



## Donor 6224

### Genetic Testing Summary

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

Last Updated: 06/02/20

Donor Reported Ancestry: Italian, German, Honduran

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	Carrier: Beta Thalassemia	Partner testing recommended before using this donor.
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	Carrier: Beta-Globin Related Hemoglobinopathies (HBB)- Beta Thalassemia variant	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 6224  
Date of Birth: [REDACTED]  
Sema4 ID: [REDACTED]  
Client ID: [REDACTED]  
Indication: Carrier Testing

**Specimen Information**

Specimen Type: Blood  
Date Collected: 07/10/2019  
Date Received: 07/12/2019  
Final Report: 07/25/2019

**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><b>Carrier of Beta-Globin-Related Hemoglobinopathies (AR)</b> Associated gene(s): <i>HBB</i> Variant(s) Detected: c.g2+6T&gt;C, Pathogenic, Heterozygous (one copy)</p>	<p><b>Negative for all other genes tested</b> 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.
- In addition to *HBB* sequencing, testing the partner for alpha-thalassemia to assess duplication status is recommended in order to rule out the possibility of being a thalassemia intermedia carrier couple.
- 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

### Beta-Globin-Related Hemoglobinopathies (AR)

#### Results and Interpretation

A heterozygous (one copy) pathogenic intronic variant, c.92+6T>C, was detected in the *HBB* gene (NM\_000518.4). When this variant is present in trans with a pathogenic variant, it is considered to be causative for a beta-globin related hemoglobinopathy. Therefore, this individual is expected to be at least a carrier for a beta-globin-related hemoglobinopathy. Carriers may be slightly anemic, but are expected to be clinically asymptomatic.

#### What is Beta-Globin-Related Hemoglobinopathies?

Pathogenic variants in the beta-globin gene (*HBB*) cause a variety of autosomal recessive diseases of aberrant hemoglobin, the protein that carries oxygen in the blood. The most frequent hemoglobinopathies are beta-thalassemia, sickle cell disease and HbC disease.

- In individuals with beta-thalassemia, hemoglobin is not properly synthesized and results in small red blood cells that are inefficient at carrying oxygen. Individuals with severe beta-thalassemia require life-long blood transfusions and chelation therapy to remove the extra iron that results from the blood transfusions. Individuals with milder forms of beta-thalassemia may not require transfusions. Although current treatments can extend the life expectancy into adulthood, patients usually do not survive beyond their 30s as a result of cardiac complications of iron overload. Individuals carrying one pathogenic allele causing beta-thalassemia in addition to 5 or more copies of HBA may develop a thalassemia intermedia phenotype with a variable clinical presentation, and may require recurrent transfusions.
- Sickle cell disease is caused by the inheritance of two copies of Hemoglobin S (HbS), encoded by a specific *HBB* variant. Symptoms typically first present in infancy or childhood and include chronic anemia, pain and/or swelling in the hands and feet, episodes of severe pain, and infections. The clinical presentation is highly variable between affected individuals. The life expectancy for individuals with sickle cell disease is in the 40s but may be increasing. HbS can also cause related diseases if it is inherited along with a different type of variant in *HBB*.
- HbC disease is caused by the inheritance of two copies of Hemoglobin C (HbC), encoded by a specific *HBB* variant. HbC disease causes mild anemia in some patients, but the majority of affected individuals do not have any symptoms and have a normal life expectancy. HbC can also cause disease if it is inherited with another type of abnormal hemoglobin, the most common being HbS. The inheritance of one copy each of HbS and HbC result in SC disease, which may cause chronic anemia, pain and/or swelling in the hands and feet, episodes of severe pain, infections, and retinal disease. The life expectancy for individuals with SC disease is in the 60s.

The type of disease that will develop can be predicted based on the variants inherited. Variants causing beta-thalassemia are prevalent in Mediterranean and South-East Asian populations, whereas HbS is most common in people of African, Mediterranean, Middle Eastern, and Indian ancestry. HbC is most common in people of African descent.

## 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](https://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.



Wang

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## Genes and diseases tested

For specific detection rates and residual risk by ethnicity, please visit [go.sema4.com/residualrisk](https://go.sema4.com/residualrisk)

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

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
<b>⊕ Positive</b>				
Beta-Globin-Related Hemoglobinopathies	<i>HBB</i>	AR	Carrier	c.92+6T>C, Pathogenic, Heterozygous (one copy)
<b>⊖ Negative</b>				
3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	<i>HSD3B2</i>	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-Related)	<i>MCCC1</i>	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)	<i>MCCC2</i>	AR	Reduced Risk	
3-Methylglutaconic Aciduria, Type III	<i>OPA3</i>	AR	Reduced Risk	
3-Phosphoglycerate Dehydrogenase Deficiency	<i>PHGDH</i>	AR	Reduced Risk	
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	<i>PTS</i>	AR	Reduced Risk	
Abetalipoproteinemia	<i>MTTP</i>	AR	Reduced Risk	
Achromatopsia	<i>CNGB3</i>	AR	Reduced Risk	
Acrodermatitis Enteropathica	<i>SLC39A4</i>	AR	Reduced Risk	
Acute Infantile Liver Failure	<i>TRMU</i>	AR	Reduced Risk	
Acyl-CoA Oxidase I Deficiency	<i>ACOX1</i>	AR	Reduced Risk	
Adenosine Deaminase Deficiency	<i>ADA</i>	AR	Reduced Risk	
Adrenoleukodystrophy, X-Linked	<i>ABCD1</i>	XL	Reduced Risk	
Aicardi-Goutières Syndrome (SAMHD1-Related)	<i>SAMHD1</i>	AR	Reduced Risk	
Alpha-Mannosidosis	<i>MAN2B1</i>	AR	Reduced Risk	
Alpha-Thalassemia	<i>HBA1/HBA2</i>	AR	Reduced Risk	<i>HBA1</i> Copy Number: 2 <i>HBA2</i> Copy Number: 2 No pathogenic copy number variants detected <i>HBA1/HBA2</i> Sequencing: Negative
Alpha-Thalassemia Mental Retardation Syndrome	<i>ATRX</i>	XL	Reduced Risk	
Alport Syndrome (COL4A3-Related)	<i>COL4A3</i>	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-Ketothiolase Deficiency	ACAT1	AR	Reduced Risk
Bilateral Frontoparietal Polymicrogyria	GPR56	AR	Reduced Risk
Biotinidase Deficiency	BTBD	AR	Reduced Risk
Bloom Syndrome	BLM	AR	Reduced Risk
Canavan Disease	ASPA	AR	Reduced Risk
Carbamoylphosphate Synthetase I Deficiency	CPS1	AR	Reduced Risk
Carnitine Palmitoyltransferase IA Deficiency	CPT1A	AR	Reduced Risk
Carnitine 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	<i>GJB1</i>	XL	Reduced Risk
Choreoacanthocytosis	<i>VPS13A</i>	AR	Reduced Risk
Choroideremia	<i>CHM</i>	XL	Reduced Risk
Chronic Granulomatous Disease (CYBA-Related)	<i>CYBA</i>	AR	Reduced Risk
Chronic Granulomatous Disease (CYBB-Related)	<i>CYBB</i>	XL	Reduced Risk
Citrin Deficiency	<i>SLC25A13</i>	AR	Reduced Risk
Citrullinemia, Type 1	<i>ASS1</i>	AR	Reduced Risk
Cohen Syndrome	<i>VPS13B</i>	AR	Reduced Risk
Combined Malonic and Methylmalonic Aciduria	<i>ACSF3</i>	AR	Reduced Risk
Combined Oxidative Phosphorylation Deficiency 1	<i>GFM1</i>	AR	Reduced Risk
Combined Oxidative Phosphorylation Deficiency 3	<i>TSFM</i>	AR	Reduced Risk
Combined Pituitary Hormone Deficiency 2	<i>PROP1</i>	AR	Reduced Risk
Combined Pituitary Hormone Deficiency 3	<i>LHX3</i>	AR	Reduced Risk
Combined SAP Deficiency	<i>PSAP</i>	AR	Reduced Risk
Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency	<i>CYP17A1</i>	AR	Reduced Risk
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	<i>CYP21A2</i>	AR	Reduced Risk CYP21A2 copy number: 2 CYP21A2 sequencing: Negative
Congenital Amegakaryocytic Thrombocytopenia	<i>MPL</i>	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ia	<i>PMM2</i>	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ib	<i>MPI</i>	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ic	<i>ALG6</i>	AR	Reduced Risk
Congenital Insensitivity to Pain with Anhidrosis	<i>NTRK1</i>	AR	Reduced Risk
Congenital Myasthenic Syndrome (CHRNE-Related)	<i>CHRNE</i>	AR	Reduced Risk
Congenital Myasthenic Syndrome (RAPSN-Related)	<i>RAPSN</i>	AR	Reduced Risk
Congenital Neutropenia (HAX1-Related)	<i>HAX1</i>	AR	Reduced Risk
Congenital Neutropenia (VPS45-Related)	<i>VPS45</i>	AR	Reduced Risk
Corneal Dystrophy and Perceptive Deafness	<i>SLC4A11</i>	AR	Reduced Risk
Corticosterone Methyloxidase Deficiency	<i>CYP11B2</i>	AR	Reduced Risk
Cystic Fibrosis	<i>CFTR</i>	AR	Reduced Risk
Cystinosis	<i>CTNS</i>	AR	Reduced Risk
D-Bifunctional Protein Deficiency	<i>HSD17B4</i>	AR	Reduced Risk
Deafness, Autosomal Recessive 77	<i>LOXHD1</i>	AR	Reduced Risk
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	<i>DMD</i>	XL	Reduced Risk
Dyskeratosis Congenita (RTEL1-Related)	<i>RTEL1</i>	AR	Reduced Risk
Dystrophic Epidermolysis Bullosa	<i>COL7A1</i>	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 <i>FMR1</i> CGG repeat sizes: Not Performed <i>FMR1</i> 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 <i>BCS1L</i> -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 ( <i>AMT</i> -Related)	AMT	AR	Reduced Risk
Glycine Encephalopathy ( <i>GLDC</i> -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	TECPR2	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, cbIE Type	MTRR	AR	Reduced Risk
Hydrolethals Syndrome	HYLS1	AR	Reduced Risk
Hyperornithinemia-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	RPGRIP1L	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	<i>LRPPRC</i>	AR	Reduced Risk
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogryposis with Anterior Horn Cell Disease	<i>GLE1</i>	AR	Reduced Risk
Leukoencephalopathy with Vanishing White Matter	<i>EIF2B5</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2A	<i>CAPN3</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2B	<i>DYSF</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2C	<i>SGCG</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2D	<i>SGCA</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2E	<i>SGCB</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2I	<i>FKRP</i>	AR	Reduced Risk
Lipoamide Dehydrogenase Deficiency	<i>DLD</i>	AR	Reduced Risk
Lipoid Adrenal Hyperplasia	<i>STAR</i>	AR	Reduced Risk
Lipoprotein Lipase Deficiency	<i>LPL</i>	AR	Reduced Risk
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	<i>HADHA</i>	AR	Reduced Risk
Lysinuric Protein Intolerance	<i>SLC7A7</i>	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1a	<i>BCKDHA</i>	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1b	<i>BCKDHB</i>	AR	Reduced Risk
Meckel 1 / Bardet-Biedl Syndrome 13	<i>MKS1</i>	AR	Reduced Risk
Medium Chain Acyl-CoA Dehydrogenase Deficiency	<i>ACADM</i>	AR	Reduced Risk
Megalencephalic Leukoencephalopathy with Subcortical Cysts	<i>MLC1</i>	AR	Reduced Risk
Menkes Disease	<i>ATP7A</i>	XL	Reduced Risk
Metachromatic Leukodystrophy	<i>ARSA</i>	AR	Reduced Risk
Methylmalonic Acidemia (MMAA-Related)	<i>MMAA</i>	AR	Reduced Risk
Methylmalonic Acidemia (MMAB-Related)	<i>MMAB</i>	AR	Reduced Risk
Methylmalonic Acidemia (MUT-Related)	<i>MUT</i>	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	<i>MMACHC</i>	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	<i>MMADHC</i>	AR	Reduced Risk
Microphthalmia / Anophthalmia	<i>VSX2</i>	AR	Reduced Risk
Mitochondrial Complex I Deficiency (ACAD9-Related)	<i>ACAD9</i>	AR	Reduced Risk
Mitochondrial Complex I Deficiency (NDUFA5-Related)	<i>NDUFA5</i>	AR	Reduced Risk
Mitochondrial Complex I Deficiency (NDUFS6-Related)	<i>NDUFS6</i>	AR	Reduced Risk
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	<i>MPV17</i>	AR	Reduced Risk
Mitochondrial Myopathy and Sideroblastic Anemia 1	<i>PUS1</i>	AR	Reduced Risk



Mucopolipidosis II / IIIA	GNPTAB	AR	Reduced Risk
Mucopolipidosis III Gamma	GNPTG	AR	Reduced Risk
Mucopolipidosis 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	HYAL1	AR	Reduced Risk
Mucopolysaccharidosis type VI	ARSB	AR	Reduced Risk
Multiple Sulfatase Deficiency	SUMF1	AR	Reduced Risk
Muscle-Eye-Brain Disease and Other POMGNT1-Related Congenital Muscular Dystrophy-Dystroglycanopathies	POMGNT1	AR	Reduced Risk
Myoneurogastrointestinal Encephalopathy	TYMP	AR	Reduced Risk
Myotubular Myopathy 1	MTM1	XL	Reduced Risk
N-Acetylglutamate Synthase Deficiency	NAGS	AR	Reduced Risk
Nemaline Myopathy 2	NEB	AR	Reduced Risk
Nephrogenic Diabetes Insipidus, Type II	AQP2	AR	Reduced Risk
Nephrotic Syndrome (NPHS1-Related) / Congenital Finnish Nephrosis	NPHS1	AR	Reduced Risk
Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome	NPHS2	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (CLN3-Related)	CLN3	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (CLN5-Related)	CLN5	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (CLN6-Related)	CLN6	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (CLN8-Related)	CLN8	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (MFSD8-Related)	MFSD8	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (PPT1-Related)	PPT1	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (TPP1-Related)	TPP1	AR	Reduced Risk
Niemann-Pick Disease (SMPD1-Related)	SMPD1	AR	Reduced Risk
Niemann-Pick Disease, Type C (NPC1-Related)	NPC1	AR	Reduced Risk
Niemann-Pick Disease, Type C (NPC2-Related)	NPC2	AR	Reduced Risk
Nijmegen Breakage Syndrome	NBN	AR	Reduced Risk
Non-Syndromic Hearing Loss (GJB2-Related)	GJB2	AR	Reduced Risk



Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome	WNT10A	AR	Reduced Risk
Omenn Syndrome (RAG2-Related)	RAG2	AR	Reduced Risk
Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type	DCLRE1C	AR	Reduced Risk
Ornithine Aminotransferase Deficiency	OAT	AR	Reduced Risk
Ornithine Transcarbamoylase Deficiency	OTC	XL	Reduced Risk
Osteopetrosis 1	TCIRG1	AR	Reduced Risk
Pendred Syndrome	SLC26A4	AR	Reduced Risk
Phenylalanine Hydroxylase Deficiency	PAH	AR	Reduced Risk
Polycystic Kidney Disease, Autosomal Recessive	PKHD1	AR	Reduced Risk
Polyglandular Autoimmune Syndrome, Type 1	AIRE	AR	Reduced Risk
Pontocerebellar Hypoplasia, Type 1A	VRK1	AR	Reduced Risk
Pontocerebellar Hypoplasia, Type 6	RARS2	AR	Reduced Risk
Primary Carnitine Deficiency	SLC22A5	AR	Reduced Risk
Primary Ciliary Dyskinesia (DNAH5-Related)	DNAH5	AR	Reduced Risk
Primary Ciliary Dyskinesia (DNAH1-Related)	DNAH1	AR	Reduced Risk
Primary Ciliary Dyskinesia (DNAH2-Related)	DNAH2	AR	Reduced Risk
Primary Hyperoxaluria, Type 1	AGXT	AR	Reduced Risk
Primary Hyperoxaluria, Type 2	GRHPR	AR	Reduced Risk
Primary Hyperoxaluria, Type 3	HOGA1	AR	Reduced Risk
Progressive Cerebello-Cerebral Atrophy	SEPSECS	AR	Reduced Risk
Progressive Familial Intrahepatic Cholestasis, Type 2	ABCB11	AR	Reduced Risk
Propionic Acidemia (PCCA-Related)	PCCA	AR	Reduced Risk
Propionic Acidemia (PCCB-Related)	PCCB	AR	Reduced Risk
Pycnodysostosis	CTSK	AR	Reduced Risk
Pyruvate Dehydrogenase E1-Alpha Deficiency	PDHA1	XL	Reduced Risk
Pyruvate Dehydrogenase E1-Beta Deficiency	PDHB	AR	Reduced Risk
Renal Tubular Acidosis and Deafness	ATP6V1B1	AR	Reduced Risk
Retinitis Pigmentosa 25	EYS	AR	Reduced Risk
Retinitis Pigmentosa 26	CERKL	AR	Reduced Risk
Retinitis Pigmentosa 28	FAM161A	AR	Reduced Risk
Retinitis Pigmentosa 59	DHDDS	AR	Reduced Risk
Rhizomelic Chondrodysplasia Punctata, Type 1	PEX7	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: 2 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. AmpliDeX® *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 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 due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. These 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 with SMA have an *SMN1* mutation that occurred *de novo*. Typically in these cases, only one parent is an SMA carrier.

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 carrier.

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testing for the c.\*3+80T>G variant allele; these will be reported if confirmed to be located in *SMN1* using locus-specific Sanger primers

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testing for the c.\*3+80T>G variant allele; these will be reported if confirmed to be located in *SMN1* using locus-specific Sanger primers.

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 SureSelect™QXT 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. Samples were pooled and sequenced on the Illumina HiSeq 2500 platform in the Rapid Run mode or the Illumina NovaSeq platform in the Xp workflow, using 100 bp paired-end 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. The exons contained within these regions are noted within Table 1 (as "Exceptions") and 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.

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.

#### **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 >28,000 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.

#### **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.