Counsyl

RESULTS RECIPIENT
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Report Date: 11/12/2015

MALE
DONOR 9925
DOB: [redacted]
Ethnicity: Southern European
Sample Type: OG-510 Saliva
Date of Collection: 10/05/2015
Date Received: 10/29/2015
Date Tested: 11/12/2015
Barcode: 55101505030104
Indication: Egg or sperm donor

FEMALE
N/A

Family Prep Screen

NEGATIVE

ABOUT THIS TEST

The Counsyl Family Prep Screen (version 2.0) utilizes sequencing, maximizing coverage across all DNA regions tested, to help you learn about your chance to have a child with a genetic disease.

PANEL DETAILS

Fundamental Plus Panel **(21 conditions tested)**

VERSION

DONOR 9925 **(Family Prep Screen 2.0)**

RESULTS SUMMARY

NEGATIVE

No known disease-causing mutations were detected. A complete list of all conditions tested can be found on page 4.

CLINICAL NOTES

- None

NEXT STEPS

- If necessary, patients can discuss residual risks with their physician or a genetic counselor.
- To schedule a complimentary appointment with a genetic counselor, visit counsyl.com/my/consults/.

Methods and Limitations

DONOR 9925 [Family Prep Screen 2.0]**: sequencing, targeted genotyping, copy number analysis, and analysis of homologous regions.**

Sequencing: High-throughput sequencing is used to analyze 262 exons in 18 genes, as well as selected intergenic and intronic regions. These regions are sequenced to high coverage and the sequences are compared to standards and references of normal variation. Mutations may not be detected in areas of lower sequence coverage. On average, more than 99% of all bases in the exons listed for each gene are sequenced at the minimum read depth. Variants discovered in other exons of these genes will also be reported if they meet quality control criteria. Triplet repeats and large deletions and duplications may not be detected. Small insertions and deletions may not be as accurately determined as single nucleotide variants. Genes that have closely related pseudogenes are not well analyzed by this method.

High-throughput sequencing detects, on average, 94% of known clinically significant variants. Disease-specific detection rates and residual risks are reported as "greater than (>)" and "less than (<)" the values for targeted genotyping, respectively. More precise values are not currently available, but may become available in the future.

All variants that are a recognized cause of the disease will be reported. In addition, variants that have not previously been established as a recognized cause of disease may be identified. In these cases, only variants classified as "predicted" or "likely" pathogenic are reported. Predicted/likely pathogenic variants are described elsewhere in the report as "predicted/likely to have a negative impact on gene function". In general, predicted pathogenic variants are those which are predicted to be pathogenic based on the nature of the sequence change, while likely pathogenic variants are evaluated by reviewing reports of allele frequencies in cases and controls, functional studies, variant annotation and effect prediction, and segregation studies. Benign variants, variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported. Literature citations validating reported variants are available upon request.

Targeted genotyping: Targeted DNA mutation analysis is used to simultaneously determine the genotype of 182 variants associated with 19 diseases. The test is not validated for detection of homozygous mutations, and although rare, asymptomatic individuals affected by the disease may not be genotyped accurately.

Copy number analysis: Targeted copy number analysis is used to determine the copy number of exon 7 of the *SMN1* gene relative to other genes. Other mutations may interfere with this analysis. Some individuals with two copies of *SMN1* are carriers with two *SMN1* genes on one chromosome and a *SMN1* deletion on the other chromosome. In addition, a small percentage of spinal muscular atrophy (SMA) cases are caused by nondeletion mutations in the *SMN1* gene. Thus, a test result of two *SMN1* copies significantly reduces the risk of being a carrier; however, there is still a residual risk of being a carrier and subsequently a small risk of future affected offspring for individuals with two or more *SMN1* gene copies. Some SMA cases arise as the result of *de novo* mutation events which will not be detected by carrier testing.

Analysis of homologous regions: A combination of high-throughput sequencing, read depth-based copy number analysis, and targeted genotyping is used to determine the number of functional gene copies and/or the presence of selected loss of function mutations in certain genes that have homology to other regions. The precise breakpoints of large deletions in these regions cannot be determined, but are estimated from copy number analysis. Patients who have one or more additional copies of the *CYP21A2* gene and a loss of function mutation may not actually be a carrier of 21-hydroxylase-deficient congenital adrenal hyperplasia (CAH). In addition, some individuals with four alpha globin genes are carriers with three genes on one chromosome and a deletion on the other chromosome. This and similar carrier states, where complementary changes exist in both the gene and a pseudogene, may not be detected by the assay.

Limitations: In an unknown number of cases, nearby genetic variants may interfere with mutation detection. Other possible sources of diagnostic error include sample mix-up, trace contamination, bone marrow transplantation, blood transfusions and technical errors. If more than one variant is detected in a gene, additional studies may be necessary to determine if those variants lie on the same chromosome or different chromosomes. The Family Prep Screen does not fully address all inherited forms of intellectual disability, birth defects and genetic disease. A family history of any of these conditions may warrant additional evaluation. Furthermore, not all mutations will be identified in the genes analyzed and additional testing may be beneficial for some patients. For example, individuals of African, Southeast Asian, and Mediterranean ancestry are at increased risk for being carriers for hemoglobinopathies, which can be identified by CBC and hemoglobin electrophoresis or HPLC (*ACOG Practice Bulletin No. 78. Obstet. Gynecol. 2007;109:229-37*) and additional Tay-Sachs disease testing can be performed using a biochemical assay (*Gross et al. Genet. Med. 2008:10(1):54-56*).

This test was developed and its performance characteristics determined by Counsyl, Inc. It has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA does not require this test to go through premarket review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These results are adjunctive to the ordering physician's evaluation. CLIA Number: **#05D1102604**.

Conditions Tested

Autosomal Recessive Disorders

SEQUENCING AND TARGETED GENOTYPING

ABCC8-related Hyperinsulinism - Gene: ABCC8. **Variants (3):** 3992-9G>A, F1388del, V187D. **Exons:** NM_000352:1-39. **Detection rate**: Unknown due to rarity of disease.

Bloom Syndrome - Gene: BLM. **Variant (1):** Y736Lfs*5. **Exons:** NM_000057:2-22. **Detection rate**: Southern European > 10%.

Canavan Disease - Gene: ASPA. **Variants (4):** A305E, E285A, IVS2-2A>G, Y231*. **Exons:** NM_000049:1-6. **Detection rate**: Southern European > 53%.

Cystic Fibrosis - Gene: CFTR. **Variants (99):** 1288insTA, 1812-1G>A, 1898+5G>T, 2043delG, 2055del9->A, 2108delA, 2143delT, 2183AA>G, 2184insA, 2307insA, 2789+5G>A, 296+12T>C, 3199del6, 3272-26A>G, 3791delC, 3849+10kbC>T, 3849+4A>G, 394delTT, 405+1 G>A, 405+3A>C, 444delA, 457TAT>G, 663delT, 711+5G>A, 712-1G>T, 935delA, 936delTA, A455E, A559T, C524*, D1152H, E60*, E92*, F508del, G178R, G330*, G480C, G542*, G551D, G622D, G85E, I507del, K710*, L206W, M1101K, M607_Q643del, N1303K, P574H, Q1238*, Q493*, Q552*, Q890*, Q996, R1066C, R1158*, R1162*, R117C, R117H, R334W, R347H, R347P, R352Q, R553*, R560T, R709*, R75*, R764*, S1196*, S1251N, S1255*, S364P, S549N, S549R(c.1645A>C), S549R(c.1647T>G), T338I, V520F, W1089*, W1204*, W1282*, Y1092X, Y122*, c.1075_1079del5ins5, c.1545_1546delTA, c.1585-1G>A, c.1766+1G>A, c.1766+1G>T, c.2052delA, c.2738insG, c.274-1G>A, c.2988+1G>A, c.3039delC, c.3528delC, c.3536_3539delCCAA, c.3744delA, c.3773dupT, c.442delA, c.489+1G>T, c.579+1G>T, c.948delT. **Exons:** NM_000492:1-27. IVS8-5T allele analysis is only reported in the presence of the R117H mutation. **Detection rate**: Southern European > 91%.

Familial Dysautonomia - Gene: IKBKAP. **Variants (2):** IVS20+6T>C, R696P. **Exons:** NM_003640:19-20,26. **Detection rate**: Unknown due to rarity of disease.

Fanconi Anemia Type C - Gene: FANCC. **Variants (3):** R548*, c.456+4A>T, c.67delG. **Exons:** NM_000136:2-15. **Detection rate**: Southern European > 54%.

Glycogen Storage Disease Type Ia - Gene: G6PC. **Variants (7):** G188R, Q242*, Q347*, R83C, R83H, c.379_380dupTA, c.79delC. **Exons:** NM_000151:1-5. **Detection rate**: Southern European > 61%.

Hb Beta Chain-Related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease) - Gene: HBB. **Variants (28):** -28A>G, -29A>G, -87C>G, -88C>T, E122K, E122Q, G25=, Hb C, Hb E, Hb S, IVS-I-1, IVS-I-5, IVS-I-6T>C, IVS2-745C>G, K18Rfs*2, K9Vfs*14, Q40*, W16*, c.126_129delCTTT, c.20delA, c.27dupG, c.315+1G>A, c.316-197C>T, c.316-2A>C, c.316-2A>G, c.93-21G>A, p.K18*, p.S73Kfs*2. **Exons:** NM_000518:1-3. **Detection rate**: Southern European > 93%.

Hexosaminidase A Deficiency (Including Tay-Sachs Disease) - Gene: HEXA. **Variants (9):** 7.6kb del, G250D, G269S, R170W, R178H, c.1073+1G>A, c.1274_1277dupTATC, c.1421+1G>C, c.805+1G>A. **Exons:** NM_000520:1-14. **Detection rate**: Southern European > 23%.

Joubert Syndrome 2 - Gene: TMEM216. **Variant (1):** R73L. **Exons:** NM_001173990:1-5. **Detection rate**: Unknown due to rarity of disease.

Lipoamide Dehydrogenase Deficiency - Gene: DLD. **Variants (2):** G194C, c.104dupA. **Exons:** NM_000108:1-14. **Detection rate**: Unknown due to rarity of disease.

Maple Syrup Urine Disease Type 1B - Gene: BCKDHB. **Variants (3):** E372*, G278S, R183P. **Exons:** NM_183050:1-10. **Detection rate**: Unknown due to rarity of disease.

Mucolipidosis IV - Gene: MCOLN1. **Variants (2):** 511_6944del, c.406-2A>G. **Exons:** NM_020533:1-14. **Detection rate**: Southern European > 10%.

NEB-related Nemaline Myopathy - Gene: NEB. **Variant (1):** c.(?_7431+1917)_(7536+373_?)del. **Exons:** NM_004543:7-8,18,25,28,33,36,45,48,54-55,58,61,71,73-74,91,94,101,111-112,114,118-119,122-123,127,129,132-135,138,140,143,146-147. **Detection rate**: Unknown due to rarity of disease.

Niemann-Pick Disease, SMPD1-associated - Gene: SMPD1. **Variants (4):** L302P, R496L, c.1829_1831delGCC, fsP330. **Exons:** NM_000543:1-6. **Detection rate**: Southern European > 38%.

Usher Syndrome Type 1F - Gene: PCDH15. **Variant (1):** R245*. **Exons:** NM_033056:2-33. **Detection rate**: Unknown due to rarity of disease.

Usher Syndrome Type 3 - Gene: CLRN1. **Variant (1):** N48K. **Exons:** NM_174878:1-3. **Detection rate**: Unknown due to rarity of disease.

Walker-Warburg Syndrome - Gene: FKTN. **Variant (1):** c.1167dupA. **Exons:** NM_001079802:3-11. **Detection rate**: Unknown due to rarity of disease.

ANALYSIS OF HOMOLOGOUS REGIONS

Alpha Thalassemia - Genes: HBA1, HBA2. **Variants (13):** -(alpha)20.5, --BRIT, --MEDI, --MEDII, --SEA, --THAI or --FIL, -alpha3.7, -alpha4.2, HBA1+HBA2 deletion, Hb Constant Spring, anti3.7, anti4.2, del HS-40. **Detection rate**: Southern European 90%.

COPY NUMBER ANALYSIS

Spinal Muscular Atrophy - Gene: SMN1. **Variant (1):** SMN1 copy number. **Detection rate**: Southern European 94%.

TARGETED GENOTYPING

Gaucher Disease - Gene: GBA. **Variants (10):** D448H, D448V, L483P, N409S, R463C, R502H, R535H, V433L, c.115+1G>A, c.84dupG. **Detection rate**: Southern European 60%.

Risk Calculations

Below are the risk calculations for all conditions tested. Since negative results do not completely rule out the possibility of being a carrier, the **residual risk** represents the patient's post-test likelihood of being a carrier and the **reproductive risk** represents the likelihood the patient's future children could inherit each disease. These risks are inherent to all carrier screening tests, may vary by ethnicity, are predicated on a negative family history and are present even after a negative test result. Inaccurate reporting of ethnicity may cause errors in risk calculation. The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group.

Disease	**DONOR 9925 Residual Risk**	**Reproductive Risk**
ABCC8-related Hyperinsulinism	< 1 in 110	< 1 in 50,000
Alpha Thalassemia	Not calculated	Not calculated
Bloom Syndrome	< 1 in 500	< 1 in 1,000,000
Canavan Disease	< 1 in 500	< 1 in 1,000,000
Cystic Fibrosis	< 1 in 300	< 1 in 33,000
Familial Dysautonomia	< 1 in 500	< 1 in 1,000,000
Fanconi Anemia Type C	< 1 in 340	< 1 in 220,000
Gaucher Disease	1 in 280	1 in 120,000
Glycogen Storage Disease Type Ia	< 1 in 450	< 1 in 320,000
Hb Beta Chain-Related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease)	< 1 in 1,300	< 1 in 500,000
Hexosaminidase A Deficiency (Including Tay-Sachs Disease)	< 1 in 390	< 1 in 470,000
Joubert Syndrome 2	< 1 in 500	< 1 in 1,000,000
Lipoamide Dehydrogenase Deficiency	< 1 in 500	< 1 in 1,000,000
Maple Syrup Urine Disease Type 1B	< 1 in 250	< 1 in 250,000
Mucolipidosis IV	< 1 in 500	< 1 in 1,000,000
NEB-related Nemaline Myopathy	< 1 in 500	< 1 in 1,000,000
Niemann-Pick Disease, SMPD1-associated	< 1 in 400	< 1 in 400,000
Spinal Muscular Atrophy	SMN1: 2 copies 1 in 890	1 in 200,000
Usher Syndrome Type 1F	< 1 in 190	< 1 in 150,000
Usher Syndrome Type 3	< 1 in 500	< 1 in 1,000,000
Walker-Warburg Syndrome	< 1 in 500	< 1 in 1,000,000