GeneID
The Future Today

NewbornGene ID
Genetic Carrier Testing

136 Summit Avenue, East Wing
Montvale, NJ 07645
Phone: (201) 825-0186
Fax: (201) 825-0191
NewbornGeneID.com
Info@GeneIDLab.com

Dr. Daniel Cohen, M.D. **Laboratory Director**

PATIENT INFORMATION		SPECIMEN INFORMATION	
PATIENT NAME:	Sample Patient	SPECIMEN TYPE:	Saliva
AMD ACCESS #:	NBP-XX-XXXXXX	DATE RECEIVED:	XX/XX/XXXX
DATE OF BIRTH:	XX/XX/XXXX	INITIATION OF TESTING:	XX/XX/XXXX
GENDER:	Male	COMPLETION OF TESTING:	XX/XX/XXXX

ORDERED BY			
ORDERING PHYSICIAN'S NAME:	Dr. Sample Doctor, M.D.	PHYSICIAN'S ADDRESS:	123 Strong Ave, Suite #100 Laredo, TX 78041
PHONE:	XXX-XXX-XXXX	FAX:	XXX-XXX-XXXX

REPORT SUMMARY

POSITIVE RESULTS	
DISEASE:	Cystic Fibrosis
GENE:	CFTR (cystic fibrosis transmembrane conductance regulator)
RESULTS:	Missense mutation
MUTATION:	NM_000492.3(CFTR):c.617T>G (p.Leu206Trp); Chr7: 117175339 (on Assembly GRCh37); p.L206W; rs121908752

Dr. Daniel Cohen, MD, Laboratory Director

This report was electronically signed

Disclaimer: The accompanying Technical Specifications summary describes the analysis, method, performance characteristics, nomenclature, and interpretive criteria of this test. This test result does not exclude the possibility of other predisposing mutations that have been reported in individuals with increased risk. This test may be considered investigational by some states. This test and its performance characteristics were determined by Advanced Molecular Diagnostics Laboratory. It has not been reviewed by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

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EXPLANATION OF POSITIVE RESULTS

The p.L206W variant in the CFTR gene has been reported previously in individuals with CFTR-related disorders who also harbor additional variants in the CFTR gene (Clain et al., 2005; Claustres et al., 1993). The p.L206W variant is a semi-conservative amino acid substitution, which may impact secondary protein structure as these residues differ in some properties. This substitution occurs at a position that is conserved across species. In vitro studies of the L206W variant demonstrate significant reduction in CFTR processing in HeLa cells resulting in a decrease in protein production at the cell surface compared to wild type cells (Clain et al., 2005; Van Goor et al., 2014). A missense variant in the same residue (L206F) has been reported previously in association with a CFTR-related disorder (Claustres et al., 2000), supporting the functional importance of this region of the protein.

The CFTR protein is a chloride and bicarbonate channel that controls the flux of these ions, thereby ultimately controlling electrolyte balance and the flow of water across intercellular and intracellular membranes in epithelial cells. In particular, the CFTR protein is important for adequate function of the lungs, sinuses, gastrointestinal and reproductive tracts, and sweat glands. Disease causing mutations in CFTR disrupt the ability of this protein to effectively transport these anions across the membrane, preventing an appropriate flow of water. The lack of water resulting from abnormal ion flux causes the luminal fluids (mucus) to be excessively thick, to the extent that the mucus congeals and becomes entrapped within the lumina. This process is particularly evident in the lungs and in the gastrointestinal system, eventually creating mucus plugs that prevent appropriate mucosal function.

Cystic Fibrosis is present in approximately 1 in 2500 Europeans and 1 in 3000 individuals in the United States. As one of the most common inherited genetic diseases, there are approximately 30,000 affected individuals in the United States. The average life expectancy of an individual with cystic fibrosis is about 37 years of age.

Cystic Fibrosis is inherited as an autosomal recessive disease, so an affected individual must inherit a mutant copy of the CFTR gene from each parent. Two carriers of the disease that have offspring, have a 25% chance of having a child with cystic fibrosis, a 50% chance of the offspring being an unaffected carrier, and a 25% chance that the offspring will inherit only normal copies of the CFTR gene. The carrier frequency is dependent on race/ethnicity: Ashkenazi Jews 1:24, Non-Hispanic Caucasians 1:25, Hispanic Americans 1:46, African Americans 1:65, and Asian Americans 1:94.

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List of Targeted Genes and Diseases:

DISEASE	GENE
Alpha Thalassemia	HBA1
	HBA2
Arterial Tortuosity Syndrome	SLC2A10
Beta Thalassemia	HBB
Bloom Syndrome	BLM
Canavan Disease	ASPA
Classical Galactosemia	GALT
Congenital Aneurysms	COL4A1
Cystic Fibrosis	CFTR
Cystic Fibrosis-related – CA12	CA12
Cystic Fibrosis-related – SCNN1A	SCNN1A
Cystic Fibrosis-related – SCNN1B	SCNN1B
Cystic Fibrosis-related – SCNN1G	SCNN1G
Dihydrolipoamide Dehydrogenase Deficiency	DLD
Ehlers Danlos Syndrome Type 4	COL3A1
Familial Dysautonomia	IKBKAP
Familial TAAD – ACTA2-related	ACTA2
Familial TAAD – MYH11-related	MYH11
Familial TAAD – MYLK-related	MYLK
Fanconi Anemia Type A	FANCA
Fanconi Anemia Type C	FANCC
Fanconi Anemia Type F	FANCF
Fanconi Anemia Type G	FANCG
Fragile-X Syndrome (available upon request)	FMR1
Gaucher Disease	GBA
Glycogen Storage Disease II – Pompe Disease	GAA
Glycogen Storage Disease IV	GBE1
Jervell and Lange-Nielsen – LQT5	KCNE1
Jervell and Lange-Nielsen – LQT11	KCNQ1
Loeys-Dietz Syndrome Type 1	TGFBR1
Loeys-Dietz Syndrome Type 2	TGFBR2

DISEASE	GENE
Loeys-Dietz Syndrome Type 3	SMAD3
Long QT Syndrome 3	SCN5A
Long QT Syndrome 6	KCNE2
Long QT Syndrome 11	AKAP9
Maple Syrup Urine Disease Type 1A	BCKDHA
Maple Syrup Urine Disease Type 1B	BCKDHB
Maple Syrup Urine Disease Type 2	DBT
Marfan Syndrome	FBN1
Mucolipidosis IV	MCOLN1
Niemann-Pick Disease Type C1	NPC1
Niemann-Pick Disease Type C2	NPC2
Nonsyndromic Hearing Loss (Connexin 26)	GJB2
Nonsyndromic Hearing Loss (Connexin 30)	GJB6
Nonsyndromic Hearing Loss (Connexin 31)	GJB3
Nonsyndromic Hearing Loss (DFNA2)	KCNQ4
Nonsyndromic Hearing Loss (DFNA13)	COL11A2
Ornithine Transcarbamylase Deficiency	OTC
Pendred Syndrome	SLC26A4
Phenylketonuria	PAH
Sickle Cell Disease	HBB
Spinal Muscular Atrophy (Werdnig-Hoffman)	SMN1
Spinal Muscular Atrophy – Modifier	SMN2
Spinal Muscular Atrophy – DYNC1H1-related	DYNC1H1
Spinal Muscular Atrophy – UBA1-related	UBA1
Spinal Muscular Atrophy – VAPB-related	VAPB
Tay Sachs Disease	HEXA
Usher Syndrome Type 1B	MYO7A
Usher Syndrome Type 1C	USH1C
Usher Syndrome Type 1D	CDH23
Usher Syndrome Type 1F	PCDH15
Usher Syndrome Type 2A	USH2A

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TEST METHODOLOGY

Genomic DNA from Sample Patient's submitted specimen was enriched for the complete coding regions and splice site junctions of the genes described in the panel. The products were sequenced on two different massive parallel sequencing platforms; Miniseq Illumina platform (clonal bridge amplification/reversible dye terminator) and Ion Torrent Platform (Ion sphere particles- Chef System/S5XL). The sequences were aligned to reference sequences based on Human Genome build GRCh37/UCSChg19. SMN-1 (survival motor neuron-1 gene) exon 7 and exon 8, deletion/duplication testing was performed by Multiple Ligation Probe Amplification (MLPA). Fragment analysis and comparative analysis were performed by Coffalyser DB software, v.140701 (MRC-Holland). SMN-1 risk estimates includes testing for presence or absence of the intron 7 polymorphism g.27134T>G, which improves the accuracy of residual risk in different populations (1).

Sequencing bio-informatics pipelines were analyzed by Illumina VariantStudio v.3.0 and Torrent Suite Software v.4.0.2., respectively. Discrepancies between platforms, if any, were resolved by selective incorporation of chain-terminating dideoxynucleotides (Sanger Sequencing) targeting with specific FWD/REV primer 5' M13 tailed and HPLC purified. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Genetic data are stored under Variant Call Format (VCF). (2)(3).

(1) Luo, M. et al. Genetics in Medicine 16, 149–156, 2014. (2) Bio-IT World, Davies, K. Powering Preventative Medicine. Bio-IT World, 2011. (3) GenomeWeb DNA Electronics Licenses IP to Ion Torrent. August 2010.

RECOMMENDATIONS

It is recommended that this test result be communicated to the patient in a setting that includes appropriate genetic counseling by a licensed/certified genetic counselor. This test result should only be used in conjunction with the patient's clinical history and any previous analysis of appropriate family members.

DISCLAIMERS & TEST LIMITATIONS

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Clinically significant long homopolymer tracts, triplet repeat expansions, large genomic rearrangements, deep intronic variants and mutations located in regulatory regions may not be identified with the technologies used by this assay. Genes with closely related pseudogenes are not well analyzed by this method. Rare variants in primer or probe hybridization sites may compromise analytical sensitivity. Depending on the availability of parental DNA, the chromosomal phase of identified pathogenic variants may not be determined (i.e., whether variants are in cis or trans).

AMD follows internal policies and ACMG recommendations for variant classification (4). Pathogenic and Likely pathogenic variants are evaluated by reviewing reports of allele frequencies in cases and controls, population data, functional studies, variant annotation and effect prediction, previous classification in reputable databases and segregation studies.

All variants that are recognized cause of disease will be reported. In addition, variants that have not previously been established as a recognized cause of pathology may be identified. In these cases, only variants classify as "pathogenic" or "likely pathogenic" are described. Benign variants, variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported, but are available upon request.

(4) Richards, S. et al. Genetics in Medicine. May; 17(5):405-24, 2015.