (<i>NPHS1</i> -Related) / Congenital Finnish Nephrosis	<i>NPHS1</i>	AR	Reduced Risk
Nephrotic Syndrome (<i>NPHS2</i> -Related) / Steroid-Resistant Nephrotic Syndrome	<i>NPHS2</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>CLN3</i> -Related)	<i>CLN3</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>CLN5</i> -Related)	<i>CLN5</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>CLN6</i> -Related)	<i>CLN6</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>CLN8</i> -Related)	<i>CLN8</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>MFSD8</i> -Related)	<i>MFSD8</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>PPT1</i> -Related)	<i>PPT1</i>	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (<i>TPP1</i> -Related)	<i>TPP1</i>	AR	Reduced Risk
Niemann-Pick Disease (<i>SMPD1</i> -Related)	<i>SMPD1</i>	AR	Reduced Risk
Niemann-Pick Disease, Type C (<i>NPC1</i> -Related)	<i>NPC1</i>	AR	Reduced Risk
Niemann-Pick Disease, Type C (<i>NPC2</i> -Related)	<i>NPC2</i>	AR	Reduced Risk
Nijmegen Breakage Syndrome	<i>NBN</i>	AR	Reduced Risk
Non-Syndromic Hearing Loss (<i>GJB2</i> -Related)	<i>GJB2</i>	AR	Reduced Risk
Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome	<i>WNT10A</i>	AR	Reduced Risk
Omenn Syndrome (<i>RAG2</i> -Related)	<i>RAG2</i>	AR	Reduced Risk
Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type	<i>DCLRE1C</i>	AR	Reduced Risk
Ornithine Aminotransferase Deficiency	<i>OAT</i>	AR	Reduced Risk
Ornithine Transcarbamylase Deficiency	<i>OTC</i>	XL	Reduced Risk
Osteopetrosis 1	<i>TCIRG1</i>	AR	Reduced Risk
Pendred Syndrome	<i>SLC26A4</i>	AR	Reduced Risk
Phenylalanine Hydroxylase Deficiency	<i>PAH</i>	AR	Reduced Risk
Polycystic Kidney Disease, Autosomal Recessive	<i>PKHD1</i>	AR	Reduced Risk
Polyglandular Autoimmune Syndrome, Type 1	<i>AIRE</i>	AR	Reduced Risk
Pontocerebellar Hypoplasia, Type 1A	<i>VRK1</i>	AR	Reduced Risk
Pontocerebellar Hypoplasia, Type 6	<i>RARS2</i>	AR	Reduced Risk
Primary Carnitine Deficiency	<i>SLC22A5</i>	AR	Reduced Risk
Primary Ciliary Dyskinesia (<i>DNAH5</i> -Related)	<i>DNAH5</i>	AR	Reduced Risk
Primary Ciliary Dyskinesia (<i>DNAI1</i> -Related)	<i>DNAI1</i>	AR	Reduced Risk
Primary Ciliary Dyskinesia (<i>DNAI2</i> -Related)	<i>DNAI2</i>	AR	Reduced Risk
Primary Hyperoxaluria, Type 1	<i>AGXT</i>	AR	Reduced Risk
Primary Hyperoxaluria, Type 2	<i>GRHPR</i>	AR	Reduced Risk
Progressive Cerebello-Cerebral Atrophy	<i>SEPSECS</i>	AR	Reduced Risk
Progressive Familial Intrahepatic Cholestasis, Type 2	<i>ABCB11</i>	AR	Reduced Risk
Propionic Acidemia (<i>PCCA</i> -Related)	<i>PCCA</i>	AR	Reduced Risk
Propionic Acidemia (<i>PCCB</i> -Related)	<i>PCCB</i>	AR	Reduced Risk
Pycnodysostosis	<i>CTSK</i>	AR	Reduced Risk
Pyruvate Dehydrogenase E1-Alpha Deficiency	<i>PDHA1</i>	XL	Reduced Risk
Pyruvate Dehydrogenase E1-Beta Deficiency	<i>PDHB</i>	AR	Reduced Risk
Renal Tubular Acidosis and Deafness	<i>ATP6V1B1</i>	AR	Reduced Risk
Retinitis Pigmentosa 25	<i>EYS</i>	AR	Reduced Risk
Retinitis Pigmentosa 26	<i>CERKL</i>	AR	Reduced Risk
Retinitis Pigmentosa 28	<i>FAM161A</i>	AR	Reduced Risk
Retinitis Pigmentosa 59	<i>DHDDS</i>	AR	Reduced Risk
Rhizomelic Chondrodysplasia Punctata, Type 1	<i>PEX7</i>	AR	Reduced Risk

Rhizomelic Chondrodysplasia Punctata, Type 3	AGPS	AR	Reduced Risk	
Roberts Syndrome	ESCO2	AR	Reduced Risk	
Salla Disease	SLC17A5	AR	Reduced Risk	
Sandhoff Disease	HEXB	AR	Reduced Risk	
Schimke Immunoosseous Dysplasia	SMARCAL1	AR	Reduced Risk	
Segawa Syndrome	TH	AR	Reduced Risk	
Sjogren-Larsson Syndrome	ALDH3A2	AR	Reduced Risk	
Smith-Lemli-Opitz Syndrome	DHCR7	AR	Reduced Risk	
Spinal Muscular Atrophy	SMN1	AR	Reduced Risk	SMN1 copy number: 2 SMN2 copy number: 1 c.:3+80T>G: Negative
Spondylothoracic Dysostosis	MESP2	AR	Reduced Risk	
Steel Syndrome	COL27A1	AR	Reduced Risk	
Stuve-Wiedemann Syndrome	LIFR	AR	Reduced Risk	
Sulfate Transporter-Related Osteochondrodysplasia	SLC26A2	AR	Reduced Risk	
Tay-Sachs Disease	HEXA	AR	Reduced Risk	
Tyrosinemia, Type I	FAH	AR	Reduced Risk	
Usher Syndrome, Type IB	MYO7A	AR	Reduced Risk	
Usher Syndrome, Type IC	USH1C	AR	Reduced Risk	
Usher Syndrome, Type ID	CDH23	AR	Reduced Risk	
Usher Syndrome, Type IF	PCDH15	AR	Reduced Risk	
Usher Syndrome, Type IIA	USH2A	AR	Reduced Risk	
Usher Syndrome, Type III	CLRN1	AR	Reduced Risk	
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	ACADVL	AR	Reduced Risk	
Walker-Warburg Syndrome and Other FKTN-Related Dystrophies	FKTN	AR	Reduced Risk	
Wilson Disease	ATP7B	AR	Reduced Risk	
Wolman Disease / Cholesteryl Ester Storage Disease	LIPA	AR	Reduced Risk	
X-Linked Juvenile Retinoschisis	RS1	XL	Reduced Risk	
X-Linked Severe Combined Immunodeficiency	IL2RG	XL	Reduced Risk	
Zellweger Syndrome Spectrum (PEX10-Related)	PEX10	AR	Reduced Risk	
Zellweger Syndrome Spectrum (PEX1-Related)	PEX1	AR	Reduced Risk	
Zellweger Syndrome Spectrum (PEX2-Related)	PEX2	AR	Reduced Risk	
Zellweger Syndrome Spectrum (PEX6-Related)	PEX6	AR	Reduced Risk	

AR=Autosomal recessive; XL=X-linked

Test methods and comments

Genomic DNA isolated from this patient was analyzed by one or more of the following methodologies, as applicable:

Fragile X CGG Repeat Analysis (Analytical Detection Rate >99%)

PCR amplification using Asuragen, Inc. AmpliX[®]FMR1 PCR reagents followed by capillary electrophoresis for allele sizing was performed. Samples positive for FMR1 CGG repeats in the premutation and full mutation size range were further analyzed by Southern blot analysis to assess the size and methylation status of the FMR1 CGG repeat.

Genotyping (Analytical Detection Rate >99%)

Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY[®] System were used to identify certain recurrent variants that are complex in nature or are present in low copy repeats. Rare sequence variants may interfere with assay performance.

Multiplex Ligation-Dependent Probe Amplification (MLPA) (Analytical Detection Rate >99%)

MLPA[®] probe sets and reagents from MRC-Holland were used for copy number analysis of specific targets versus known control samples. False positive or negative results may occur due to rare sequence variants in target regions detected by MLPA probes. Analytical sensitivity and specificity of the MLPA method are both 99%.

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. This test is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, may not be detected. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported. Analyses of *HBA1* and *HBA2* are performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For Duchenne muscular dystrophy, the copy numbers of all *DMD* exons were analyzed. Potentially pathogenic single exon deletions and duplications are confirmed by a second method. Analysis of *DMD* is performed in association with sequencing of the coding regions.

For congenital adrenal hyperplasia, the copy number of the *CYP21A2* gene was analyzed. This analysis can detect large deletions typically due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. Classic 30-kb deletions make up approximately 20% of *CYP21A2* pathogenic alleles. This test may also identify certain point mutations in *CYP21A2* caused by gene conversion events between *CYP21A2* and *CYP21A1P*. Some carriers may not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *CYP21A2* gene on one chromosome and loss of *CYP21A2* (deletion) on the other chromosome. Analysis of *CYP21A2* is performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For spinal muscular atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected with this assay. Depending on ethnicity, 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 2+0 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals diagnosed with SMA have a causative *SMN1* variant that occurred *de novo*, and therefore cannot be picked up by carrier screening in the parents. Analysis of *SMN1* is performed in association with short-read sequencing of exons 2a-7, followed by confirmation using long-range PCR (described below).

The presence of the c.*3+80T>G (chr5:70,247,901T>G) variant allele in an individual with Ashkenazi Jewish or Asian ancestry is typically indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, c.*3+80T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of c.*3+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

MLPA for Gaucher disease (*GBA*), cystic fibrosis (*CFTR*), and non-syndromic hearing loss (*GJB2/GJB6*) will only be performed if indicated for confirmation of detected CNVs. If *GBA* analysis was performed, the copy numbers of exons 1, 3, 4, and 6 - 10 of the *GBA* gene (of 11 exons total) were analyzed. If *CFTR* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number of the two *GJB2* exons were analyzed, as well as the presence or absence of the two upstream deletions of the *GJB2* regulatory region, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854).

Next Generation Sequencing (NGS) (Analytical Detection Rate >95%)

NGS was performed on a panel of genes for the purpose of identifying pathogenic or likely pathogenic variants.

Agilent SureSelectTMXT Low Input technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Libraries were pooled and sequenced on the Illumina NovaSeq 9000 platform, using paired-end 100 bp reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

The coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage (minimum of 20X) and data quality threshold values. Most exons not meeting a minimum of >20X read depth across the exon are further analyzed by Sanger sequencing. Please note that several genomic regions present difficulties in mapping or obtaining read depth >20X. These regions, which are described below, will not be reflexed to Sanger sequencing if the mapping quality or coverage is poor. Any variants identified during testing in these regions are confirmed by a second method and reported if determined to be pathogenic or likely pathogenic. However, as there is a possibility of false negative results within these regions, detection rates and residual risks for these genes have been calculated with the presumption that variants in these exons will not be detected, unless included in the MassARRAY[®] genotyping platform.

Exceptions: *ABCD1* (NM_000033.3) exons 8 and 9; *ADA* (NM_000022.2) exon 1; *ADAMTS2* (NM_014244.4) exon 1; *AGPS* (NM_003659.3) chr2:178,257,512 - 178,257,649 (partial exon 1); *ALMS1* (NM_015120.4) chr2:73,612,990 - 73,613,041 (partial exon 1); *CEP290* (NM_025114.3) exon 5, exon 7, chr12:88,519,017 - 88,519,039 (partial exon 13), chr12:88,514,049 - 88,514,058 (partial exon 15), chr12:88,502,837 - 88,502,841 (partial exon 23), chr12:88,481,551 - 88,481,589 (partial exon 32), chr12:88,471,605 - 88,471,700 (partial exon 40); *CFTR* (NM_000492.3) exon 10; *COL4A4* (NM_000092.4) chr2:227,942,604 - 227,942,619 (partial exon 25); *CYP11B2* (NM_000498.3) exons 3 - 7; *DNAI2* (NM_023036.4) chr17:72,308,136 - 72,308,147 (partial exon 12); *EVC* (NM_153717.2) exon 1; *FH* (NM_000143.3) exon 1; *GAMT* (NM_000156.5) exon 1; *GLDC* (NM_000170.2) exon 1; *GNPTAB* (NM_024312.4) chr17:4,837,000 - 4,837,400 (partial exon 2); *GNPTG* (NM_032520.4) exon 1; *HGSNAT* (NM_152419.2) exon 1; *IDS* (NM_000202.6) exon 3; *LIFR* (NM_002310.5) exon 19; *NEB* (NM_001271208.1) exons 82 - 105; *NPC1* (NM_000271.4) chr18:21,123,519 - 21,123,538 (partial exon 14); *PUS1* (NM_025215.5) ; chr12:132,414,446 - 132,414,532 (partial exon 2); *RPGRIP1L* (NM_015272.2) exon 23; *SGSH* (NM_000199.3) chr17:78,194,022 - 78,194,072 (partial exon 1); *SLC6A8* (NM_005629.3) exons 3 and 4.

This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions may not be detected, including, but not limited to, UTRs, promoters, and deep intronic areas, or regions that fall into the Exceptions mentioned above. This technology may not detect all small insertion/deletions and is not diagnostic for repeat expansions and structural genomic variation. In addition, a mutation(s) in a gene not included on the panel could be present in this patient.

Variant interpretation and classification was performed based on the American College of Medical Genetics Standards and Guidelines for the Interpretation of Sequence Variants (Richards et al, 2015). All potentially pathogenic variants may be confirmed by either a specific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likely benign variants or variants of uncertain significance identified during this analysis will not be reported.

Next Generation Sequencing for SMN1

Exonic regions and intron/exon splice junctions of *SMN1* and *SMN2* were captured, sequenced, and analyzed as described above. Any variants located within exons 2a-7 and classified as pathogenic or likely pathogenic were confirmed to be in either *SMN1* or *SMN2* using gene-specific long-range PCR analysis followed by Sanger sequencing. Variants located in exon 1 cannot be accurately assigned to either *SMN1* or *SMN2* using our current methodology, and so these variants are considered to be of uncertain significance and are not reported.

Copy Number Variant Analysis (Analytical Detection Rate >95%)

Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exome hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom arrayCGH platform, quantitative PCR, or MLPA (depending on CNV size and gene content). While this algorithm is designed to pick up deletions and duplications of 2 or more exons in length, potentially pathogenic single-exon CNVs will be confirmed and reported, if detected.

Exon Array (Confirmation method) (Accuracy >99%)

The customized oligonucleotide microarray (Oxford Gene Technology) is a highly-targeted exon-focused array capable of detecting medically relevant microdeletions and microduplications at a much higher resolution than traditional aCGH methods. Each array matrix has approximately 180,000 60-mer oligonucleotide probes that cover the entire genome. This platform is designed based on human genome NCBI Build 37 (hg19) and the CGH probes are enriched to target the exonic regions of the genes in this panel.

Quantitative PCR (Confirmation method) (Accuracy >99%)

The relative quantification PCR is utilized on a Roche Universal Library Probe (UPL) system, which relates the PCR signal of the target region in one group to another. To test for genomic imbalances, both sample DNA and reference DNA is amplified with primer/probe sets that specific to the target region and a control region with known genomic copy number. Relative genomic copy numbers are calculated based on the standard $\Delta\Delta C_t$ formula.

Long-Range PCR (Analytical Detection Rate >99%)

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where two copies of a gene are located on the same chromosome in tandem, only the second copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the

CYP21A2 gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. When an individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

Residual Risk Calculations

Carrier frequencies and detection rates for each ethnicity were calculated through the combination of internal curations of >30,000 variants and genomic frequency data from >138,000 individuals across seven ethnic groups in the gnomAD database. Additional variants in HGMD and novel deleterious variants were also incorporated into the calculation. Residual risk values are calculated using a Bayesian analysis combining the *a priori* risk of being a pathogenic mutation carrier (carrier frequency) and the detection rate. They are provided only as a guide for assessing approximate risk given a negative result, and values will vary based on the exact ethnic background of an individual. This report does not represent medical advice but should be interpreted by a genetic counselor, medical geneticist or physician skilled in genetic result interpretation and the relevant medical literature.

Personalized Residual Risk Calculations

Agilent SureSelect™XT Low-Input technology was utilized in order to create whole-genome libraries for each patient sample. Libraries were then pooled and sequenced on the Illumina NovaSeq platform. Each sequencing lane was multiplexed to achieve 0.4-2x genome coverage, using paired-end 100 bp reads. The sequencing data underwent ancestral analysis using a customized, licensed bioinformatics algorithm that was validated in house. Identified sub-ethnic groupings were binned into one of 7 continental-level groups (African, East Asian, South Asian, Non-Finnish European, Finnish, Native American, and Ashkenazi Jewish) or, for those ethnicities that matched poorly to the continental-level groups, an 8th "unassigned" group, which were then used to select residual risk values for each gene. For individuals belonging to multiple high-level ethnic groupings, a weighting strategy was used to select the most appropriate residual risk. For genes that had insufficient data to calculate ethnic-specific residual risk values, or for sub-ethnic groupings that fell into the "unassigned" group, a "worldwide" residual risk was used. This "worldwide" residual risk was calculated using data from all available continental-level groups.

Sanger Sequencing (Confirmation method) (Accuracy >99%)

Sanger sequencing, as indicated, was performed using BigDye Terminator chemistry with the ABI 3730 DNA analyzer with target specific amplicons. It also may be used to supplement specific guaranteed target regions that fail NGS sequencing due to poor quality or low depth of coverage (<20 reads) or as a confirmatory method for NGS positive results. False negative results may occur if rare variants interfere with amplification or annealing.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

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Additional disease-specific references available upon request.