

Donor 6260

Genetic Testing Summary

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

Last Updated: 5/10/21

Donor Reported Ancestry: Irish, Chilean

Jewish Ancestry: No

Genetic Test*	Result	Comments/Donor's Residual Risk**
Genetic rest	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	Carrier: Limb-Girdle Muscular Dystrophy Type 2A (CAPN3) Negative for other genes sequenced	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 InformationSpecimen InformationReferring ProviderName: Donor 6260Specimen Type: BloodImage: Constraint of the second of

Expanded Carrier Screen (283) Minus TSE

Number of genes tested: 283

SUMMARY OF RESULTS AND RECOMMENDATIONS

+ Positive	⊖ Negative
Carrier of Limb-Girdle Muscular Dystrophy, Type 2A (AR) Associated gene(s): <i>CAPN3</i> Variant(s) Detected: c.2257G>A, p.D753N, Likely Pathogenic, Heterozygous (one copy)	Negative for all other genes tested To view a full list of genes and diseases tested please see Table 1 in this report

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

Limb-Girdle Muscular Dystrophy, Type 2A (AR)

Results and Interpretation

A heterozygous (one copy) likely pathogenic missense variant, c.2257G>A, p.D753N, was detected in the *CAPN3* gene (NM_000070.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for limb-girdle muscular dystrophy, type 2A. Therefore, this individual is expected to be at least a carrier for limb-girdle muscular dystrophy, type 2A. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Limb-Girdle Muscular Dystrophy, Type 2A?

Limb-girdle muscular dystrophy, type 2A is an autosomal recessive, pan-ethnic disorder that is caused by pathogenic variants in the gene *CAPN3*. This form of muscular dystrophy presents with weakness of the pelvic girdle and legs, and eventually progresses to the upper limbs. Sometimes it presents with weakness of the upper limbs and progresses to the lower limbs. Onset is usually in childhood or early adolescence, although variability exists. Patients are usually wheelchair-bound about 20 years after diagnosis, and death usually occurs in middle age. Some patients also experience weakness of the facial muscles or contractures of the joints. Patients with at least one missense variant may experience a slightly slower rate of progression than those with two null variants, but the severity of the disease appears to be the same.

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.

Xingwu Lu, Ph.D., FACMG, Associate Laboratory Director Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

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

Positive Limb-Girdle Muscular Dystrophy, Type 2A CAPN3 AR Carrier c.2257G>A, p.D753N, Likely Pathogenic Heterozygous (one copy)	e 2A CAPN3 AR Carrier C.2257G>A, p.D753N, Likely Pathogenic, Heterozygous (one copy)	Disease	Gene	Inheritance Pattern	Status	Detailed Summary
LIMD-Girdle Muscular Lystrophy Lybe 2A CAPN3 AR Carrier	APRIL CAPNS AR Carrier	⊕ Positive				
		Limb-Girdle Muscular Dystrophy, Type 2A	CAPN3	AR	Carrier	. , .
⊖ Negative		Negative				





3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	HSD3B2	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-	MCCC1	AR	Reduced Risk	
Related)				
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	
	1.0.042.01	7.00	Reduced Hisk	HBA1 Copy Number: 2
		. –		HBA2 Copy Number: 2
Alpha-Thalassemia	HBA1/HBA2	AR	Reduced Risk	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 (<i>BBS12</i> -Related)	BBS12	AR	Reduced Risk	
Bardet-Biedl Syndrome (<i>BBS1</i> -Related)	BBS1	AR	Reduced Risk	
Bardet-Biedl Syndrome (<i>BBS2</i> -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	
, , ,,	CPT1A	AR	Reduced Risk	
Carnitine Palmitovltransferase IA Deficiencv		AR	Reduced Risk	
· · ·	CP12			
Carnitine Palmitoyltransferase II Deficiency	CPT2 RAB23	AR	Reduced Risk	
Carnitine Palmitoyltransferase II Deficiency Carpenter Syndrome	RAB23	AR AR	Reduced Risk	
Carnitine Palmitoyltransferase II Deficiency Carpenter Syndrome Cartilage-Hair Hypoplasia	RAB23 RMRP	AR	Reduced Risk	
Carnitine Palmitoyltransferase II Deficiency Carpenter Syndrome Cartilage-Hair Hypoplasia Cerebral Creatine Deficiency Syndrome 1	RAB23 RMRP SLC6A8	AR XL	Reduced Risk Reduced Risk	
Camitine Palmitoyltransferase IA Deficiency Camitine Palmitoyltransferase II Deficiency Carpenter Syndrome Cartilage-Hair Hypoplasia Cerebral Creatine Deficiency Syndrome 1 Cerebral Creatine Deficiency Syndrome 2 Cerebrotendinous Xanthomatosis	RAB23 RMRP	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	СНМ	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	TSFM	AR	Reduced Risk	
Combined Pituitary Hormone Deficiency 2	PROP1	AR	Reduced Risk	
Combined Pituitary Hormone Deficiency 3	LHX3	AR	Reduced Risk	
Combined SAP Deficiency	PSAP	AR	Reduced Risk	
Congenital Adrenal Hyperplasia due to 17-Alpha- Hydroxylase Deficiency	CYP17A1	AR	Reduced Risk	
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	CYP21A2	AR	Reduced Risk	<i>CYP21A2</i> copy number: 2 <i>CYP21A2</i> sequencing: Negative
Congenital Amegakaryocytic Thrombocytopenia	MPL	AR	Reduced Risk	
Congenital Disorder of Glycosylation, Type la	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 (<i>RTEL1</i> -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 w
				not performed at this time, as the patient has eil been previously tested or is a male.

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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 Ila	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 la	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 VI	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, cblE Type	MTRR	AR	Reduced Risk
Hydrolethalus Syndrome	HYLS1	AR	Reduced Risk
Hyperomithinemia-Hyperammonemia-	1111231	AR	Reduced Risk
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
ISOVAIEDC ACIDEMIA	,	AR	Reduced Risk Reduced Risk
Isovaleric Acidemia	IVD	AR	Reduced Risk
Joubert Syndrome 2	,		
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH	IVD	AR	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome	IVD TMEM216 RPGRIP1L	AR AR AR	Reduced Risk Reduced Risk Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related)	IVD TMEM216 RPGRIP1L LAMA3	AR AR AR AR	Reduced Risk Reduced Risk Reduced Risk Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related)	IVD TMEM216 RPGRIP1L LAMA3 LAMB3	AR AR AR AR AR	Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related)	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2	AR AR AR AR AR AR	Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC	AR AR AR AR AR AR AR	Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease Lamellar Ichthyosis, Type 1	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1	AR AR AR AR AR AR AR AR AR	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMB3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMC2</i> -Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP2go-	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC	AR AR AR AR AR AR AR	Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease Lamellar Ichthyosis, Type 1	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1	AR AR AR AR AR AR AR AR AR	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMB3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMC2</i> -Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP2go- Related Ciliopathies	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290	AR AR AR AR AR AR AR AR AR	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMB3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMC2</i> -Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP290- Related Ciliopathies Leber Congenital Amaurosis 13	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12	AR AR AR AR AR AR AR AR AR AR AR	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP290- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65 LCA5	AR AR AR AR AR AR AR AR AR AR AR AR AR A	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMB3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMC2</i> -Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP290- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20 Leber Congenital Amaurosis 5	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65	AR AR AR AR AR AR AR AR AR AR AR AR	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMB3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMC2</i> -Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP2go- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20 Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65 LCA5	AR AR AR AR AR AR AR AR AR AR AR AR AR A	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMB3</i> -Related) Junctional Epidermolysis Bullosa (<i>LAMC2</i> -Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP290- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20 Leber Congenital Amaurosis 5 Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65 LCA5 CRB1 LRPPRC	AR AR AR AR AR AR AR AR AR AR AR AR AR A	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP290- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20 Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy Leigh Syndrome, French-Canadian Type	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65 LCA5 CRB1	AR AR AR AR AR AR AR AR AR AR AR AR AR A	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP2g0- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20 Leber Congenital Amaurosis 5 Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy Leigh Syndrome, French-Canadian Type Lethal Congenital Contracture Syndrome 1 / Lethal	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65 LCA5 CRB1 LRPPRC	AR AR AR AR AR AR AR AR AR AR AR AR AR A	Reduced Risk
Joubert Syndrome 2 Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome Junctional Epidermolysis Bullosa (<i>LAMA</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMB</i> 3-Related) Junctional Epidermolysis Bullosa (<i>LAMC</i> 2-Related) Krabbe Disease Lamellar Ichthyosis, Type 1 Leber Congenital Amaurosis 10 and Other CEP2g0- Related Ciliopathies Leber Congenital Amaurosis 13 Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20 Leber Congenital Amaurosis 5 Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy Leigh Syndrome, French-Canadian Type Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogryposis with Anterior Horn Cell Disease	IVD TMEM216 RPGRIP1L LAMA3 LAMB3 LAMC2 GALC TGM1 CEP290 RDH12 RPE65 LCA5 CRB1 LRPPRC GLE1	AR AR AR AR AR AR AR AR AR AR AR AR AR A	Reduced Risk 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 21	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	ACADIM		Neutrea Nisk
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 (<i>MUT</i> -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 Deficiency (ACADg-Related)	ACAD9	AR	Reduced Risk
Mitochondrial Complex Deficiency (<i>NDUFAF5</i> -Related)	NDUFAF5	AR	Reduced Risk
Mitochondrial Complex 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
Mucolipidosis II / IIIA	GNPTAB	AR	Reduced Risk
	GNPTAB		
Mucolipidosis III Gamma		AR	Reduced Risk
Mucolipidosis 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	MTMP	XL	Reduced Risk
N-Acetylglutamate Synthase Deficiency		AR	Reduced Risk
	NAGS		
Nemaline Myopathy 2	NEB	AR	Reduced Risk
Nephrogenic Diabetes Insipidus, Type II	AQP2	AR	Reduced Risk
Nephrotic Syndrome (<i>NPHS1</i> -Related) / Congenital Finnish Nephrosis	NPHS1	AR	Reduced Risk
•	NPHS2	AR	Reduced Risk
Nephrotic Syndrome (<i>NPHS2</i> -Related) / Steroid- Resistant Nephrotic Syndrome			
Resistant Nephrotic Syndrome		AR	Reduced Risk
Resistant Nephrotic Syndrome Neuronal Ceroid-Lipofuscinosis (<i>CLN3</i> -Related)	CLN3	AR AR	Reduced Risk Reduced Risk
Resistant Nephrotic Syndrome Neuronal Ceroid-Lipofuscinosis (<i>CLN3</i> -Related) Neuronal Ceroid-Lipofuscinosis (<i>CLN5</i> -Related)	CLN3 CLN5	AR	Reduced Risk
Resistant Nephrotic Syndrome	CLN3		





Nacoral Card Lipotacions (PPP-164040) PP1 AR Reduced Tisk: Niemarch Fick Desse (SMPD: Related) SMPD: AR Reduced Tisk: Niemarch Fick Desse (SMPD: Related) APC: AR Reduced Tisk: Niemarch Fick Desse (SMPD: Related) APC: AR Reduced Tisk: Niemarch Fick Desse (SMPD: Related) APC: AR Reduced Tisk: Non-Synchronic Nearing Loss (SR: Related) J.R.2 AR Reduced Tisk: Non-Synchronic Nearing Loss (SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Loss (SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Loss (SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Section (SR: SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Section (SR: SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Section (SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Loss (SR: Related) J.R.2 AR Reduced Tisk: Ormen Synchronic Nearing Loss (SR: Related)					
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		MYO7A	AR		





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	FKTN	AR	Reduced Risk
Dystrophies	FRIN	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 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 *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 numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* 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_00092.4) 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_00022.6) 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_00199.3) 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 ΔΔCt 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 trough 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 SureSelectTMXT 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.