



Donor 4840

Genetic Testing Summary

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

Last Updated: 03/10/20

Donor Reported Ancestry: German, Irish, Norwegian, Scottish, Swedish 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 for 99 mutations in the CFTR gene	1/300
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/610
Hb Beta Chain Related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease)	Negative for 28 mutations in the HBB gene	1/290
Tay Sachs Enzyme Analysis	Non-carrier by Hexosaminidase A Activity	
Special Testing		
Argininemia (ARG1)	Negative by gene sequencing in the ARG1 gene	1/6500

*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.



Results Recipient



Report Date: 03/04/2014

Male

Name: DONOR 4840

DOB: [REDACTED]

Ethnicity: Northern European

Sample Type: OG-510 Saliva

Date of Collection: 02/28/2014

Date Received: 03/03/2014

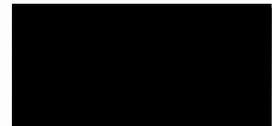
Barcode: [REDACTED]

Indication: Egg or Sperm Donor

Test Type: The Counsyl Test

Female

Not tested



Counsyl Test Results Summary (Egg or Sperm Donor)

The Counsyl test (Fairfax Cryobank Fundamental Panel) uses targeted genotyping and copy number analysis as described in the methods section on page 2 to determine carrier status associated with 3 diseases. Please refer to page 3 for a complete list of diseases and genes included in this panel.



DONOR 4840



DONOR 4840's DNA test shows that he is not a carrier of any disease-causing mutation tested.



Partner

The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group.

Reproductive Risk Summary

No increased reproductive risks to highlight. Please refer to the following pages for detailed information about the results.

Clinical Notes

- If necessary, patients can discuss residual risks with their physician or a genetic counselor. To schedule a complimentary appointment to speak with a genetic counselor about these results, please visit counsyl.com/counseling/.



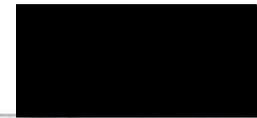
Male

Name: DONOR 4840

DOB: [REDACTED]

Female

Not tested



Methods and Limitations

DONOR 4840: The Counsyl Test - targeted genotyping and copy number analysis.

Targeted genotyping: Targeted DNA mutation analysis is used to simultaneously determine the genotype of 127 variants associated with 2 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 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.

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. The Counsyl test 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*).

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 workup. CLIA Number: #05D1102604.

Lab Directors:

H. Peter Kang

H. Peter Kang, MD, MS, FCAP

Jelena Brezo

Jelena Brezo, PhD, FACMG



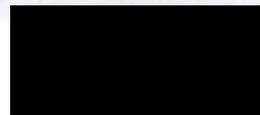
Male

Name: DONOR 4840

DOB: [REDACTED]

Female

Not tested



Diseases Tested

Cystic Fibrosis - Gene: CFTR. Variants (99): G85E, R117H, R334W, R347P, A455E, G542*, G551D, R553*, R560T, R1162*, W1282*, N1303K, c.1521_1523delCTT, c.1519_1521delATC, c.2052delA, c.3528delC, c.489+1G>T, c.579+1G>T, c.1585-1G>A, c.1766+1G>A, 2789+5G>A, c.2988+1G>A, 3849+10kbC>T, E60*, R75*, E92*, Y122*, G178R, R347H, Q493*, V520F, S549N, P574H, M1101K, D1152H, c.2012delT, c.262_263delTT, c.313delA, c.948delT, c.3744delA, c.3773dupT, c.1680-1G>A, 3272-26A>G, c.2051_2052delAAinsG, S549R, R117C, L206W, G330*, T338I, R352Q, S364P, G480C, C524*, S549R, Q552*, A559T, G622D, R709*, K710*, R764*, Q890*, R1066C, W1089*, Y1092X, R1158*, S1196*, W1204*, Q1238*, S1251N, S1255*, c.3067_3072del6, c.442delA, c.531delT, c.803delA, c.805_806delAT, c.1545_1546delTA, 1949del84, c.1911delG, c.1923_1931del9ins1, c.1976delA, c.3039delC, c.3536_3539delCCAA, c.3659delC, c.1155_1156dupTA, c.2052dupA, c.2175dupA, c.2738insG, 296+12T>C, c.273+1G>A, 405+3A>C, c.274-1G>A, 711+5G>A, c.580-1G>T, c.1766+1G>T, 1898+5G>T, Q996, c.325_327delTATinsG, 3849+4A>G, c.1075_1079del5ins5. **Detection rate:** Northern European 91%.

Hb Beta Chain-Related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease) - Gene: HBB. Variants (28): E7V, K18*, Q40*, c.126_129delCTTT, c.27dupG, IVS-II-654, IVS-II-745, c.315+1G>A, IVS-I-6, IVS-I-110, IVS-I-5, c.92+1G>A, -88C>T, -28A>G, -29A>G, c.25_26delAA, c.217dupA, c.316-2A>C, c.316-2A>G, G25, -87C>G, E7K, W16*, c.51delC, c.20delA, E27K, E122Q, E122K. **Detection rate:** Northern European 83%.

Spinal Muscular Atrophy (copy number analysis only) - Gene: SMN1. Variant (1): SMN1 copy number. **Detection rate:** Northern European 95%.



Male

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Female

Not tested



Risk Calculations

Below are the risk calculations for all diseases 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.

Disease	DONOR 4840 Residual Risk	Reproductive Risk
Cystic Fibrosis	1 in 300	1 in 33,000
Hb Beta Chain-Related Hemoglobinopathy (Including Beta Thalassemia and Sickle Cell Disease)	1 in 290	1 in 58,000
Spinal Muscular Atrophy	SMN1: 2 copies 1 in 610	1 in 84,000

Patient	Sample	Referring Doctor
Patient Name: Donor 4840 Date of Birth: [REDACTED] Reference #: [REDACTED] Indication: Carrier Testing Test Type: Custom Carrier Screen (ECS)	Specimen Type: Blood Lab #: [REDACTED] Date Collected: 2/4/2020 Date Received: 2/6/2020 Final Report: 3/4/2020	[REDACTED] Fairfax Cryobank, Inc. [REDACTED] [REDACTED] [REDACTED] [REDACTED]

RESULT SUMMARY

Custom Carrier Screen (ECS)

Negative: No clinically significant variant(s) detected

Gene(s) analyzed: *ARG1*

Recommendations:

Consideration of residual risk by ethnicity after a negative carrier screen is recommended, especially in the case of a positive family history for a specific disorder.

Interpretation:

Screening for the presence of pathogenic variants in the *ARG1* gene which is associated with Argininemia was performed by next generation sequencing and possibly genotyping for select variants on DNA extracted from this patient's sample. No clinically significant variants were detected during this analysis.

Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for the disorder(s) tested. Please see table of residual risks 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.

Comments:

This carrier screening test masks likely benign variants and variants of uncertain significance (VUS) if there are any. Only known pathogenic variants or likely pathogenic variants which are expected to result in deleterious effects on protein function are reported. If reporting of likely benign variants and VUS is desired in this patient, please contact the laboratory (tel. 212-241-2537) to request an amended report.

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.

Patient: Donor 4840

DOB: [REDACTED]

Lab #: [REDACTED]

Table of Residual Risks by Ethnicity

Please note: This table displays residual risks after a negative result for each of the genes and corresponding disorders. **If a patient is reported to be a carrier of a disease, their residual risk is 1 and this table does not apply for that disease.**

Disease (Inheritance)	Gene	Ethnicity	Carrier Frequency	Detection Rate	Residual Risk	Analytical Detection Rate
Argininemia (AR) NM_000045.3	ARG1	African	1 in 644	85%	1 in 4,240	95%
		Ashkenazi Jewish	1 in 614	95%	1 in 12,300	
		East Asian	1 in 1,754	39%	1 in 2,860	
		Caucasian	1 in 2,326	64%	1 in 6,500	
		Latino	1 in 369	66%	1 in 1,080	
		South Asian	1 in 5,130	63%	1 in 14,000	
		Worldwide	1 in 1,210	67%	1 in 3,660	

AR: Autosomal Recessive

This case has been reviewed and electronically signed by Rebekah Zimmerman, Ph.D., FACMG, Laboratory Director

Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

Patient: Donor 4840

DOB: [REDACTED]

Lab #: [REDACTED]

Test Methods and Comments

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

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.

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

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

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

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

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

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

Residual Risk Calculations

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

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

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

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including

Patient: Donor 4840

DOB: [REDACTED]

Lab #: [REDACTED]

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.

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.

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.