Fairfax Cryobank
The Trusted Choice for Donor Sperm

Donor 4386

Genetic Testing Summary

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

Last Updated: 02/15/19

Donor Reported Ancestry: Dutch, Welsh Jewish Ancestry: Yes

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) by genotyping	Negative for 28 mutations tested in the HBB gene	1/290
ABCC8-related Hyperinsulinism	Negative for 3 mutations tested in the ABCC8 gene	1/670
Bloom Syndrome	Negative for 1 mutation tested in the BLM gene	1/11,000
Canavan Disease	Negative for 4 mutations tested in the ASPA gene	1/2700

Familial Dysautonomia	Negative for 2 mutations tested in the IKBKAP gene	1/6,100
Fanconi Anemia Type C	Negative for 3 mutations tested in the FANCC gene	1/8,900
Gaucher Disease	Negative for 10 mutations tested in the GBA gene	1/310
Glycogen Storage Disease 1 A	Negative for 7 mutations tested in the G6PC gene	1/7,000
Hexosaminidase A Deficiency (including Tay Sachs Disease)	Negative for 9 mutations tested in the HEXA gene	1/370
Lipoamide Dehydrogenase Deficiency	Negative for 2 mutations tested in the DLD gene	1/93,000
Maple Syrup Urine Disease Type 1 B	Negative for 3 mutations tested in the BCKDHB gene	1/9,600
Mucolipidosis IV	Negative for 2 mutations tested in the MCOLN1 gene	1/2700
Neimann-Pick Disease, SMPD1-associated	Negative for 4 mutations tested in the SMPD1 gene	1/3,300
Usher Syndrome Type 1 F	Negative for 1 mutation tested in the PCDH15 gene	1/400
Usher Syndrome Type 3	Negative for 1 mutation tested in the CLRN1 gene	1/6,000
Tay Sachs enzyme analysis	Non-carrier by Hexosaminidase A activity	
Special Testing		
Retinitis Pigementosa Type 25	Negative by gene sequencing in the EYS gene	1/161
Cartilage-Hair Hypoplasia	Negative by gene sequencing in the RMRP gene	1/999

Ethylmalonic Aciduria	Negative by gene sequencing in the ETHE1 gene	1/1783
Mucopolysaccharidosis, Type 1 (IDUA, Type II (IDS), Type IIIA (SGSH), Type IIIB (NAGLU), Type IIIC (HGSNAT), Type IIID (GNS), Type IVb/GM1 Gangliosidosis (GLB1), Type VI (ARSB) and Type IX (HYAL1)	Negative by gene sequencing	See attached report for individual gene residual risks

*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: 4386 Donor **Date of Birth:** [redacted] **Reference #:** P0209249 **Indication:** Carrier Testing **Test Type:** Unmask Additional Gene(s)	**Specimen Type:** Blood **Lab #:** [redacted] **Date Collected:** 3/22/2016 **Date Received:** 5/4/2018 **Final Report:** 5/21/2018	**Harvey Stern, M.D.** **Fairfax Cryobank, Inc.** **2015 Williams Drive** **Suite 110** **Fairfax, VA 22031** Fax: **703-698-3933**

RESULT SUMMARY

Results: No clinically significant variant(s) detected

Gene(s) analyzed: *ETHE1* and *RMRP*

Interpretation: Screening for the presence of pathogenic variants in the *ETHE1* and *RMRP* genes, which are associated with ethylmalonic encephalopathy and cartilage-hair hypoplasia, respectively, 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 genes 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.

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.

Patient:	4386 Donor	DOB:	[redacted]	Lab #:	[redacted]

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 Ruth Kornreich, Ph.D., FACMG, Co-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
Cartilage-Hair Hypoplasia (AR) NR_003051.3	*RMRP*	Worldwide	< 1 in 500	50%	1 in 999	>95%
		Amish	1 in 19	>95%	1 in 361	>95%
		Finnish	1 in 76	>95%	1 in 1501	>95%
Ethylmalonic Encephalopathy (AR) NM_014297.3	*ETHE1*	Worldwide	< 1 in 500	72%	1 in 1783	94%

AR: Autosomal Recessive

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CARRIER SCREENING REPORT

Patient	Sample	Referring Doctor
Patient Name: Donor 4386 **Date of Birth:** [redacted] **Reference #:** P0209249 **Indication:** Carrier Testing **Test Type:** Unmask Additional Gene(s)	**Specimen Type:** Blood **Lab #:** [redacted] **Date Collected:** 3/22/2016 **Date Received:** 1/4/2019 **Final Report:** 1/18/2019	[redacted] **Fairfax Cryobank, Inc.** [redacted] [redacted] [redacted] Fax: [redacted]

RESULT SUMMARY

Negative: No clinically significant variant(s) detected

Gene(s) analyzed: *IDS, SGSH, NAGLU, HGSNAT, GNS, GLB1, HYAL1, ARSB,* and *IDUA*

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 *IDS, SGSH, NAGLU, HGSNAT, GNS, GLB1, HYAL1, ARSB,* and *IDUA* genes which are associated with mucopolysaccharidosis type II, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type IIIB, mucopolysaccharidosis type IIIC, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IVb / GM1 gangliosidosis, mucopolysaccharidosis type IX, mucopolysaccharidosis type VI, and mucopolysaccharidosis type I, respectively, 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 4386	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
Mucopolysaccharidosis, Type I (AR) NM_000203.4	*IDUA*	Worldwide	1 in 144	72%	1 in 512	>95%
Mucopolysaccharidosis, Type II (XL) NM_000202.6 *Exception:* Exon 3	*IDS*	Worldwide	< 1 in 500	67%	1 in 1513	86%
Mucopolysaccharidosis, Type IIIA (AR) NM_000199.3	*SGSH*	Caucasian Worldwide	1 in 253 1 in 415	68% 56%	1 in 789 1 in 942	95% >95%
Mucopolysaccharidosis, Type IIIB (AR) NM_000263.3	*NAGLU*	Caucasian Asian Worldwide	1 in 346 1 in 298 < 1 in 500	59% 70% 64%	1 in 842 1 in 991 1 in 1387	80% >95% >95%
Mucopolysaccharidosis, Type IIIC (AR) NM_152419.2	*HGSNAT*	Caucasian Asian Worldwide	1 in 259 < 1 in 500 1 in 482	81% >95% 77%	1 in 1359 1 in 9981 1 in 2092	93% >95% >95%
Mucopolysaccharidosis, Type IIID (AR) NM_002076.3	*GNS*	Worldwide	< 1 in 500	90%	1 in 4991	90%
Mucopolysaccharidosis, Type IVb / GM1 Gangliosidosis (AR) NM_000404.2	*GLB1*	Caucasian Worldwide Roma South Brazilian	1 in 278 1 in 158 1 in 50 1 in 58	57% 69% >95% >95%	1 in 645 1 in 507 1 in 981 1 in 1141	>95% >95% >95% >95%
Mucopolysaccharidosis, Type VI (AR) NM_000046.3	*ARSB*	Caucasian Asian Worldwide	1 in 273 1 in 423 1 in 291	67% 53% 54%	1 in 825 1 in 899 1 in 631	>95% >95% >95%
Mucopolysaccharidosis, Type IX (AR) NM_153281.1	*HYAL1*	Worldwide	< 1 in 500	>95%	1 in 9981	>95%

AR: Autosomal Recessive
XL: X-Linked

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 4386	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:

Fragile X CGG Repeat Analysis
PCR amplification using Asuragen, Inc. AmplideX® *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 are further analyzed by Southern blot analysis to assess the size and methylation status of the *FMR1* CGG repeat.

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.

Multiplex Ligation-Dependent Probe Amplification (MLPA)
MLPA® probe sets and reagents, MRC-Holland, were used for the analysis of copy number of specific targets versus known control samples. Each target region was assayed with two adjacent oligonucleotide probes which following hybridization were ligated and used as template for subsequent rounds of amplification. Each complete probe within the assay has a unique length and amplicons are separated and identified by capillary electrophoresis. False positive or negative results may also 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. However, it does not detect all known alpha-thalassemia mutations such as point mutations. In addition, carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, will not be detected. This test detects most alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation using Multiplex Ligation-Dependent Probe Amplification (MLPA). It is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Therefore, this result reduces, but does not eliminate, the chance that this patient is a carrier of alpha-thalassemia. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported.

For Duchenne Muscular Dystrophy, the copy numbers of all *DMD* exons were analyzed. Please note that single-exon deletions and duplications will not be reported unless they are confirmed by NGS data (for example, if breakpoints occurring in an exon can be visualized).

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 2+0 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.

Patient:	Donor 4386	DOB:	[redacted]	Lab #:	[redacted]

The presence of the g.27134T>G variant allele in an individual with Ashkenazi Jewish or Asian ancestry is indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, g.27134T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of g.27134T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

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.

Tay-Sachs Disease (TSD) Enzyme Analysis
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. 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, such as pseudodeficiency alleles, may occur if benign variants interfere with the enzymatic assay. False negative results may occur if both *HEXA* and *HEXB* pathogenic 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.

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

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

Alpha-thalassemia:

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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:

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.

Spinal Muscular Atrophy:

Hendrickson BC et al. Differences in SMN1 allele frequencies among ethnic groups within North America. *J Med Genet*. 2009 46:641-4.

Ogino S et al. Genetic risk assessment in carrier testing for spinal muscular atrophy. *Am J Med Genet*. 2002 110:301-7.

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.

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.