



Donor 5360

Genetic Testing Summary

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

Last Updated: 06/27/23

Donor Reported Ancestry: Mexican, Spanish

Jewish Ancestry: No

Genetic Test*	Result	Comments/Donor's Residual Risk**
Chromosome analysis (karyotype)	Normal male karyotype	No evidence of clinically significant chromosome abnormalities
Hemoglobin evaluation	Normal hemoglobin fractionation and MCV/MCH results	Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies
Cystic Fibrosis (CF) carrier screening	Negative by genotyping of 150 mutations- in the CFTR gene	1/212
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/1061
Standard testing attached- 22 diseases by genotyping	Negative for mutations tested	
Special Testing		
Congenital Disorder of Glycosylation Type 1A (PMM2)	Negative by gene sequencing in the PMM2 gene	1/540
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)	Negative by gene sequencing in the MCCC2 gene	1/1300
Genes: SERPINA1, BTD	Negative by gene sequencing	

*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.

Ordering Practice:

Practice Code: [REDACTED]
Fairfax Cryobank - [REDACTED],
[REDACTED]
Physician: [REDACTED]
Report Generated: 2016-07-11

Donor 5360

DOB: [REDACTED]
Gender: Male
Ethnicity: Latin American
Procedure ID: 58095
Kit Barcode: [REDACTED]
Specimen: Blood, #61071
Specimen Collection: 2016-06-28
Specimen Received: 2016-06-29
Specimen Analyzed: 2016-07-11

Partner Not Tested

TEST INFORMATION


Test: CarrierMap^{GEN} (Genotyping)
Panel: Fairfax Cryobank Panel V2
Diseases Tested: 22
Genes Tested: 22
Mutations Tested: 452

SUMMARY OF RESULTS: NO MUTATIONS IDENTIFIED

Donor 5360 was not identified to carry any of the mutation(s) tested.

No pathogenic mutations were identified in the genes tested, reducing but not eliminating the chance to be a carrier for the associated genetic diseases. CarrierMap assesses carrier status for genetic disease via molecular methods including targeted mutation analysis and/ or next-generation sequencing; other methodologies such as CBC and hemoglobin electrophoresis for hemoglobinopathies and enzyme analysis for Tay-Sachs disease may further refine risks for these conditions. Results should be interpreted in the context of clinical findings, family history, and/or other testing. A list of all the diseases and mutations screened for is included at the end of the report. This test does not screen for every possible genetic disease.

For additional disease information, please visit recombine.com/diseases. To speak with a Genetic Counselor, call [855.OUR.GENES](tel:855.OUR.GENES).

Assay performed by 
Reprogenetics
CLIA ID: 31D1054821
3 Regent Street, Livingston, NJ 07039
Lab Technician: Bo Chu

Recombine CLIA # 31D2100763
Reviewed by Pere Colls, PhD, HCLD, Lab Director

ADDITIONAL RESULTS: NO INCREASED REPRODUCTIVE RISK

The following results are not associated with an increased reproductive risk.

Disease (Gene)	Donor 5360	Partner Not Tested
Spinal Muscular Atrophy: SMN1 Linked (SMN1)*	SMN1 Copy Number: 2 or more copies Method: Genotyping & dPCR	

* SMA Risk Information for Individuals with No Family History of SMA

	Detection Rate	Pre-Test Carrier Risk	Post-Test Carrier Risk (2 SMN1 copies)	Post-Test Carrier Risk (3 SMN1 copies)
European	95%	1/35	1/632	1/3,500
Ashkenazi Jewish	90%	1/41	1/350	1/4,000
Asian	93%	1/53	1/628	1/5,000
African American	71%	1/66	1/121	1/3,000
Hispanic	91%	1/117	1/1,061	1/11,000

For other unspecified ethnicities, post-test carrier risk is assumed to be <1%. For individuals with multiple ethnicities, it is recommended to use the most conservative risk estimate.

Methods and Limitations

Genotyping: Genotyping is performed using the Illumina Infinium Custom HD Genotyping assay to identify mutations in the genes tested. The assay is not validated for homozygous mutations, and it is possible that individuals affected with disease may not be accurately genotyped.

Spinal Muscular Atrophy: Carrier status for SMA is assessed via copy number analysis by dPCR and via genotyping. Some individuals with a normal number of SMN1 copies (2 copies) may carry both copies of the gene on the same allele/chromosome; this analysis is not able to detect these individuals. Thus, a normal SMN1 result significantly reduces but does not eliminate the risk of being a carrier. Additionally, SMA may be caused by non-deletion mutations in the SMN1 gene; CarrierMap tests for some, but not all, of these mutations. Some SMA cases arise as the result of de novo mutation events which will not be detected by carrier testing.

Limitations: In some cases, genetic variations other than that which is being assayed may interfere with mutation detection, resulting in false-negative or false-positive results. Additional sources of error include, but are not limited to: sample contamination, sample mix-up, bone marrow transplantation, blood transfusions, and technical errors. The test does not test for all forms of genetic disease, birth defects, and intellectual disability. All results should be interpreted in the context of family history; additional evaluation may be indicated based on a history of these conditions. Additional testing may be necessary to determine mutation phase in individuals identified to carry more than one mutation in the same gene. All mutations included within the genes assayed may not be detected, and additional testing may be appropriate for some individuals.

This test was developed and its performance determined by Recombine, Inc., and it has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

Diseases & Mutations Assayed

Alpha Thalassemia (HBA1, HBA2): Mutations (9): ♂ Genotyping | SEA deletion, c.207C>A (p.N69K), c.223G>C (p.D75G), c.2T>C (p.M1T), c.207C>G (p.N69K), c.340_351delCTCCCGCCGAG (p.L114_E117del), c.377T>C (p.L126P), c.427T>C (p.X143Qext32), c.*+94A>G

Beta Thalassemia (HBB): Mutations (82): ♂ Genotyping | c.124_127delTTCT (p.F42Lfs), c.17_18delCT, c.20delA (p.E7Gfs), c.217insA (p.S73Kfs), c.223+702_444+342del620insAAGTAGA, c.230delC, c.25_26delAA, c.315+1G>A, c.315+2T>C, c.316-197C>T, c.316-146T>G, c.315+745C>G, c.316-1G>A, c.316-1G>C, c.316-2A>G, c.316-3C>A, c.316-3C>G, c.4delG (p.V2Cfs), c.51delC (p.K18Rfs), c.93-21G>A, c.92+1G>A, c.92+5G>A, c.92+5G>C, c.92+5G>T, c.92+6T>C, c.93-1G>A, c.93-1G>T, c.-50A>C, c.-78a>g, c.-79a>g, c.-81a>g, c.52A>T (p.K18X), c.-137c>g, c.-138c>t, c.-151c>t, c.118C>T (p.Q40X), c.169G>C (p.G57R), c.295G>A (p.V99M), c.34G>A (p.V12I), c.415G>C (p.A139P), c.47G>A (p.W16X), c.48G>A (p.W16X), c.-80t>a, c.2T>C (p.M1T), c.75T>A (p.G25G), c.444+111A>G, c.-29g>a, c.68_74delAAGTTGG, c.92G>C (p.R31T), c.92+1G>T, c.93-15T>G, c.93-1G>C, c.112delT, c.113G>A (p.W38X), c.114G>A (p.W38X), c.126delC, c.444+113A>G, c.250delG, c.225delC, c.383_385delAGG (p.Q128_A129delQAinsP), c.321_322insG (p.N109fs), c.316-1G>T, c.316-2A>C, c.287_288insA (p.L97fs), c.271G>T (p.E91X), c.203_204delITG (p.V68Afs), c.154delC (p.P52fs), c.135delC (p.F46fs), c.92+2T>A, c.92+2T>C, c.90C>T (p.G30G), c.84_85insC (p.L29fs), c.59A>G (p.N20S), c.46delT (p.W16Gfs), c.55_46insG (p.L16fs), c.36delT (p.T13fs), c.2T>G (p.M1R), c.1A>G (p.M1V), c.-137c>t, c.-136c>g, c.-142c>t, c.-140c>t

Bloom Syndrome (BLM): Mutations (25): ♂ Genotyping | c.2207_2212delATCTGAinsTAGATTC (p.Y736Lfs), c.2407insT, c.557_559delCAA (p.S186X), c.1284G>A (p.W428X), c.1701G>A (p.W567X), c.1933C>T (p.Q645X), c.2528C>T (p.T843I), c.2695C>T (p.R899X), c.3107G>T (p.C1036F), c.2923delC (p.Q975K), c.3558+1G>T, c.3875-2A>G, c.2074+2T>A, c.2343_2344dupGA (p.781EfsX), c.318_319insT (p.L107fs), c.380delC (p.127Tfs), c.3564delC (p.1188Dfs), c.4008delG (p.1336Rfs), c.947C>G (p.S316X), c.2193+1_2193+9del9, c.1642C>T (p.Q548X), c.3143delA (p.1048NfsX), c.356_357delTA (p.C120Hfs), c.4076+1delG, c.3281C>A (p.S1094X)

Canavan Disease (ASPA): Mutations (8): ♂ Genotyping | c.433-2A>G, c.854A>C (p.E285A), c.693C>A (p.Y231X), c.914C>A (p.A305E), c.71A>G (p.E24G), c.654C>A (p.C218X), c.2T>C (p.M1T), c.79G>A (p.G27R)

Cystic Fibrosis (CFTR): Mutations (150): ♂ Genotyping | c.1029delC, 1153_1154insAT, c.1477delCA, c.1519_1521delATC (p.507delI), c.1521_1523delCTT (p.508delF), c.1545_1546delTA (p.Y515Xfs), c.1585-1G>A, c.164+12T>C, c.1680-886A>G, c.1680-1G>A, c.1766+1G>A, c.1766+1G>T, c.1766+5G>T, c.1818del84, c.1911delG, c.1923delCTCAAACTinsA, c.1973delGAAATTCATCTTinsAGAAA, c.2052delA (p.K684fs), c.2052insA (p.Q685fs), c.2051_2052delAAinsG (p.K6845fsX38), c.2174insA, c.261delIT, c.2657+5G>A, c.273+1G>A, c.273+3A>C, c.274-1G>A, c.2988+1G>A, c.3039delC, c.3140-26A>G, c.325delTATinsG, c.3527delC, c.3535delACCA, c.3691delT, c.3717+12191C>T, c.3744delA, c.3773_3774insT (p.L1258fs), c.442delA, c.489+1G>T, c.531delT, c.579+1G>T, c.579+5G>A (IVS4+5G>A), c.803delA (p.N268fs), c.805_806delAT (p.L269fs), c.933_935delCTT (p.311delF), c.946delT, c.1645A>C (p.S549R), c.2128A>T (p.K710X), c.1000C>T (p.R334W), c.1013C>T (p.T338I), c.1364C>A (p.A455E), c.1477C>T (p.Q493X), c.1572C>A (p.C524X), c.1654C>T (p.Q552X), c.1657C>T (p.R553X), c.1721C>A (p.P574H), c.2125C>T (p.R709X), c.223C>T (p.R75X), c.2668C>T (p.Q890X), c.3196C>T (p.R1066C), c.3276C>G (p.Y1092X), c.3472C>T (p.R1158X), c.3484C>T (p.R1162X), c.349C>T (p.R117C), c.3587C>G (p.S1196X), c.3712C>T (p.Q1238X), c.3764C>A (p.S1255X), c.3909C>G (p.N1303K), c.1040G>A (p.R347H), c.1040G>C (p.R347P), c.1438G>T (p.G480C), c.1558G>T (p.V520F), c.1624G>T (p.G542X), c.1646G>A (p.S549R), c.1646G>T (p.S549I), c.1652G>A (p.G551D), c.1675G>A (p.A559T), c.1679G>C (p.R560T), c.178G>T (p.E60X), c.1865G>A (p.G622D), c.254G>A (p.G85E), c.271G>A (p.G91R), c.274G>T (p.E92X), c.3209G>A (p.R1070Q), c.3266G>A (p.W1089X), c.3454G>C (p.D1152H), c.350G>A (p.R117H), c.3611G>A (p.W1204X), c.3752G>A (p.S1251N), c.3846G>A (p.W1282X), c.3848G>T (p.R1283M), c.532G>A (p.G178R), c.988G>T (p.G330X), c.1090T>C (p.S364P), c.3302T>A (p.M1101K), c.617T>G (p.L206W), c.14C>T (p.P5I), c.19G>T (p.E7X), c.171G>A (p.W57X), c.313delA (p.I105fs), c.328G>C (p.D110H), c.580-1G>T, c.1055G>A (p.R352Q), c.1075C>A (p.Q335F), c.1079C>A (p.T360K), c.1647T>G (p.S549R), c.1976delA (p.M659fs), c.2290C>T (p.R764X), c.2737_2738insG (p.Y913X), c.3067_3072delATAGTG (p.I1023_V1024delT), c.3536_3539delCCAA (p.T1179fs), c.3659delC (p.T1220fs), c.54-5940_273+10250del21080bp (p.S18fs), c.4056G>C (p.Q1352H), c.4364C>G (p.S1455X), c.4003C>T (p.Q1335F), c.2538G>A (p.W846X), c.200C>T (p.P67L), c.4426C>T (p.Q1476X), c.1116+1G>A, c.1986_1989delAACT (p.T663R), c.2089_2090insA (p.R697Kfs), c.2215delG (p.V739Y), c.263T>G (p.L196X), c.3022delG (p.V1008S), c.3908dupA (p.N1303Kfs), c.658C>T (p.Q220X), c.868C>T (p.Q290X), c.1526delG (p.G509fs), c.2908+1085-3367+260del7201, c.11C>A (p.S4X), c.3878_3881delTATT (p.V1293fs), c.3700A>G (p.I1234V), c.416A>T (p.H139L), c.366T>A (p.Y122X), c.3767_3768insC (p.A1256fs), c.613C>T (p.P205S), c.293A>G (p.Q98R), c.3731G>A (p.G1244E), c.535C>A (p.Q179K), c.3368-2A>G, c.455T>G (p.M152R), c.1610_1611delAC (p.D537fs), c.3254A>G (p.H1085R), c.496A>G (p.K166E), c.1408_1417delGTGATTATGG (p.V470fs), c.1585-8G>A, c.2909G>A (p.G970D), c.653T>A (p.L218X), c.1175T>G (p.V392G), c.3139_3139+1delGG

Familial Dysautonomia (IKBKAP): Mutations (4): ♂ Genotyping | c.2204+6T>C, c.2741C>T (p.P914L), c.2087G>C (p.R696P), c.2128C>T (p.Q710X)

Familial Hyperinsulinism: Type 1: ABCC8 Related (ABCC8): Mutations (10): ♂ Genotyping | c.3989-9G>A, c.4159_4161delITC (p.1387delF), c.4258C>T (p.R1420C), c.4477C>T (p.R1493W), c.2147G>T (p.G716V), c.4055G>C (p.R1352P), c.560T>A (p.V187D), c.4516G>A (p.E1506K), c.2506C>T (p.Q836X), c.579+2T>A

Fanconi Anemia: Type C (FANCC): Mutations (8): ♂ Genotyping | c.456+4A>T, c.67delG, c.37C>T (p.Q13X), c.553C>T (p.R185X), c.1661T>C (p.L554P), c.1642C>T (p.R548X), c.66G>A (p.W22X), c.65G>A (p.W22X)

Gaucher Disease (GBA): Mutations (6): ♂ Genotyping | c.84_85insG, c.1226A>G (p.N409S), c.1343A>T (p.D448V), c.1504C>T (p.R502C), c.1297G>T (p.V433L), c.1604G>A (p.R535H)

Glycogen Storage Disease: Type IA (G6PC): Mutations (13): ♂ Genotyping | c.376_377insTA, c.79delC, c.979_981delITC (p.327delF), c.1039C>T (p.Q347X), c.247C>T (p.R83C), c.724C>T (p.Q242X), c.248G>A (p.R83H), c.562G>C (p.G188R), c.648G>T, c.809G>T (p.G270V), c.113A>T (p.D38V), c.975delG (p.L326fs), c.724delC

Joubert Syndrome (TMEM216): Mutations (2): ♂ Genotyping | c.218G>T (p.R73L), c.218G>A (p.R73H)

Maple Syrup Urine Disease: Type 1B (BCKDHB): Mutations (6): ♂ Genotyping | c.1114G>T (p.E372X), c.548G>C (p.R183P), c.832G>A (p.G278S), c.970C>T (p.R324X), c.487G>T (p.E163X), c.853C>T (p.R285X)

Maple Syrup Urine Disease: Type 3 (DLD): Mutations (8): ♂ Genotyping | c.104_105insA, c.685G>T (p.G229C), c.214A>G (p.K72E), c.1081A>G (p.M361V), c.1123G>A (p.E375K), c.1178T>C (p.G393T), c.1463C>T (p.P488I), c.1483A>G (p.R495G)

Mucopolidiosis: Type IV (MCOLN1): Mutations (5): ♂ Genotyping | c.-1015_788del6433, c.406-2A>G, c.1084G>T (p.D362Y), c.304C>T (p.R102X), c.244delC (p.L82fsX)

Nemaline Myopathy: NEB Related (NEB): Mutations (1): ♂ Genotyping | c.7434_7536del2502bp

Niemann-Pick Disease: Type A (SMPD1): Mutations (6): ♂ Genotyping | c.996delC, c.1493G>T (p.R498L), c.911T>C (p.L304P), c.1267C>T (p.H423Y), c.1734G>C (p.K578N), c.1493G>A (p.R498H)

Sickle-Cell Anemia (HBB): Mutations (1): ♂ Genotyping | c.20A>T (p.E7V)

Spinal Muscular Atrophy: SMN1 Linked (SMN1): Mutations (19): ♂ Genotyping | DEL EXON 7, c.22_23insA, c.43C>T (p.Q15X), c.91_92insT, c.305G>A (p.W102X), c.400G>A (p.E134K), c.439_443delGAAGT, c.558delC, c.585_586insT, c.683T>A (p.L228X), c.734C>T (p.P245L), c.768_778dupTGCTGATGCTT, c.815A>G (p.Y272C), c.821C>T (p.T274I), c.823G>A (p.G275S), c.834+2T>G, c.835-18_835-12delCCTTAT, c.835G>T, c.836G>T dPCR | DEL EXON 7

Tay-Sachs Disease (HEXA): Mutations (76): ♂ Genotyping | c.1073+1G>A, c.1277_1278insATC, c.1421+1G>C, c.805+1G>A, c.532C>T (p.R178C), c.533G>A (p.R178H), c.805G>A (p.G269S), c.1510C>T (p.R504C), c.1496G>A (p.R499H), c.509G>A (p.R170Q), c.1003A>T (p.I335F), c.910_912delITC (p.305delF), c.749G>A (p.G250D), c.632T>C (p.F211S), c.629C>T (p.S210F), c.613delC, c.611A>G (p.H204R), c.598G>A (p.V200M), c.590A>C (p.K197T), c.571-1G>T, c.540C>G (p.Y180X), c.538T>C (p.Y180H), c.533G>T (p.R178L), c.508C>T (p.R170W), c.409C>T (p.R137X), c.380T>G (p.L127R), c.346+1G>C, c.116T>G (p.L39R), c.78G>A (p.W26X), c.1A>G (p.M1V), c.1495C>T (p.R499C), c.459+5G>A (IVS4+5G>A), c.1422-2A>G, c.535C>T (p.H179Y), c.1141delG (p.V381fs), c.796T>G (p.W266G), c.155C>A (p.S52X), c.426delT (p.F142fs), c.413-2A>G, c.570+3A>G, c.536A>G (p.H179R), c.1146+1G>A, c.736G>A (p.A246T), c.1302C>G (p.F434L), c.778C>T (p.P260S), c.1008G>T (p.Q336H), c.1385A>T (p.E462V), c.964G>A (p.D322N), c.340G>A (p.E114K), c.1432G>A (p.G478R), c.1178G>C (p.R393P), c.805+1G>C, c.1426A>T (p.R476X), c.623A>T (p.D208V), c.1537C>T (p.Q513X), c.1511G>T (p.R504L), c.1307_1308delTA (p.L436fs), c.571-8A>G, c.624_627delTTCT (p.D208fs), c.1211_1212delTG (p.L404fs), c.621T>G (p.D207E), c.1511G>A (p.R504H), c.1177C>T (p.R393X), c.2T>C (p.M1T), c.1292G>A (p.W431X), c.947_948insA (p.Y316fs), c.607T>G (p.W203G), c.1061_1063delITC (p.F354_Y355delinsX), c.615delG (p.L205fs), c.805+2T>C, c.1123delG (p.E375fs), c.1121A>G (p.Q374R), c.1043_1046delTCAA (p.F348fs), c.1510delC (p.R504fs), c.1451T>C (p.L484P), c.964G>T (p.D322Y)

Usher Syndrome: Type 1F (PCDH15): Mutations (7): ♂ Genotyping | c.733C>T (p.R245X), c.2067C>A (p.Y684X), c.7C>T (p.R3X), c.1942C>T (p.R648X), c.1101delT (p.A367fsX), c.2800C>T (p.R934X), c.4272delA (p.L1425fs)

Usher Syndrome: Type 3 (CLRN1): Mutations (5): ♂ Genotyping | c.144T>G (p.N48K), c.131T>A (p.M120K), c.567T>G (p.Y189X), c.634C>T (p.Q212X), c.221T>C (p.L74P)

Walker-Warburg Syndrome (FKN1): Mutations (1): ♂ Genotyping | c.1167insA (p.F390fs)

Residual Risk Information

Detection rates are calculated from the primary literature and may not be available for all ethnic populations. The values listed below are for genotyping. Sequencing provides higher detection rates and lower residual risks for each disease. More precise values for sequencing may become available in the future.

Disease	Carrier Rate	Detection Rate	Residual Risk
Alpha Thalassemia	♂ General: 1/48	50.67%	1/97
Beta Thalassemia	♂ African American: 1/75	84.21%	1/475
	♂ Indian: 1/24	74.12%	1/93
	♂ Sardinians: 1/23	97.14%	1/804
	♂ Spaniard: 1/51	93.10%	1/739
Bloom Syndrome	♂ Ashkenazi Jewish: 1/134	96.67%	1/4,020
	♂ European: Unknown	66.22%	Unknown
	♂ Japanese: Unknown	50.00%	Unknown
Canavan Disease	♂ Ashkenazi Jewish: 1/55	98.86%	1/4,840
	♂ European: Unknown	53.23%	Unknown
Cystic Fibrosis	♂ African American: 1/62	69.99%	1/207
	♂ Ashkenazi Jewish: 1/23	96.81%	1/721
	♂ Asian: 1/94	66.40%	1/280
	♂ European: 1/25	94.96%	1/496
	♂ Hispanic American: 1/48	77.32%	1/212
	♂ Native American: 1/53	84.34%	1/338
Familial Dysautonomia	♂ Ashkenazi Jewish: 1/31	>99%	<1/3,100
Familial Hyperinsulinism: Type 1: ABCC8 Related	♂ Ashkenazi Jewish: 1/52	98.75%	1/4,160
	♂ Finnish: 1/101	45.16%	1/184
Fanconi Anemia: Type C	♂ Ashkenazi Jewish: 1/101	>99%	<1/10,100
	♂ General: Unknown	30.00%	Unknown
Gaucher Disease	♂ Ashkenazi Jewish: 1/15	87.16%	1/117
	♂ General: 1/112	31.60%	1/164
	♂ Spaniard: Unknown	44.29%	Unknown
	♂ Turkish: 1/236	59.38%	1/581
Glycogen Storage Disease: Type IA	♂ Ashkenazi Jewish: 1/71	>99%	<1/7,100
	♂ Chinese: 1/159	80.00%	1/795
	♂ European: 1/177	76.88%	1/765
	♂ Hispanic American: 1/177	27.78%	1/245
	♂ Japanese: 1/177	89.22%	1/1,641
Joubert Syndrome	♂ Ashkenazi Jewish: 1/92	>99%	<1/9,200
Maple Syrup Urine Disease: Type 1B	♂ Ashkenazi Jewish: 1/97	>99%	<1/9,700
Maple Syrup Urine Disease: Type 3	♂ Ashkenazi Jewish: 1/94	>99%	<1/9,400
	♂ General: Unknown	68.75%	Unknown
Mucopolipidosis: Type IV	♂ Ashkenazi Jewish: 1/97	96.15%	1/2,522
Nemaline Myopathy: NEB Related	♂ Ashkenazi Jewish: 1/108	>99%	<1/10,800

Disease	Carrier Rate	Detection Rate	Residual Risk
Niemann-Pick Disease: Type A	♂ Ashkenazi Jewish: 1/101	95.00%	1/2,020
Sickle-Cell Anemia	♂ African American: 1/10	>99%	<1/1,000
	♂ Hispanic American: 1/95	>99%	<1/9,500
Tay-Sachs Disease	♂ Argentinian: 1/280	82.35%	1/1,587
	♂ Ashkenazi Jewish: 1/29	99.53%	1/6,177
	♂ Cajun: 1/30	>99%	<1/3,000
	♂ European: 1/280	25.35%	1/375
	♂ General: 1/280	32.09%	1/412
	♂ Indian: Unknown	85.71%	Unknown
	♂ Iraqi Jewish: 1/140	56.25%	1/320
	♂ Japanese: 1/127	82.81%	1/739
	♂ Moroccan Jewish: 1/110	22.22%	1/141
	♂ Portuguese: 1/280	92.31%	1/3,640
	♂ Spaniard: 1/280	67.65%	1/865
	♂ United Kingdom: 1/161	71.43%	1/564
Usher Syndrome: Type 1F	♂ Ashkenazi Jewish: 1/126	93.75%	1/2,016
Usher Syndrome: Type 3	♂ Ashkenazi Jewish: 1/120	>99%	<1/12,000
	♂ Finnish: 1/134	>99%	<1/13,400
Walker-Warburg Syndrome	♂ Ashkenazi Jewish: 1/150	>99%	<1/15,000

Patient Information

Name: Donor 5360

Date of Birth: [REDACTED]

Sema4 ID: [REDACTED]

Client ID: [REDACTED]

Indication: Carrier Testing

Specimen Information

Specimen Type: Purified DNA

Date Collected: 08/11/2020

Date Received: 08/14/2020

Final Report: 08/28/2020

Referring Provider

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Custom Carrier Screen (ECS)

Number of genes tested: 1

SUMMARY OF RESULTS AND RECOMMENDATIONS

 **Negative****Negative for all genes tested: *PMM2***To view a full list of genes and diseases tested
please see Table 1 in this report*AR=Autosomal recessive; XL=X-linked***Recommendations**

- 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.

Test description

This patient was tested for the genes listed above using one or more of the following methodologies: target capture and short-read sequencing, long-range PCR followed by short-read sequencing, targeted genotyping, and/or 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 view the Table of Residual Risks Based on Ethnicity at the end of this report or at go.sema4.com/residualrisk for gene transcripts, sequencing exceptions, specific detection rates, and residual risk estimates after a negative screening result. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only known pathogenic or likely pathogenic variants are reported. This carrier screening test does not report likely benign variants and variants of uncertain significance (VUS). If reporting of likely benign variants and VUS are desired in this patient, please contact the laboratory at 800-298-6470, option 2 to request an amended report.

**Anastasia Larmore, Ph.D., Assistant 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
⊖ Negative				
Congenital Disorder of Glycosylation, Type Ia	PMM2	AR	Reduced Risk (see table below)	

AR=Autosomal recessive; XL=X-linked

Table 2: Residual Risk by ethnicity for negative results

Disease (Inheritance)	Gene	Ethnicity	Carrier Frequency	Detection Rate	Residual Risk	Analytical Detection Rate
Congenital Disorder of Glycosylation, Type Ia (AR) NM_000303.2	PMM2	African	1 in 245	99%	1 in 24,400	99%
		Ashkenazi Jewish	1 in 66	99%	1 in 6,500	
		East Asian	1 in 133	76%	1 in 550	
		Finnish	1 in 58	99%	1 in 5,700	
		European (Non-Finnish)	1 in 58	89%	1 in 540	
		Native American	1 in 114	91%	1 in 1,200	
		South Asian	1 in 278	86%	1 in 2,000	
		Worldwide	1 in 80	91%	1 in 840	

* Carrier detection by HEXA enzyme analysis has a detection rate of approximately 98% (Applies to *HEXA* gene testing only).

† Carrier frequencies include milder and reduced penetrance forms of the disease. Therefore, carrier frequencies may appear higher than reported in the literature (Applies to *BTBD*, *Fg*, *GJB2*, *GJB1*, *GLA*, and *MEFV* gene testing only).

‡ Please note that *GJB2* testing includes testing for the two upstream deletions, del(GJB6-D13S1830) and del(GJB6-D13S1854) (PMID:11807148 and 15994881) (Applies to *GJB2* gene testing only).

AR: Autosomal recessive; N/A: Not available; 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:

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 SureSelectTMQXT technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Samples were pooled and sequenced on the Illumina HiSeq 2500 platform in the Rapid Run mode or the Illumina NovaSeq platform in the Xp workflow, using 100 bp paired-end reads. These sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

The coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage (minimum of 20X) and data quality threshold values. Most exons not meeting a minimum of >20X read depth across the exon are further analyzed by Sanger sequencing. Please note that several genomic regions present difficulties in mapping or obtaining read depth >20X. The exons contained within these regions are noted within Table 1 (as "Exceptions") and will not be reflexed to Sanger sequencing if the mapping quality or coverage is poor. Any variants identified during testing in these regions are confirmed by a second method and reported if determined to be pathogenic or likely pathogenic. However, as there is a possibility of false negative results within these regions, detection rates and residual risks for these genes have been calculated with the presumption that variants in these exons will not be detected, unless included in the MassARRAY[®] genotyping platform.

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

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

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

Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exon hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom array CGH 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 are specific to the target region and a control region with known genomic copy number. Relative genomic copy numbers are calculated based on the standard $\Delta\Delta C_t$ formula.

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

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where two copies of a gene are located on the same chromosome in tandem, only the second copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the *CYP21A2* gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. When an individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

Residual Risk Calculations

Carrier frequencies and detection rates for each ethnicity were calculated through the combination of internal curations of >28,000 variants and genomic frequency data from >138,000 individuals across seven ethnic groups in the gnomAD database. Additional variants in HGMD and novel deleterious variants were also incorporated into the calculation. Residual risk values are calculated using a Bayesian analysis combining the *a priori* risk of being a pathogenic mutation carrier (carrier frequency) and the detection rate. They are provided only as a guide for assessing approximate risk given a negative result, and values will vary based on the exact ethnic background of an individual. This report does not represent medical advice but should be interpreted by a genetic counselor, medical geneticist or physician skilled in genetic result interpretation and the relevant medical literature.

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

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

SELECTED REFERENCES

Carrier Screening

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

Variant Classification:

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

Additional disease-specific references available upon request.

Patient Information

Name: Donor 5360

Date of Birth: [REDACTED]

Sema4 ID: [REDACTED]

Client ID: [REDACTED]

Indication: Carrier Testing

Specimen Information

Specimen Type: Purified DNA

Date Collected: 08/11/2020

Date Received: 08/14/2020

Final Report: 02/05/2021

Referring Provider

Harvey Stern, M.D.

Genetics & IVF Institute

3015 Williams Drive

Fairfax, VA, 22031

Fax:

Unmask Additional Gene(s) V1E

Number of genes tested: 1

SUMMARY OF RESULTS AND RECOMMENDATIONS **Negative****Negative for all genes tested: MCCC2**To view a full list of genes and diseases tested
please see Table 1 in this report*AR=Autosomal recessive; XL=X-linked***Recommendations**

- 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.

Test description

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested, and [go.sema4.com/residualrisk](https://www.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.

**Ruth Kornreich, Ph.D., FACMG, 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
⊖ Negative				
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)	MCCC2	AR	Reduced Risk (see table below)	

AR=Autosomal recessive; XL=X-linked

Table 2: Residual Risk by ethnicity for negative results

Disease (Inheritance)	Gene	Ethnicity	Carrier Frequency	Detection Rate	Residual Risk	Analytical Detection Rate
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related) (AR) NM_022132.4	MCCC2	African	1 in 407	81%	1 in 2,200	99%
		Ashkenazi Jewish	1 in 267	99%	1 in 26,600	
		East Asian	1 in 192	62%	1 in 500	
		Finnish	1 in 2230	79%	1 in 10,700	
		European (Non-Finnish)	1 in 204	83%	1 in 1,200	
		Native American	1 in 125	98%	1 in 5,100	
		South Asian	1 in 308	69%	1 in 1,000	
		Worldwide	1 in 213	83%	1 in 1,300	

* Carrier detection by HEXA enzyme analysis has a detection rate of approximately 98% (Applies to *HEXA* gene testing only).

† Carrier frequencies include milder and reduced penetrance forms of the disease. Therefore, carrier frequencies may appear higher than reported in the literature (Applies to *BTBD*, *Fg*, *GJB2*, *GJB1*, *GLA*, and *MEFV* gene testing only).

‡ Please note that *GJB2* testing includes testing for the two upstream deletions, del(GJB6-D13S1830) and del(GJB6-D13S1854) (PMID:11807148 and 15994881) (Applies to *GJB2* gene testing only).

AR: Autosomal recessive; N/A: Not available; XL: X-linked

Test methods and comments

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

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

PCR amplification using Asuragen,

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

Genotyping (Analytical Detection Rate >99%)

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

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

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

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

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

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

For spinal muscular atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected with this assay. Depending on ethnicity, 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 20 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals with SMA have an *SMN1* mutation that occurred *de novo*. Typically in these cases, only one parent is an SMA carrier.

The presence of the c.*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 of c.*380T>G significantly increases or decreases, respectively, the likelihood of being a silent 20 carrier.

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testing for the c.*380T>G variant allele; these will be reported if confirmed to be located in *SMN1* using locus-specific Sanger primers

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

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

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

Agilent SureSelectTMQXT technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Samples were pooled and sequenced on the Illumina HiSeq 2500 platform in the Rapid Run mode or the Illumina NovaSeq platform in the Xp workflow, using 100 bp paired-end reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

The coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage (minimum of 20X) and data quality threshold values. Most exons not meeting a minimum of >20X read depth across the exon are further analyzed by Sanger sequencing. Please note that several genomic regions present difficulties in mapping or obtaining read depth >20X. The exons contained within these regions are noted within Table 1 (as "Exceptions") and will not be reflexed to Sanger sequencing if the mapping quality or coverage is poor. Any variants identified during testing in these regions are confirmed by a second method and reported if determined to be pathogenic or likely pathogenic. However, as there is a possibility of false negative results within these regions, detection rates and residual risks for these genes have been calculated with the presumption that variants in these exons will not be detected, unless included in the MassARRAY[®] genotyping platform.

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

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

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

Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exome hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom

arrayCGH platform, quantitative PCR, or MLPA (depending on CNV size and gene content). While this algorithm is designed to pick up deletions and duplications of 2 or more exons in length, potentially pathogenic single-exon CNVs will be confirmed and reported, if detected.

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

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

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

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

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

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where two copies of a gene are located on the same chromosome in tandem, only the second copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the *CYP21A2* gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. When an individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

Residual Risk Calculations

Carrier frequencies and detection rates for each ethnicity were calculated through the combination of internal curations of >28,000 variants and genomic frequency data from >138,000 individuals across seven ethnic groups in the gnomAD database. Additional variants in HGMD and novel deleterious variants were also incorporated into the calculation. Residual risk values are calculated using a Bayesian analysis combining the *a priori* risk of being a pathogenic mutation carrier (carrier frequency) and the detection rate. They are provided only as a guide for assessing approximate risk given a negative result, and values will vary based on the exact ethnic background of an individual. This report does not represent medical advice but should be interpreted by a genetic counselor, medical geneticist or physician skilled in genetic result interpretation and the relevant medical literature.

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

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

Tay-Sachs Disease (TSD) Enzyme Analysis (Analytical Detection Rate \geq 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 and individuals affected with TSD. Normal ranges of Hex A% activity are 55.0-72.0 for white blood cells and 58.0-72.0 for plasma. It is estimated that less than 0.5% of Tay-Sachs carriers 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 benign variants, such as pseudodeficiency alleles, interfere with the enzymatic assay. False negative 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.

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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.

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

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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: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015 May;17(5):405-24

Additional disease-specific references available upon request.



Patient Information:

5360, Donor

DOB: [REDACTED]

Sex: M

MR#: 5360

Patient#: [REDACTED]

Partner Information:

Not Tested

Physician:

Seitz, Suzanne

ATTN: Seitz, Suzanne

Fairfax Cryobank

3015 Williams Drive

Fairfax, VA 22031

Laboratory:

Fulgent Genetics

CAP#: 8042697

CLIA#: 05D2043189

Laboratory Director:

Dr. Hanlin (Harry) Gao

Report Date: **Jun 18, 2023**

Accession:

[REDACTED]

Test#: [REDACTED]

Specimen Type: DNA

Collected: May 24, 2023

Accession:

N/A

FINAL RESULTS



No carrier mutations identified

TEST PERFORMED

Custom Beacon Carrier Screening Panel

(2 Gene Panel: *BTB* and *SERPINA1*;
gene sequencing with deletion and
duplication analysis)

INTERPRETATION:

Notes and Recommendations:

- No carrier mutations were identified in the submitted specimen. A negative result does not rule out the possibility of a genetic predisposition nor does it rule out any pathogenic mutations in areas not assessed by this test or in regions that were covered at a level too low to reliably assess. Also, it does not rule out mutations that are of the sort not queried by this test; see Methods and Limitations for more information.
- This carrier screening test does not screen for all possible genetic conditions, nor for all possible mutations in every gene tested. Individuals with negative test results may still have up to a 3-4% risk to have a child with a birth defect due to genetic and/or environmental factors.
- Patients may wish to discuss any carrier results with blood relatives, as there is an increased chance that they are also carriers. These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- X-linked genes are not routinely analyzed for male carrier screening tests. Gene specific notes and limitations may be present. See below.
- This report does not include variants of uncertain significance.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; <https://www.nsgc.org>)

GENES TESTED:

Custom Beacon Carrier Screening Panel - 2 Genes

This analysis was run using the Custom Beacon Carrier Screening Panel gene list. 2 genes were tested with 100.0% of targets sequenced at >20x coverage. For more gene specific information and assistance with residual risk calculation, see the SUPPLEMENTAL TABLE.

BTD, SERPINA1

METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 100.00% and 100.00% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications are analyzed using Fulgent Germline proprietary pipeline for this specimen. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

LIMITATIONS:

General Limitations

These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or otherwise, to future pregnancies, and negative results do not rule out the genetic risk to a pregnancy. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (<https://www.genenames.org>) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions other than specified genes. DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution

of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations of genomic regions which include one whole gene (buccal swab specimens and whole blood specimens) and are two or more contiguous exons in size (whole blood specimens only); single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

Gene Specific Notes and Limitations

BTD: If detected, the variant NM_001370658.1:c.1270G>C (p.Asp424His) will not be reported as this variant is associated with low disease penetrance and is primarily associated with reduced enzyme activity when homozygous. SERPINA1: If detected the variant NM_000295.5:c.863A>T (p.Glu288Val) will not be reported as this variant is associated with low disease penetrance and is not associated with severe early onset disease.

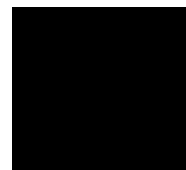
SIGNATURE:

A handwritten signature in black ink, appearing to read "H. Gao".

Dr. Harry Gao, DABMG, FACMG on 6/18/2023 3:58 PM PDT
Electronically signed

DISCLAIMER:

This test was developed and its performance characteristics determined by **Fulgent Genetics**. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at (626) 350-0537 or info@fulgentgenetics.com. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.



Supplemental Table							
Gene	Condition	Inheritance	Ethnicity	Carrier Rate	Detection Rate	Post-test Carrier Probability*	Residual Risk*
<i>BTBD</i>	Biotinidase deficiency	AR	General Population	1 in 124	99%	1 in 12,301	1 in 6,101,296
			Caucasian / European Population	1 in 71	99%	1 in 7,001	1 in 1,988,284
			Latino Population	1 in 136	99%	1 in 13,501	1 in 7,344,544
			Middle-Eastern Population	1 in 55	99%	1 in 5,401	1 in 1,188,220
<i>SERPINA1</i>	Alpha-1 antitrypsin deficiency	AR	General Population	1 in 33	95%	1 in 641	1 in 84,612
			Caucasian / European Population	1 in 19	95%	1 in 361	1 in 27,436

* For genes that have tested negative
 Abbreviations: AR, autosomal recessive; XL, X-linked