Genesys Diagnostics, Inc.
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CLIA #07D2046796

Patient Information

Name Test Patient
Gender Female
Date of Birth 05/01/2000
Lab Number NA00248

Provider Information

Ordering Physician Dr. Test Doctor
Referring Facility Example Facility

Sample Information

Collection Date 05/01/2022 **Sample Type** Buccal Swab
Receipt Date 05/02/2022 **Report Date** 06/01/2022
Indication Encounter for Screening of Normal First Pregnancy, First Trimester.
Test(s) Performed: Comprehensive Carrier Panel

Result Summary

Positive: Individual is a carrier of classic homocystinuria

Interpretation:

Pathogenic mutation for classic homocystinuria were detected by the Genesys Diagnostics Carrier Panel. This disorder has an autosomal recessive mode of inheritance.

Result Details

Gene	Disease	Mode of Inheritance	Result
FMR1	Fragile X Syndrome	X-Linked Recessive	Normal
SMN1	Spinal Muscular Atrophy	Autosomal Recessive	Normal
DMD	Duchenne or Becker Muscular Dystrophy	X-Linked Recessive	Normal
HBA Gene Cluster	Hemoglobin Bart hydrops fetalis syndrome or Hemoglobin disorders	Autosomal Recessive	Normal

Interpretation:

28 / 29 CGG Repeats within FMR1 were noted for this individual.
2 Copies of SMN1 were noted for this individual. The SMN1 silent carrier risk factor SNPs g.27134T>G and g.27706-27707delAT were not detected.
No deletions or duplications of DMD were noted for this individual.
No deletions or duplications of the HBA gene cluster were noted for this individual.

Sequencing Details

Sequencing Positive: Mutation(s) with an established pathogenic link have been detected.

Primary Findings

One pathogenic variant in CBS was identified in this individual. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

Gene	Location	Variant	Zygosity	Classification	Disease or Disorder	Mode of Inheritance
CBS	21:44483185	p.Ile278Thrfs*16	Homozygous	Pathogenic	Classic homocystinuria	Autosomal Recessive

Information

Homocystinuria due to cystathionine beta-synthase deficiency is caused by a mutation in the CBS gene, which is involved in the transsulfuration pathway that functions to create proteins. Homocystinuria exhibits an autosomal recessive inheritance pattern and affects between 1 in 100,000 and 1 in 344,000 individuals annually (Moorthie, Cameron, Sagoo, Bonham & Burton, 2014; Mudd, Levy & Skovby, 2001; Skovby, Gaustadnes & Mudd, 2010). Onset of symptoms occurs in early childhood at an average of 4 years old for non-responsive variations, and information available indicates that responsive variations have milder symptoms. Symptoms of non-responsive homocystinuria include developmental delay/mental retardation, osteoporosis, lens dislocation and thromboembolism (Poloni et al., 2018; Sacharow, Picker & Levy, 2017; Yap, Rushe, Howard & Naughten, 2001). Genetic counseling is available upon request for this individual and their family. Genesys Diagnostics provides assistance in genetic counseling services, please contact the laboratory at (860) 574-9172 for further information.

Individual Variant Interpretations

p.Ile278Thrfs*16 in Exon 10 of CBS

Classification: Pathogenic

Interpretation: The frameshift insertion NM_000071.3(CBS):c.832_833ins(68) (p.Ile278Thrfs*16) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. This variant is predicted to cause loss of normal protein function through protein truncation caused a frameshift mutation. The frame shifted sequence continues 16 residues until a stop codon is reached. This variant is a frameshift variant which occurs in an exon of CBS upstream of where nonsense mediated decay is predicted to occur. There are 35 downstream pathogenic loss of function variants, with the furthest variant being 257 residues downstream of this variant. This indicates that the region is critical to protein function. The p.Ile278Thrfs*16 variant is a loss of function variant in the gene CBS, which is intolerant of Loss of Function variants, as indicated by the presence of existing pathogenic loss of function variant NP_000062.1:p.Q7Rfs*75 and 29 others. For these reasons, this variant has been classified as Pathogenic.

Transcript and Coding Change: NM_000071.3:c.832_833ins(68) (p.Ile278Thrfs*16)

Additional Information

NGS Coverage Report

COVERAGE STATISTICS:

Coverage statistics were computed over 2995 targets.

Average Coverage (x)	% of Targeted Bp Covered
	≥ 20X
337.04x	**97.58%**

Methods

Electrophoresis Methodology - Genomic DNA was extracted from the patient's sample submitted to our laboratory using QIAamp mini kit or MagMAX DNA Multi-Sample Ultra 2.0 kit. Multiplex PCR is performed using the MRC Holland MLPA SALSA Probe Mixes or ThermoFisher™ CarrierMax Reagent Kits on targeted regions within the gDNA. Amplified fluorescently tagged PCR product is

denatured and analyzed for fragment size with an Applied Biosystems 3500 genetic analyzer. Results are analyzed through semi-automatic comparison of fragment sizes to a combination of known reference samples and bin sets algorithmically.

Sequencing Methodology - Genomic DNA was extracted from the patient's sample submitted to our laboratory using QIAamp mini kit or MagMAX DNA Multi-Sample Ultra 2.0 kit. The TruSight Rapid Capture Kit (Illumina™) was used with a custom probe set to target the requested genes of tagmented gDNA. These targeted regions were then sequenced using Illumina™ MiSeq with paired end reads. Reads from the sequence output were aligned to the human reference genome (UCSC hg19/GRCh37 reference sequence). The targeted regions were assessed for the average depth of coverage and the required data quality threshold values. The quality threshold refers to the defined target region where read depth was at least 20x coverage to permit high quality variant base calling, annotation, and evaluation. Average quality thresholds may range from >85% of the targeted region, indicating a small portion of the target region may not be covered with sufficient depth or quality to call variant positions with high confidence. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). This laboratory developed test has been independently validated by Genesys Diagnostics, Inc. The FDA has determined that such clearance or approval is not necessary.

The genes covered in this sequencing panel and the accession numbers of the reference are: ABCA3 (NM_001089.3), ABCC8 (NM_000352.6), ABCD1 (NM_000033.4), ACADM (NM_000016.6), ACADS (NM_000017.4), ACADVL (NM_000018.4) ACAT1 (NM_000019.4), ACSF3 (NM_174917.5), AFF2 (NM_002025.4), AGA (NM_000027.4), AGXT (NM_000030.3), AHI1 (NM_017651.5), AIRE (NM_000383.4), ALDOB (NM_000035.4), ALMS1 (NM_015120.4), ALPL (NM_000478.6), ANO10 (NM_018075.5), ARSA (NM_000487.6), ARX (NM_139058.3), ASL (NM_000048.4), ASPA (NM_000049.4), ATM (NM_000051.4), ATP7B (NM_000053.4), BBS1 (NM_024649.5), BBS2 (NM_031885.5), BCKDHA (NM_000709.4), BCKDHB (NM_183050.4), BLM (NM_000057.4), BTD (NM_001281723.3), CAPN3 (NM_000070.3), CBS(NM_000071.3) , CC2D2A (NM_001080522.2), CCDC88C (NM_001080414.4), CDH23 (NM_022124.6), CEP290 (NM_025114.4), CFTR (NM_000492.4), CHRNE (NM_000080.4), CLCN1 (NM_000083.3), CLRN1 (NM_174878.3), CNGB3 (NM_019098.5), COL7A1 (NM_000094.4), CPT2 (NM_000098.3), CYP11A1 (NM_000781.3), CYP1B1 (NM_000104.4), CYP21A2 (NM_000500.9), CYP27A1 (NM_000784.4), CYP27B1 (NM_000785.4), DBT (NM_001918.5), DHCR7 (NM_001360.3), DHDDS (NM_205861.3), DLD (NM_000108.5), DMD (NM_004006.3), DNAH5 (NM_001369.3), DYNC2H1 (NM_001377.3), DYSF (NM_003494.4), ELP1 (aka IKBKAP) (NM_003640.5), ERCC2 (NM_000400.4), EVC2 (NM_147127.5), EYS (NM_001142800.2), F11 (NM_000128.4), F8 (NM_000132.4), F9 (NM_000133.4), FAH (NM_001374377.1), FANCA (NM_000135.4), FANCC (NM_000136.3), FANCG (NM_004629.2), FKRP (NM_024301.5), FKTN (NM_006731.2), FMO3 (NM_006894.6), FXN (NM_000144.5), G6PC (NM_008061.4), GAA (NM_000152.5), GALC (NM_000153.4), GALT (NM_000155.4), GBA (NM_000157.4), GBE1 (NM_000158.4), GJB2 (NM_004004.6), GLA (NM_000169.3), GNE (NM_005476.7), GNPTAB (NM_024312.5), GRIP1 (NM_001366722.1), HBB (NM_000518.5), HEXA (NM_000520.6), HFE (NM_000410.4), HOGA1 (NM_138413.4), HPS1 (NM_000195.5), HPS3 (NM_032383.5), IDUA (NM_000203.5), L1CAM (NM_001278116.2), LDLR (NM_000527.5), LOXHD1 (NM_144612.7), LRP2 (NM_004525.3), MCCC2 (NM_022132.5), MCOLN1 (NM_020533.3), MCPH1 (NM_024596.5), MEFV (NM_000243.3), MID1 (NM_000381.4), MLC1 (NM_139202.3), MMACHC (NM_015506.3), MMUT (NM_000255.4), MVK (NM_000431.4), MYO7A (NM_000260.4), NAGA (NM_000262.3), NEB (NM_001164507.2), NPC1 (NM_000271.5), NPC2 (NM_006432.5), NPHS1 (NM_004646.4), NPHS2 (NM_014625.4), NR0B1 (NM_000475.5), OCA2 (NM_000275.3), OTC (NM_000531.6), PAH (NM_000277.3), PCDH15 (NM_001384140.1), PEX6 (NM_000287.4), PKHD1 (NM_138694.4), PLP1 (NM_000533.5), PMM2 (NM_000303.3), POLG (NM_002693.3), PRF1 (NM_001083116.3), PYGM (NM_005609.4), RARS2 (NM_020320.5), RMRP (NR_003051.3), RNASEH2B (NM_024570.4), RPGR (NM_000328.3), RS1 (NM_000330.4), SCO2 (NM_005138.3), SERPINA1 (NM_000295.5), SLC12A3 (NM_000339.3), SLC19A3 (NM_025243.4), SLC22A5 (NM_001308122.2), SLC26A2 (NM_000112.4), SLC26A4 (NM_000441.2), SLC37A4 (NM_001164277.2), SLC6A8 (NM_005629.4), SMPD1 (NM_000543.5), TF (NM_001063.4), TMEM216 (NM_016499.6), TNXB (NM_019105.8), TYR(NM_000372.5), USH2A (NM_007123.6), XPC (NM_004628.5)

Limitations

Despite best efforts by Genesys Diagnostics Inc., a negative genetic testing result using the Carrier Screening Sequencing Panel does not exclude the possibility of being a carrier of the disease(s) for which the test is conducted. It should be noted that this test is limited to a finite number of genes and does not include all intronic and non-coding regions. Results are limited to targeted genomic regions and will not detect mutations present outside of the targeted regions. Certain regions in various genes have poor

coverage and are not included in the panel. Additional coverage information regarding any specific gene(s) of interest, can be provided upon request. Mutations in primer/probe binding regions may result in erroneous results. *SMN* results do not preclude the existence of point mutations or small deletions in the SMN1 gene that may disrupt SMN protein function in the absence of exon 7 deletions. The assay cannot identify silent carriers of the (2+0) haplotype that do not carry the tested SNPs, nor can it preclude *de novo* loss of exon 7 in the SMN1 gene during gamete formation. A negative *FMR1* result does not preclude the existence of size mosaicism or methylation mosaicism. The presence of AGG repeats that may stabilize strand slippage is not precluded by this assay. This assay will not detect the presence of point mutations or small deletions in *FMR1* that may disrupt FMRP protein function in the absence of CGG repeat expansion. While the assay is able to accurately determine the number of CGG repeats in normal, intermediate, and pre-mutation alleles (≤ 200 repeats), as well as detect full mutation alleles (> 200 repeats), it cannot accurately determine the specific number of CGG repeats in full mutation alleles. Point mutations within *DMD* and the HBA gene clusters are the second most common causes of genetic defects in these genes and will not be detected by the MLPA technique. The combination of a deletion on one chromosome and a similarly sized duplication on the other chromosome may result in a false negative *DMD* or HBA result. Not all HBA deletions can be discriminated from each other using this technique. The -FIL and -THAI deletions will return identical HBA results. The -MED2 and –Dutch1 deletions will also return identical HBA results. This report only includes variants that meets a level of evidence threshold for cause or contribute to disease. Certain classes of genomic variants are also not covered using the NGS testing technology, including triplet repeat expansions, copy number alterations, translocations and gene fusions or other complex structural rearrangements. As more evidence for disease association of genes and causal pathogenic variants are discovered, it is recommended that genetic variants are re-interpreted with updated software and annotations periodically. Data from this next generation sequencing analysis can be reassessed for the presence of any new variants that may be newly linked to established genes or to newly characterized genes and/or disorders identified since the data used in this report was generated. A charge may be applied for reanalysis. Please contact the laboratory for more information at the time reanalysis is requested.

Incidence Rates of Disorders Covered

For the incidence rates of disorders covered within the Genesys Diagnostics carrier screening panel, please visit www.gdilabs.com

References

CITATIONS

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Report Signed Electronically by Matthew Russell | 06/04/2022