Fairfax Cryobank
The Trusted Choice for Donor Sperm

Donor 4817

Genetic Testing Summary

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

Last Updated: 05/08/20

Donor Reported Ancestry: German, French 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	1/300
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 by genotyping in the HBB gene	1/290
Special Testing		
Usher Syndrome, Type 2 A	Negative by gene sequencing in the USH2A gene	1/314
Isovaleric Acidemia (IVD)	Negative by gene sequencing in the IVD gene	1/462

*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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CARRIER SCREENING REPORT

Patient	Sample	Referring Doctor
Patient Name: Donor 4817 **Date of Birth:** [redacted] **Reference #:** [redacted] **Indication:** [redacted] **Test Type:** NGS single gene full sequencing test	**Specimen Type:** Semen **Lab #:** [redacted] **Date Collected:** 2/14/2018 **Date Received:** 2/24/2018 **Final Report:** 3/6/2018	[redacted] **Fairfax Cryobank, Inc.** [redacted] [redacted] [redacted] Fax: [redacted]

RESULT SUMMARY

NGS single gene full sequencing test

Results: No clinically significant variant(s) detected

Gene(s) analyzed: *USH2A*

Interpretation: Screening for the presence of pathogenic variants in the *USH2A* gene which is associated with Usher syndrome, type IIA 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. This negative result does not rule out the possibility that a pathogenic variant in the gene examined is present.

Genetic counseling is recommended.

This technology may not detect all small insertion/deletions and is not diagnostic for large duplications/deletions and structural genomic variation. The coding DNA sequence of the gene plus at least five base pairs flanking splice sites were sequenced and analyzed relative to the hg19 assembly. A mutation(s) deep in intronic sequences or in untranslated regions of the gene except a portion described above or a pathogenic variant(s) in other genes not included in this test could be present in this patient. The analytical sensitivity of this test is estimated at 99% for single base substitutions and 97% overall. All potentially pathogenic variants were subjected to Sanger sequencing or genotyping by allele specific primer extension analysis for confirmation of the result. Any benign variants identified during this analysis were not reported.

Please note that 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.

Comments: This test was developed and its performance characteristics were determined by Mount Sinai Genomics, Inc. It is considered acceptable for patient testing. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary.

Patient:	Donor 4817	DOB:	[redacted]	[redacted]#:	[redacted]

This type of mutation analysis generally provides highly accurate genotype information for point mutations and single nucleotide polymorphisms. Despite this level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, mosaicism or other rare genetic variants that interfere with analysis. In addition, families should understand the limitations of the testing and that rare diagnostic errors may occur for the reasons described.

For Disease Specific Standards and Guidelines:
https://www.acmg.net/
Additional disease-specific references available upon request.

This case has been reviewed and electronically signed by Guiqing Cai, Ph.D., DABMGG, Associate Laboratory Director

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

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
Usher Syndrome, Type IIA (AR)	*USH2A*	Caucasian	1 in 73	77%	1 in 314	88%
NM_206933.2		Worldwide	1 in 126	69%	1 in 404	>95%
		Sephardic Jewish – Iraqi and Iranian	1 in 36	71%	1 in 122	75%

AR: Autosomal Recessive

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CARRIER SCREENING REPORT

Patient	Sample	Referring Doctor
Patient Name: Donor 4817 **Date of Birth:** [redacted] **Reference #:** [redacted] **Indication:** Carrier Testing **Test Type:** Unmask Additional Gene(s)	**Specimen Type:** Blood **Lab #:** [redacted] **Date Received:** 3/30/2020 **Final Report:** 4/14/2020	[redacted] **Fairfax Cryobank, Inc.** [redacted]

RESULT SUMMARY

Negative: No clinically significant variant(s) detected

Gene(s) analyzed: *IVD*

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 *IVD* gene which is associated with isovaleric acidemia 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.

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

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

Patient:	Donor 4817	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
Isovaleric Acidemia (AR)	*IVD*	Caucasian	1 in 144	69%	1 in 462	>95%
NM_002225.3		Asian	1 in 75	55%	1 in 165	>95%
		Worldwide	1 in 158	68%	1 in 492	>95%

AR: Autosomal Recessive

Test Methods and Comments

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

Genotyping
Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY® System or Luminex® xMAP® technology were used to identify variants that are complex in nature or are present in low copy repeat regions and are, therefore, not amenable to Next Generation Sequencing technologies. Rare sequence variants may interfere with assay performance.

Next Generation Sequencing (NGS)
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 custom capture library to target the guaranteed list of mutations and exonic regions of the relevant genes. These targeted regions were sequenced using the Illumina HiSeq2500 system with 100 bp paired-end reads. The DNA sequences were mapped to and analyzed in comparison with the published human genome build UCSC hg19 reference sequence. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage and data quality threshold values. This technology may not detect all small insertion/deletions and is not diagnostic for large duplications/deletions, repeat expansions, and structural genomic variation. This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions will either not be detected or are not guaranteed to be detected. These regions include, but are not limited to, UTRs, promoters, and deep intronic areas or regions that fall within low copy repeat segments. In addition, a mutation(s) in a gene not included on the panel could be present in this patient. 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 were not reported.

Sanger Sequencing
Sanger sequencing, as indicated, was performed in both directions 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.

Patient:	Donor 4817	DOB:	[redacted]	Lab #:	[redacted]

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SELECTED REFERENCES

Carrier Screening

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

Umbarger MA. Next-generation carrier screening. *Genet Med*. 2014 16:132-40.

Alpha-thalassemia:

Galanello R et al. Gene test review: Alpha-thalassemia. *Genet Med*. 2011 13:83-8.

Waye JS et al. Diagnostic testing for α-globin gene disorders in a heterogeneous North American population. *Int J Lab Hematol*. 2013 35:306-13.

Cystic Fibrosis:

ACOG Committee Opinion. Number 325, Update on carrier screening for cystic fibrosis. 2005.

Fragile X syndrome:

Ashkenazi Jewish Disorders:

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

Duchenne Muscular Dystrophy:

Aartsma-Rus A et al. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve*. 2006b 34:135-44.

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.

Beta Globin-related Disorders:

Cao A et al. Beta-Thalassemia. GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1426/)

Modell B et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest. 2007 67:39-69.

For further reading:

Orphanet: http://www.orpha.net/consor/cgi-bin/index.php

GeneReviews: <http://www.ncbi.nlm.nih.gov/books/NBK1116/>

For Disease Specific Standards and Guidelines:

https://www.acmg.net/

Additional disease-specific references available upon request.