Donor 6639-PRS

Genetic Testing Summary

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

Last Updated: 06/27/23

Donor Reported Ancestry: Norwegian 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 97 mutations- in the CFTR gene	1/343
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/632
Fragile X, PCR DNA Analysis	Normal Male	
Special Testing		
Autosomal Recessive ACSF3-related conditions (ACSF3) performed in March 2023	Carrier: Autosomal Recessive ACSF3-related conditions (ACSF3)	Partner testing is recommended before using this donor
Genes: CEP290, GAA	Negative by gene sequencing	

*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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[redacted]

Patient Information:
6639 PRS, Donor
DOB: [redacted]
Sex: M
MR#: 6639 PRS
Patient#: [redacted]

Accession:
[redacted]
Test#: [redacted]
Order# [redacted]
Ext Test#: [redacted]
Ext Order#: [redacted]
Specimen Type: DNA
Collected: Jan 30,2023
Received Date: Feb 14,2023
Authorized Date: Feb 18,2023

Physician:
Seitz, Suzanne
ATTN: Seitz, Suzanne
Fairfax Cryobank
3015 Williams Drive
Fairfax, VA 22031
Phone:
Fax:

Laboratory:
Fulgent Genetics
CAP#: 8042697
CLIA#: 05D2043189
Laboratory Director:
Dr. Hanlin (Harry) Gao
Report Date: **Mar 02,2023**

Final Report

TEST PERFORMED

ACSF3 Single Gene
(1 Gene Panel: *ACSF3*; gene sequencing with deletion and duplication analysis)

RESULTS:

No clinically significant sequence or copy-number variants were identified which are sufficient for a molecular diagnosis.
However, one variant of potential clinical relevance is reported.

Clinically significant Variants

None

Additional Variants of Potential Clinical Relevance

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
ACSF3 NM_174917.5	Autosomal Recessive	c.1672C>T p.Arg558Trp	Heterozygous	**Likely Pathogenic (carrier)**

INTERPRETATION:

Notes and Recommendations:

- As requested, this report only includes variants classified as Pathogenic, Likely Pathogenic, or Risk Allele at the time of analysis. If detected, this report does not include variants classified as of uncertain significance.
- Gene specific notes and limitations may be present. See below.
- These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; https://www.nsgc.org)
- Guide to Interpreting Genomic Reports: A Genomics Toolkit (CSER Consortium; February 2017) (https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources#hep)

About *ACSF3*

Biallelic mutations in ACSF3 have been reported in patients with combined malonic and methylmalonic aciduria (CMAMMA; OMIM: 614265; PubMed: 21841779, 21785126).

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The gene product of the *ACSF3* gene is a protein called Acyl-CoA synthetase family member 3. See OMIM gene entry for*ACSF3* (OMIM: 614245) for further information.

100% of the coding sequence of the NM_174917.5 transcript of*ACSF3* gene was sequenced to a minimum depth of 20x in the submitted specimen. A second sequencing mutation was not detected in this gene, nor were copy number variants observed, however, the presence of mutations in the deep intronic or regulatory regions cannot be ruled out. As the clinical condition(s) associated with mutations in the *ACSF3* gene are recessive and only a single heterozygous variant has been detected, this result is interpreted as carrier status only. Further clinical evaluation may be warranted to clarify these findings.

ACSF3 NM_174917.5:c.1672C>T (p.Arg558Trp)

Classification: **Likely Pathogenic**

Zygosity and Inheritance	• This heterozygous Likely Pathogenic variant is consistent with this individual being a carrier for an autosomal recessive ACSF3-related condition.
Variant Type	• Genomic change: Chr16(GRCh37):g.89220556C>T. • This variant is in the dbSNP database: rs141090143 • This variant is predicted to result in a single amino acid substitution (missense) of **Arg** to **Trp** at codon 558 in exon 11 of the *ACSF3* gene.
Variant in Cases	• This variant has been reported in the homozygous and compound heterozygous state in multiple individuals with either combined malonic and methylmalonic aciduria and/ or elevated MMA on a newborn screening panel which depending on the response to intervention can result in a range of phenotypes from generally good health, to febrile seizures and mild developmental delay (PubMed: 21841779, 26827111, 33879512, 34440436). • This variant is classified as a "Disease Mutation" (DM) in the Human Gene Mutation Database (HGMD). • This variant has one or more entries in ClinVar: RCV000024130.10, RCV000185751.6
Variant in Controls	• This variant has been observed at a frequency of 0.26% (724/279804 alleles). • The highest allele frequency that this variant has been observed at in any sub-population with available data is 0.48% in the European (Non-Finnish) population. • There is one homozygous control individual for this variant. • The Broad Institute gnomAD database (>120,000 Individuals with no known severe, pediatric onset disease) was used for this analysis.

Other Variant Information	• This variant is classified as "Pathogenic" or "Likely Pathogenic" in ClinVar, with multiple submitters in agreement (ClinVar: 31134).
	• Analysis of amino acid conservation indicates that the wild-type amino acid Arg is completely conserved across vertebrate species, suggesting that a change at this position may not be tolerated and could adversely affect the structure and/or function of the protein.
	• Amino acid conservation data:
	  ◦ Primates: 9 out of 9 match the wild type.
	  ◦ Mammals: 52 out of 52 match the wild type.
	  ◦ Vertebrates: 80 out of 80 match the wild type.
	• The physiochemical difference between Arg and Trp as measured by Grantham's Distance is 101. This score is considered a "moderate" change. (PubMed: 4843792, 6442359).
	• Computational predictions for p.Arg558Trp (1P/1B SIFT/AGVGD) (REVEL = 0.503) (gnomAD: Z = -1.3005 [Exp: 356.87, Obs: 426]) (granthamDist = 101).

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[redacted]

GENES TESTED:

ACSF3 Single Gene
1 genes tested (100.00% at >20x).

ACSF3

Gene Specific Notes and Limitations

No gene specific limitations apply to the genes on the tested panel.

METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 100.00% and 100.00% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications identified by NGS are confirmed by an orthogonal method (qPCR or MLPA), unless exceeding an internally specified and validated quality score, beyond which deletions and duplications are considered real without further confirmation. New York patients: diagnostic findings are confirmed by Sanger, MLPA, or qPCR; exception SNV variants in genes for which confirmation of NGS results has been performed >=10 times may not be confirmed if identified with high quality by NGS. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

LIMITATIONS:

These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or otherwise, to this individual's phenotype, and negative results do not rule out a genetic cause for the indication for testing. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (https://www.genenames.org) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is designed and validated for detection of germline variants only. It is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions (eg. trinucleotide or hexanucleotide repeat expansion). DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations of genomic regions which are two or more contiguous exons in size; single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the

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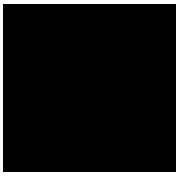

effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

SIGNATURE:

Yan Meng, Ph.D., CGMB, FACMG on **3/2/2023 07:19 PM PST**
Electronically signed

DISCLAIMER:

This test was developed and its performance characteristics determined by**Fulgent Genetics**. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at **(626) 350-0537** or **info@fulgentgenetics.com**. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.

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[redacted]

Patient Information:
6639 PRS, Donor
DOB: [redacted]
Sex: M
MR#: 6639 PRS
Patient#: [redacted]

Partner Information:
Not Tested

Physician:
Seitz, Suzanne
ATTN: Seitz, Suzanne
Fairfax Cryobank
3015 Williams Drive
Fairfax, VA 22031

Laboratory:
Fulgent Genetics
CAP#: 8042697
CLIA#: 05D2043189
Laboratory Director:
Dr. Hanlin (Harry) Gao
Report Date: **May 16,2023**

Accession:
[redacted]
Test#: [redacted]
Specimen Type: DNA
Collected: Jan 30,2023

Accession:
N/A

FINAL RESULTS

No carrier mutations identified

TEST PERFORMED

Custom Beacon Carrier Screening Panel

(2 Gene Panel: *CEP290 and GAA*; gene sequencing with deletion and duplication analysis)

INTERPRETATION:

Notes and Recommendations:

- No carrier mutations were identified in the submitted specimen. A negative result does not rule out the possibility of a genetic predisposition nor does it rule out any pathogenic mutations in areas not assessed by this test or in regions that were covered at a level too low to reliably assess. Also, it does not rule out mutations that are of the sort not queried by this test; see Methods and Limitations for more information.
- This carrier screening test does not screen for all possible genetic conditions, nor for all possible mutations in every gene tested. Individuals with negative test results may still have up to a 3-4% risk to have a child with a birth defect due to genetic and/or environmental factors.
- Patients may wish to discuss any carrier results with blood relatives, as there is an increased chance that they are also carriers. These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- X-linked genes are not routinely analyzed for male carrier screening tests. Gene specific notes and limitations may be present. See below.
- This report does not include variants of uncertain significance.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; https://www.nsgc.org)

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GENES TESTED:

Custom Beacon Carrier Screening Panel - 2 Genes

This analysis was run using the Custom Beacon Carrier Screening Panel gene list. 2 genes were tested with 100.0% of targets sequenced at >20x coverage. For more gene specific information and assistance with residual risk calculation, see the SUPPLEMENTAL TABLE.

CEP290, GAA

METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 100.00% and 100.00% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications are analyzed using Fulgent Germline proprietary pipeline for this specimen. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

LIMITATIONS:

General Limitations

These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or otherwise, to future pregnancies, and negative results do not rule out the genetic risk to a pregnancy. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (https://www.genenames.org) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions other than specified genes. DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution

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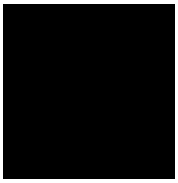

of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations of genomic regions which include one whole gene (buccal swab specimens and whole blood specimens) and are two or more contiguous exons in size (whole blood specimens only); single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

Gene Specific Notes and Limitations

No gene specific limitations apply to the genes on the tested panel.

SIGNATURE:

Yan Meng, Ph.D., CGMB, FACMG on **5/16/2023 9:40 AM PDT**
Electronically signed

DISCLAIMER:

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Supplemental Table

Gene	Condition	Inheritance	Ethnicity	Carrier Rate	Detection Rate	Post-test Carrier Probability*	Residual Risk*
CEP290	Meckel syndrome 4	AR	General Population	1 in 190	98%	1 in 9,451	1 in 7,182,760
CEP290	Leber congenital amaurosis 10	AR	General Population	1 in 190	98%	1 in 9,451	1 in 7,182,760
CEP290	CEP290-related disorders	AR	General Population	1 in 190	98%	1 in 9,451	1 in 7,182,760
CEP290	Senior-Løken syndrome 6	AR	General Population	1 in 190	98%	1 in 9,451	1 in 7,182,760
CEP290	Joubert syndrome 5	AR	General Population	1 in 190	98%	1 in 9,451	1 in 7,182,760
CEP290	Bardet-Biedl syndrome 14	AR	General Population	1 in 190	98%	1 in 9,451	1 in 7,182,760
GAA	Pompe disease	AR	General Population	1 in 100	98%	1 in 4,951	1 in 1,980,400
			African/African American Population	1 in 60	98%	1 in 2,951	1 in 708,240
			East Asian Population	1 in 112	98%	1 in 5,551	1 in 2,486,848
			Ashkenazi Jewish Population	1 in 76	99%	1 in 7,501	1 in 2,280,304

* For genes that have tested negative

Abbreviations: AR, autosomal recessive; XL, X-linked