PerkinElmer
For the Better

PerkinElmer GENOMICS **Whole Genome Sequencing and Deletion/Duplication Trio Analysis**

Patient Name:
Date of Birth:
Gender:
Accession ID:
Cross Reference:

Specimen Type:
Receive Date:
Collection Date:
Report Date:

Client Name:
Hospital/Institution:
Mailing Address:
Phone Number:
Fax Number:

Test Performed: Whole Genome Sequencing and Deletion/Duplication Analysis, Trio
Reason for Referral: Clinical features of disease

Pathogenic sequence variant(s) in gene related to reported phenotype detected.

Pathogenic sequence variant(s) in carrier status detected.

No reportable copy number variants (CNV) related to phenotype detected.

Correlation with clinical profile and family history is required.

Relevant Findings and Interpretation

Phenotypic terms applied: XXXXX

Sequence variants related to phenotype:

Classification	Gene	Exon/ Intron	DNA Change	Protein Change	Zygosity	Inheritance	Associated Disease
Pathogenic	*LAMB2*	9	c.1037_1038del	-	Heterozygous	Autosomal Recessive	Nephrotic syndrome, type 5, with or without ocular abnormalities; Pierson syndrome
Pathogenic	*LAMB2*	27	c.4285C>T	p.Arg1429Ter	Heterozygous	Autosomal Recessive	Nephrotic syndrome, type 5, with or without ocular abnormalities; Pierson syndrome

***LAMB2* c.1037_1038del (-) - Pathogenic.** The c.1037_1038del variant results in the deletion of two nucleotides at positions c.1037 through c.1038 of the *LAMB2* gene, causing a frameshift in the protein reading frame. This variant has not been reported in individuals with disease to our knowledge but is of a type expected to cause disease. This variant has been observed in two alleles in the general population (11/12/19 PMID: 27535533). Loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay is expected. The c.1037_1038del *LAMB2* variant is classified as pathogenic. Clinical and biochemical correlation is required.

One copy of this variant was identified in this individual's mother.

Patient Name:

Accession ID:

Cross Reference:

***LAMB2* c.4285C>T (p.Arg1429Ter) - Pathogenic.** The c.4285C>T (p.Arg1429Ter) nonsense variant results in the substitution of the arginine codon at amino acid position 1429 with a termination codon. This variant has not been reported in individuals with disease to our knowledge but is of a type expected to cause disease. This variant has been observed in a single allele in the general population (11/12/19 PMID: 27535533). Protein truncation or nonsense-mediated mRNA decay is expected to cause loss of normal protein function. The c.4285C>T (p.Arg1429Ter) *LAMB2* variant is classified as pathogenic. Clinical and biochemical correlation is required.

One copy of this variant was identified in this individual's father.

Findings Unrelated To Phenotype

Diagnostic findings in genes defined as highly penetrant and medically actionable by ACMG (PMID: 27854360):

No pathogenic variants detected.

Diagnostic findings in other disease-causing genes not related to indications for testing:

No pathogenic variants detected.

Carrier status for autosomal recessive conditions:

Gene	OMIM	Disease	Inheritance	Exon/ Intron	DNA Change	Protein Change	Zygosity	Classification
ANO10	613726	Spinocerebellar ataxia, autosomal recessive 10	Autosomal Recessive	2	c.132dup	-	Heterozygous	Pathogenic (Maternal)
HFE	613609	Hemochromatosis	Autosomal Recessive	4	c.845G>A	p.Cys282Tyr	Heterozygous	Pathogenic (Maternal or Paternal)
SERPINA1	107400	Emphysema due to AAT deficiency; Emphysema-cirrhosis, due to AAT deficiency; Hemorrhagic diathesis due to antithrombin Pittsburgh	Autosomal Recessive	3	c.863A>T (also known as *S allele)	p.Glu288Val	Heterozygous	Pathogenic (Paternal)

Pharmacogenetic variants (only selected CPIC Class 1A alleles with clinical utility are evaluated):

Consultation with a physician to discuss relevant Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines is recommended.

Gene	Allele Haplotype	Phenotype
CYP2C19	*1/*2	Intermediate Metabolizer
SLCO1B1	*1A/*5	Decreased Function

Recommendations

The detection of two pathogenic variants in the *LAMB2* gene is consistent with a diagnosis of disease in this individual; however, these results must be interpreted in the context of this individual's clinical and biochemical profile. Genetic counseling is recommended.

Targeted testing is available for family members at risk to carry the pathogenic variants identified in this individual. For more information, please contact the laboratory at 1-866-354-2910.

Identified data will be stored at PerkinElmer Genomics.

Notes

Variants related to phenotype are reported based on analysis of clinical information provided by the ordering provider. There may be variants of uncertain significance present in the sample with partial overlap to some of the given phenotypic information which were not determined to be relevant enough for reporting. A list of all variants identified in this individual is available upon request. Variants are evaluated by their reported

frequency in databases such as the Genome Aggregation Database (gnomAD), Human Gene Mutation Database (HGMD), and ClinVar. Variants that have a population frequency greater than expected given the prevalence of the disease in the general population are considered to be benign variants. Benign and likely benign variants are not reported. Silent variants and intronic variants beyond +/-3 are not reported unless known or suspected to be pathogenic. Only pathogenic and likely pathogenic mitochondrial variants related to disease are reported. The interpretation of variants is based on our current understanding of the genes involved. These interpretations may change over time as more information about the gene(s) and this individual's clinical phenotype becomes available. Raw sequencing data is available upon request.

Variant Statistics:

Gene	Transcript	DNA Change	Protein Change	Genomic Location	Coverage	Alternate Allele Fraction	dbSNP rsID
ANO10	NM_018075.3	c.132dup	-	Chr3:43647212-43647213	52	61.5%	rs540331226
HFE	NM_000410.3	c.845G>A	p.Cys282Tyr	Chr6:26093141-26093141	54	53.7%	rs1800562
LAMB2	NM_002292.3	c.1037_1038del	-	Chr3:49167851-49167852	58	46.6%	rs746302982
LAMB2	NM_002292.3	c.4285C>T	p.Arg1429Ter	Chr3:49160425-49160425	61	39.3%	.
SERPINA1	NM_000295.4	c.863A>T (also known as *S allele)	p.Glu288Val	Chr14:94847262-94847262	48	50.0%	rs17580
CYP2C19	NM_000769.1	c.681G>A	p.Pro227=	Chr10:96541616-96541616	50	48.0%	rs4244285
SLCO1B1	NM_006446.4	c.521T>C	p.Val174Ala	Chr12:21331549-21331549	45	40.0%	rs4149056

Data Quality Statistics:

% Fully Covered Disease Causative Gene Target Bases	99.3
% Fully Covered Disease Causative Gene Exons	99.2
Average Coverage per Target Base	56

Methods and Limitations

Whole genome sequencing is performed on genomic DNA using 2X150bp reads on Illumina next generation sequencing (NGS) systems at a mean coverage of 30X in the target region. The target region includes coding exons and 10bp of flanking intronic sequence of the known protein-coding RefSeq genes. This sequencing provides >97% coverage of the 22,000 genes in the genome at >30x. A base is considered to have sufficient coverage at 20X and an exon is considered fully covered if all coding bases plus three nucleotides of flanking sequence on either side are covered at 20X or more. A list of low coverage regions is available upon request. Alignment to the human reference genome (hg19) is performed and annotated variants are identified in the targeted region. Variants are called at a minimum coverage of 8X and an alternate allele frequency of 20% or higher. Single nucleotide variants (SNVs) meeting internal quality assessment guidelines are confirmed by Sanger sequence analysis for records after results are reported. Indels and SNVs may be confirmed by Sanger sequence analysis before reporting at director discretion. This assay cannot detect variants in areas containing large numbers of tandem repeats. Mitochondrial DNA is sequenced and analyzed using the same pipeline. Copy number variation (CNV) analysis is designed to detect deletions and duplications of three exons or more; in some instances, due to the size of the exons or other factors, not all CNVs may be analyzed. Only CNVs related to phenotype are reported. This assay is not designed to detect mosaicism; possible cases of mosaicism may be investigated at the discretion of the laboratory director. Primary data analysis is performed using Illumina DRAGEN Bio-IT Platform v.2.03. Secondary and tertiary data analysis is performed using PerkinElmer's internal ODIN v.1.01 software for SNVs and Biodiscovery's NxClinical v.4.3 or Illumina DRAGEN Bio-IT Platform v.2.03 for CNV and absence of heterozygosity (AOH).

Possible sources of testing error include rare genetic variants that interfere with analysis, sample misidentification, and other sources. Pursuant to the requirements of CLIA '88, this test was developed and its performance validated by PerkinElmer Genomics. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

Director Signature(s)