4845 Knightsbridge Blvd.
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Genetic Testing Summary

Enclosed are the genetic testing results for

PC 1110

No amount of genetic testing can guarantee that a child will not be affected with a genetic condition. Genetic testing can inform you of the likelihood of passing on the genetic conditions that are tested for, but it cannot eliminate the risk of passing on any genetic condition.

The genetic conditions Cryobio tests for are inherited in an autosomal recessive manner. This means that the child would have to inherit a genetic mutation from both the sperm source and the egg source to be affected with the condition. When both the sperm source and the egg source have undergone genetic carrier screening and the test results are negative, the risk of a child being affected with the conditions tested for is significantly reduced, but it cannot be completely eliminated.

All recipients should discuss both or their own risk for passing on genetic conditions and whether would benefit from genetic counseling and testing with their health care provider. Before using a donor that is a carrier for a specific recessive genetic condition or conditions, we strongly recommend that the recipient (or egg source, if different) consider genetic counseling and testing to determine if they are a carrier for the same genetic condition or conditions as the donor.

Screening and testing have changed dramatically over the years, and so the screening and testing done on each donor may very depending on the testing that was in place when he was actively in Cryobio's donor program. Earlier donors may not have had as extensive testing as later donors. Screening and testing may change again in the future, so please review the results each time before ordering as both the testing done and the results may change.

Patient Information
Name: Pc 1110
Date of Birth: [redacted]
Sema4 ID: [redacted]
Client ID: [redacted]
Indication: Carrier Testing

Specimen Information
Specimen Type: Blood
Date Collected: [redacted]
Date Received: [redacted]
Final Report: [redacted]

Referring Provider
David Prescott, M.D.
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Expanded Carrier Screen (283)

Number of genes tested: 283

SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
Carrier of Tay-Sachs Disease (AR) Associated gene(s): *HEXA* Variant(s) Detected: c.806-7G>A, Likely Pathogenic, Heterozygous (one copy) Enzyme results in the carrier range	**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

Tay-Sachs Disease (AR)

Results and Interpretation

HEXA Sequence Analysis:

A heterozygous (one copy) likely pathogenic intronic variant, c.806-7G>A, was detected in the *HEXA* gene (NM_000520.4). When this variant is present in trans with a pathogenic variant, it is considered to be causative for Tay-Sachs disease. Therefore, this individual is expected to be at least a carrier for Tay-Sachs disease. Heterozygous carriers are not expected to exhibit symptoms of this disease.

Hexosaminidase Enzyme Activity:

White blood cells: Carrier

- Hex A%: 44.8% (Non-carrier : 55.0 - 72.0%; Carrier: <50%)
- Total hexosaminidase activity: 1688 nmol/hr/mg

Plasma: Carrier

- Hex A%: 47.4 (Non-carrier : 58.0 - 72.0%; Carrier: <54%)
- Total hexosaminidase activity: 543 nmol/hr/ml

HEXA Sequencing: c.806-7G>A, Likely Pathogenic, Heterozygous (one copy)

The patient's Hex A% activity is within the **CARRIER** range. This result and positive mutation status are consistent with the patient being a carrier for Tay-Sachs disease. Testing of the reproductive partner and genetic counseling are recommended.

What is Tay-Sachs Disease?

Tay-Sachs disease is an autosomal recessive disorder resulting from pathogenic variants in the *HEXA* gene. It has been reported in individuals from different ethnicities, but there is an increased prevalence of the disease in people of Ashkenazi Jewish, French Canadian, and Irish descent. Pathogenic *HEXA* variants result in loss of function of the beta-hexosaminidase A enzyme, causing accumulation of GM2 gangliosides in body tissues. Several different forms of the disease exist, including the infantile and later-onset variants.

- The infantile form, which is the most common, has an onset of symptoms around 6 months of age. Clinical features include progressive loss of coordination, seizures, difficulty swallowing and poor pulmonary function. Affected individuals eventually become blind, severely intellectually disabled, paralyzed and unaware of their surroundings. Death usually occurs at 3 to 5 years of age.
- The subacute (or juvenile) form usually has an age of onset between 2 and 10 years. The progression of the disease is similar to that of the infantile form, and death occurs between 10 and 15 years of age.
- In the chronic form, age of onset is similar to that of the juvenile form, but the symptoms progress more slowly. The clinical presentation is one of ataxia and dystonia. Survival is long-term.
- The adult-onset form is characterized by progressive muscle loss, weakness and difficulty speaking. Age of onset, symptoms and severity are variable among individuals. Survival is long-term.

A genotype-phenotype correlation has been observed, where specific variants can be predicted to cause a later-onset form of the disease. Later-onset forms of the disease result when the residual beta-hexosaminidase A enzyme activity is between 5% and 15%. However, more than 90% of all pathogenic *HEXA* variants result in the infantile form of Tay-Sachs disease.

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

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
Positive				
Tay-Sachs Disease	*HEXA*	AR	Carrier	Tay-Sachs disease enzyme: Carrier by enzyme White blood cells: Carrier • Hex A%: 44.8% (Non-carrier : 55.0 - 72.0%; Carrier: <50%) • Total hexosaminidase activity: 1688 nmol/hr/mg Plasma: Carrier • Hex A%: 47.4 (Non-carrier : 58.0 - 72.0%; Carrier: <54%) • Total hexosaminidase activity: 543 nmol/hr/ml *HEXA* Sequencing: c.806-7G>A, Likely 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	
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	*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	*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	*CYP21A2* copy number: 2 *CYP21A2* sequencing: Negative
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	*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
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	*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
Mucolipidosis II / IIIA	*GNPTAB*	AR	Reduced Risk
Mucolipidosis III Gamma	*GNPTG*	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	*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 Transcarbamylase 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 (*DNAI1*-Related)	*DNAI1*	AR	Reduced Risk	
Primary Ciliary Dyskinesia (*DNAI2*-Related)	*DNAI2*	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	
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 bySouthern 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 genepolymorphisms 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 areconfirmed 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 meioticcrossing-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 cannotdetect 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 20 carrier) or individuals that carry anintragenic 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.*380T>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.*380T>G is likely indicative of a silent (20) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence ofc.*380T>G significantly increases or decreases, respectively, the likelihood of being asilent 20 silent carrier.

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testingfor the c.*380T>G variant allele; these will be reported if confirmed to be located inSMN1 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 ofthe *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 likelypathogenic variants.

Agilent SureSelect^{TM}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 numberof 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 thelllumina 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 aspecific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likelybenign 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 anexon-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 acustom 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 pathogenicsingle-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-targetedexon-focused array capable of detecting medically relevant microdeletions and microduplications at a much higher resolution than traditional aCGH methods. Each arraymatrix 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 CGHprobes 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/probesets that specific to the target region and a control region with known genomic copynumber. 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 locatedon 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 thetandem allele and this patient is therefore less likely to be a carrier. When anindividual carries both a duplication allele and a pathogenic variant, or multiplepathogenic variants, the current analysis may not be able to determine the phase(cisrans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing isrequired 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 theABI 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. Falsenegative results may occur if rare variants interfere with amplification or annealing.

Tay-Sachs Disease (TSD) Enzyme Analysis (Analytical Detection Rate ≥ 98%)

Hexosaminidase activity and Hex A% activity were measured by a standard heat-inactivation,fluorometric method using artificial 4-MU-β-N-acetyl glucosaminide (4-MUG) substrate. This assay is highly sensitive and accurate in detecting Tay-Sachs carriers andindividuals affected with TSD. Normal ranges of Hex A% activity are 55.0-72.0 for whiteblood cells and 58.0-72.0 for plasma. It is estimated that less than 0.5% of Tay-Sachscarriers have non-carrier levels of percent Hex A activity, and therefore may not be identified by this assay. In addition, this assay may detect individuals that are carriers of or are affected with Sandhoff disease. False positive results may occur if benignvariants, such as pseudodeficiency alleles, interfere with the enzymatic assay. Falsenegative results may occur if both *HEXA* and *HEXB* pathogenic or pseudodeficiency variants are present in the same individual.

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.

SELECTED REFERENCES

Carrier Screening

Grody W et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.*2013 15:482-3.

Fragile X syndrome:

Chen L et al. An information-rich CGG repeat primed PCR that detects the full range of Fragile X expanded alleles and minimizes the need for Southern blot analysis. *J Mol Diag* 2010 12:589-600.

Spinal Muscular Atrophy:

Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improvespan-ethnic carrier screening for spinal muscular atrophy. *Genet Med* . 2014 16:149-56.

Ashkenazi Jewish Disorders:

Scott SA et al. Experience with carrier screening and prenatal diagnosis for sixteen Ashkenazi Jewish Genetic Diseases. *Hum. Mutat.* 2010 31:1-11.

Duchenne Muscular Dystrophy:

Flanigan KM et al. Mutational spectrum of DMD mutations in dystrophinopathy patients:application of modern diagnostic techniques to a large cohort. *Hum Mutat* . 2009 30:1657-66.

Variant Classification:

Richards S et al. Standards and guidelines for the interpretation of sequence variants: ajoint consensus recommendation of the American College of Medical Genetics and Genomicsand the Association for Molecular Pathology. *Genet Med.*2015 May;17(5):405-24

Additional disease-specific references available upon request.

genzyme

Cystic Fibrosis Mutation Analysis

Patient Name: PC 1110, .
Referring Physician: David Prescott, MD
Specimen #: [redacted] **Client #:** [redacted]
Patient ID: [redacted] **Case #:** [redacted]

DOB: [redacted]
Sex: M
SSN:

Date Collected: [redacted]
Date Received: [redacted]
Lab ID:
Hospital ID:
Specimen Type: **BLDPER**

Pittsburgh Cryobank
4415 Fifth Avenue
Suite 161
Pittsburgh PA 15213 USA

Ethnicity: Not Provided

Indication: Carrier test / Gamete donor

RESULTS: Negative for the 97 mutations analyzed

INTERPRETATION

This individual is negative for the mutations analyzed. This result reduces but does not eliminate the risk to be a CF carrier.

COMMENTS:

Mutation Detection Rates among Ethnic Groups — Detection rates are based on mutation frequencies in patients affected with cystic fibrosis. Among individuals with an atypical or mild presentation (e.g. congenital absence of the vas deferens, pancreatitis) detection rates may vary from those provided here.

Ethnicity	Carrier risk reduction when no family history	Detection rate	References
African American	1/65 to 1/338	81%	Genet in Med 3:168, 2001
Ashkenazi Jewish	1/26 to 1/834	97%	Am J Hum Genet 51:951, 1994
Asian		Not Provided	Insufficient data
Caucasian	1/25 to 1/343	93%	Genet in Med 3:168, 2001; Genet in Med 4:90, 2002
Hispanic	1/46 to 1/205	78%	Genet in Med 3:168, 2001;www.dhs.ca.gov/pcfh/gdb/html/PDE/CFStudy.htm
Jewish, non-Ashkenazi		Varies by country of origin	Genet Testing 5:47, 2001, Genet Testing, 1:35, 1997
Other or Mixed Ethnicity		Not Provided	Detection rate not determined and varies with ethnicity

This interpretation is based on the clinical and family relationship information provided and the current understanding of the molecular genetics of this condition.

METHOD

DNA is isolated from the sample and tested for the 97 CF mutations listed. Regions of the *CFTR* gene are amplified enzymatically and subjected to a solution-phase multiplex allele-specific primer extension with subsequent hybridization to a bead array and fluorescent detection. The assay discriminates between ΔF508 and the following polymorphisms: F508C, I506V and I507V. In some cases, specific allele identification requires enzymatic amplification followed by hybridization to oligonucleotide probes.

Under the direction of: Zhaoqing Zhou

[redacted]

Zhaoqing Zhou, Ph.D.

Date: [redacted]

Testing Performed At Genzyme Genetics 3400 Computer Drive Westborough, MA 01581 1-800-255-7357

BCM
Baylor College of Medicine

MEDICAL GENETICS LABORATORIES
2450 Holcombe Blvd - Houston, TX 77021 - 1-800-411-4363
Fax: 713-798-6584 - www.bcmgeneticlabs.org - genetictest@bcm.edu

KLEBERG CYTOGENETICS LABORATORY

Name: DONOR PC1110

Sample Type: BLOOD

Date of birth: [redacted]
Hospital #:
Accession #:
KCL Lab #: [redacted]
Family #: [redacted]
Indication: General Population Screening

Pittsburgh Cryobank
4415 Fifth Avenue, Suite 161
Pittsburgh, PA 15213

Date collected: [redacted]
Date received:
Report date:
Telephone:
Fax No:

CHROMOSOME ANALYSIS

[redacted]

METHOD OF ANALYSIS:
GTG-Banding

Cultures:	2	***No. of images:***	10
Cells counted:	30	***Cells karyotyped:***	3
Cells analyzed:	5	***Band resolution:***	550-575

RESULTS
46,XY

INTERPRETATION
Normal male chromosome analysis. Analysis of 30 cells rules out 10% mosaicism at the 95% confidence level.

Carlos A. Bacino, M.D., FACMG
ABMG Certified Cytogeneticist and Molecular Geneticist
Medical Director

[redacted]

genzyme

SMN1 Copy Number Analysis

Patient Name: . PC 1110
DOB: [redacted] Age: [redacted]
SSN #: Gender: Male

Genzyme Specimen #: [redacted]
Case #: [redacted] Patient ID #: [redacted]
Date Collected: [redacted] Date Received: [redacted]

[redacted]
Pittsburgh Cryobank
4415 Fifth Avenue
Suite 161
Pittsburgh, PA 15213
USA

Referring Physician: David Prescott
Genetic Counselor:

Specimen Type: Peripheral Blood

Clinical Data: Carrier Test/Gamete donor

Client Lab ID #:
Hospital ID #:
Specimen ID #:
Specimen(s) Received: 1 - Lavender 7 ml round bottom tube(s)
Ethnicity: Caucasian

RESULTS: SMN1 copy number: 2 (Reduced Carrier Risk)

INTERPRETATION:

This individual has an SMN1 copy number of two. This result reduces but does not eliminate the risk to be a carrier of SMA. Ethnic specific risk reductions based on a negative family history and an SMN1 copy number of two are provided in the Comments section of this report.

COMMENT:

Spinal muscular atrophy (SMA) is an autosomal recessive disease of variable age of onset and severity caused by mutations (most often deletions or gene conversions) in the survival motor neuron (SMN1) gene. Molecular testing assesses the number of copies of the SMN1 gene. Individuals with one copy of the SMN1 gene are predicted to be carriers of SMA. Individuals with two or more copies have a reduced risk to be carriers. (Affected individuals have 0 copies of the SMN1 gene.)

This copy number analysis cannot detect individuals who are carriers of SMA as a result of either 2 (or very rarely 3) copies of the SMN1 gene on one chromosome and the absence of the SMN1 gene on the other chromosome or small intragenic mutations within the SMN1 gene. This analysis also will not detect germline mosaicism or mutations in genes other than SMN1. Additionally, de novo mutations have been reported in approximately 2% of SMA patients.

Carrier Frequency and Risk Reductions for Individuals with No Family History of SMA				
Ethnicity	**Detection Rate[1]**	**A priori Carrier Risk[1]**	**Reduced Carrier Risk for 2 copy result**	**Reduced Carrier Risk for 3 copy result**
Caucasian	94.9%	1:35	1:632	1:3,500
Ashkenazi Jewish	90.2%	1:41	1:350	1:4,000
Asian	92.6%	1:53	1:628	1:5,000
Hispanic	90.6%	1:117	1:1061	1:11,000
African American	71.1%	1:66	1:121	1:3,000
Mixed Ethnicities	For counseling purposes, consider using the ethnic background with the most conservative risk estimates.			

METHOD/LIMITATIONS:
Specimen DNA is isolated and amplified by real-time polymerase chain reaction (PCR) for exon 7 of the SMN1 gene and two reference genes. A mathematical algorithm is used to calculate the number of copies of SMN1. Sequencing of the primer and probe binding sites for the SMN1 real-time PCR reaction is performed on all fetal samples, and on samples from individuals with 1 copy of SMN1 on carrier testing, to rule out the presence of sequence variants which could interfere with analysis and interpretation. False positive or negative results may occur for reasons that include genetic variants, blood transfusions, bone marrow transplantation, erroneous representation of family relationships or contamination of a fetal sample with maternal cells.

REFERENCES:
1. Carrier frequency and detection rate are calculated based on analysis of allele frequencies among > 1000 individuals from each ethnic group noted (Genzyme Genetics, data submitted for publication). 2. Online review of SMA: http://www.genereviews.org/profiles/sma

The test was developed and its performance characteristics have been determined by Genzyme. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing. This test must be used in conjunction with clinical assessment, when available.

Electronically Signed by: Zhaoqing Zhou, Ph.D., FACMG, on [redacted]
Reported by: /