Donor 4260

Genetic Testing Summary

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

Last Updated: 05/13/21

Donor Reported Ancestry: Irish, Scottish   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 99 mutations in the CFTR gene	1/310
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/700
Hb Beta Chain-Related Hemoglobinopathy (including Beta Thalassemia and Sickle Cell Disease) by genotyping	Negative for 28 mutations tested in the HBB gene	1/1500 for Beta-Thalassemia <1/500 for Sickle Cell
Tay Sachs enzyme analysis	Non-carrier by Hexosaminidase A activity	
Special Testing		
Glycine Encephalopathy (GLDC -Related)	Negative by gene sequencing in the GLDC gene	1/760
Smith-Lemli-Opitz Syndrome (DHCR7)	Negative by gene sequencing in the DHCR7 gene	1/750

*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.

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Counsyl

Results F · ·bient

Fairfax Cryobank - ▮▮▮
Attn: Dr. Harvey Stern

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Report Date: 06/12/2012

Male

Name: DONOR 4260
DOB ▮▮▮▮
Ethnicity: Northern European
Sample Type: OG-510 Saliva
Date of Collection: 06/06/2012
Date Received: 06/08/2012
Barcode: ▮▮▮▮
Indication: Egg or Sperm Donor

Female

Not tested

Counsyl Test Results (Egg or Sperm Donor)

The Counsyl test (**Fairfax Cryobank Fundamental Panel**) uses targeted DNA mutation analysis to simultaneously determine the carrier status of an individual for **128 variants** associated with **4 diseases**. This report indicates which mutations, if any, were detected for each mutation panel. Because only select mutations are tested, the percentage of carriers detected varies by ethnicity. A full list of mutations tested is given on page 2. A negative test result does not eliminate the possibility that the individual is a carrier. Interpretation is given as an estimate of the risk of conceiving a child affected with a disease, which is based on reported ethnicity, the test results, and an assumption of no family history.•

DONOR 4260

DONOR 4260'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.
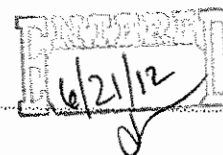
Clinical notes:

- Individuals of African, Southeast Asian, and Mediterranean ancestry are at increased risk for being carriers for hemoglobinopathies and may also benefit from carrier testing by CBC and hemoglobin electrophoresis or HPLC. *ACOG Practice Bulletin No. 78. Obstet Gynecol 2007;109:229-37.*

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

Lab Directors:

Jessica Jacobson   *William K. Seltzer*   6/21/12

Jessica Jacobson, MD   William Seltzer, PhD, FACMG

Counsyl

Mutations Tested

Beta Thalassemia - Gene: HBB. **Variants (27):** K17X, Q39X, Phe41fs, Ser9fs, IVS-II-654, IVS-II-745, IVS-II-850, IVS-I-6, IVS-I-110, IVS-I-5, IVS-I-1(G>A), -88C>T, -28A>G, -29A>G, Lys8fs, Phe71fs, IVS-II-849(A>C), IVS-II-849(A>G), Gly24 T>A, -87C>G, Hb C, W15X, Gly16fs, Glu6fs, Hb E, Hb D-Punjab, Hb O-Arab. **Detection rate:** Northern European 83%.

Cystic Fibrosis - Gene: CFTR. **Variants (99):** G85E, R117H, R334W, R347P, A455E, G542X, G551D, R553X, R560T, R1162X, W1282X, N1303K, F508del, I507del, 2184delA, 3659delC, 621+1G>T, 711+1G>T, 1717-1G>A, 1898+1G>A, 2789+5G>A, 3120+1G>A, 3849+10kbC>T, E60X, R75X, E92X, Y122X, G178R, R347H, Q493X, V520F, S549N, P574H, M1101K, D1152H, 2143delT, 394delTT, 444delA, 1078delT, 3876delA, 3905insT, 1812-1G>A, 3272-26A>G, 2183AA>G, S549R(A>C), R117C, L206W, G330X, T338I, R352Q, S364P, G480C, C524X, S549R(T>G), Q552X, A559T, G622D, R709X, K710X, R764X, Q890X, R1066C, W1089X, Y1092X, R1158X, S1196X, W1204X(c.3611G>A), Q1238X, S1251N, S1255X, 3199del6, 574delA, 663delT, 935delA, 936delTA, 1677delTA, 1949del84, 2043delG, 2055del9>A, 2108delA, 3171delC, 3667del4, 3791delC, 1288insTA, 2184insA, 2307insA, 2869insG, 296+12T>C, 405+1G>A, 405+3A>C, 406-1G>A, 711+5G>A, 712-1G>T, 1898+1G>T, 1898+5G>T, 3120G>A, 457TAT>G, 3849+4A>G, Q359K/T360K. **Detection rate:** Northern European 91%.

Sickle Cell Disease - Gene: HBB. **Variants (28):** Hb S, K17X, Q39X, Phe41fs, Ser9fs, IVS-II-654, IVS-II-745, IVS-II-850, IVS-I-6, IVS-I-110, IVS-I-5, IVS-I-1(G>A), -88C>T, -28A>G, -29A>G, Lys8fs, Phe71fs, IVS-II-849(A>C), IVS-II-849(A>G), Gly24 T>A, -87C>G, Hb C, W15X, Gly16fs, Glu6fs, Hb E, Hb D-Punjab, Hb O-Arab. **Detection rate:** Northern European 70%.

Spinal Muscular Atrophy - Gene: SMN1. **Variants (1):** Exon 7 deletion. **Detection rate:** Northern European 95%.

Risk Calculations

Below are the full test results for all diseases on the panel. Listed in this section is the patient's post-test risk of being a carrier of each disease as well as the odds that his future children could inherit each disease. A negative result does not rule out the possibility of being a carrier of untested mutations. Estimates of post-test carrier risk assume a negative family history.

Disease	Donor 4260 Residual Risk	Post-test Reproductive Risk	Pre-test Reproductive Risk
Beta Thalassemia	1 in 1,500	< 1 in 1,000,000	1 in 250,000
Cystic Fibrosis	1 in 310	1 in 34,000	1 in 3,000
Sickle Cell Disease	< 1 in 500	< 1 in 1,000,000	< 1 in 1,000,000
Spinal Muscular Atrophy	1 in 700	1 in 97,000	1 in 4,800

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Version: 1.7.89

Patient Information

Name: Donor 4260

Date of Birth:

Sema4 ID:

Client ID:

Indication: Carrier Testing

Specimen Information

Specimen Type: Purified DNA

Date Collected: 02/12/2021

Date Received: 02/23/2021

Final Report: 03/09/2021

Referring Provider

Fairfax Cryobank, Inc.

Custom Carrier Screen (ECS)

Number of genes tested: 2

SUMMARY OF RESULTS AND RECOMMENDATIONS

> ⊖ **Negative**
>
> **Negative for all genes tested:** *DHCR7, and GLDC*
> 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. Please note that residual risks for X-linked diseases (including full repeat expansions for Fragile X syndrome) may not be accurate for males and the actual residual risk is likely to be lower.

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

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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**				
Glycine Encephalopathy (*GLDC*-Related)	*GLDC*	AR	Reduced Risk (see table below)	
Smith-Lemli-Opitz Syndrome	*DHCR7*	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
Glycine Encephalopathy (GLDC -Related) (AR)	*GLDC*	African	1 in 515	49%	1 in 1,000	95%
NM_000170.2		East Asian	1 in 137	42%	1 in 240	
		Finnish	1 in 112	85%	1 in 740	
		European (Non-Finnish)	1 in 255	66%	1 in 760	
		Native American	1 in 323	51%	1 in 660	
		South Asian	1 in 570	56%	1 in 1,300	
Exception: Exon 1		Worldwide	1 in 246	64%	1 in 690	
Smith-Lemli-Opitz Syndrome (AR)	*DHCR7*	African	1 in 51	98%	1 in 2,400	99%
NM_001360.2		Ashkenazi Jewish	1 in 39	97%	1 in 1,100	
		East Asian	1 in 357	91%	1 in 3,800	
		Finnish	1 in 141	94%	1 in 2,500	
		European (Non-Finnish)	1 in 46	94%	1 in 750	
		Native American	1 in 118	93%	1 in 1,800	
		South Asian	1 in 334	71%	1 in 1,200	
		Worldwide	1 in 57	94%	1 in 970	

* 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 *BTD, F9, 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 likelypathogenic 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 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 theIllumina 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

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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.

SELECTED REFERENCES

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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: 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.

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