SAMPLE REPORT

Diagnostic Exome Sequencing Test Report

Personal Information	Specimen Information	Test Information
Name: Jason Doe	**Sample ID:**	**Test reported:**
Relation: -	**Medical record No:** -	**Ordering physician:** Dr. Smith
Sex/Birth: M/ 2020-03-15	**Date received:** 2023-05-10	**Institution:** Hospital A

TEST PERFORMED

DES (Sequence analysis of 5,870 Mendelian genes)

REASON FOR REFERRAL

clinical diagnosis: coarse face, mental development delay, hepatosplenomegaly, no cataract → suspected MPS II

RESULT POSITIVE

A homozygous pathogenic variant was identified in the NAGLU gene, related to the patient's clinical phenotype.

Gene	DNA change	Predicted AA change	Zygosity	OMIM Disease	Inherit	Class
NAGLU	c.1444C>T	p.Arg482Trp	Hom	MTISB	AR	PV

Reference sequence: NM_000263.4(NAGLU)
OMIM disease: MTISB, Mucopolysaccharidosis type IIIB (Sanfilippo B)
Abbreviation: AR, Autosomal recessive; Hom, Homozygous; PV, Pathogenic Variant

INTERPRETATION

[2023.05.24]
NAGLU, NM_000263.4:c.1444C>T (p.Arg482Trp)
This sequence change replaces 482th amino acid Arginine with Tryptophan of the NAGLU protein. This variant is present in population databases (gnomAD 0.0027%). This variant has been reported in individuals affected with Sanfilippo syndrome B (PMID: 32901917, 16447797, 23667853, 9950362). ClinVar contains an entry for this variant as Pathogenic/Likely pathogenic (Variation ID: 1571). In silico analyses, which predict the effect of the effect of missense changes on protein structure and function output, are as the following: SIFT: deleterious, PolyPhen: probably damaging, MutationTaster: disease causing. For these reasons, this variant has been classified as Pathogenic.
Pathogenic NAGLU variants are associated with Mucopolysaccharidosis type IIIB (Sanfilippo B). Mucopolysaccharidosis type III (MPS III) is a multisystem lysosomal storage disease characterized by progressive central nervous system degeneration manifest as severe intellectual disability (ID), developmental regression, and other neurologic manifestations including autism spectrum disorder (ASD), behavioral problems, and sleep disturbances. Disease onset is typically before age ten years. Disease course may be rapidly or slowly progressive; some individuals with an extremely attenuated disease course present in mid-to-late adulthood with early-onset dementia with or without a history of ID. Systemic manifestations can include musculoskeletal problems (joint stiffness, contractures, scoliosis, and hip dysplasia), hearing loss, respiratory tract and sinopulmonary infections, and cardiac disease (valvular thickening, defects in the cardiac conduction system). Neurologic decline is seen in all affected individuals; however, clinical severity varies within and among the four MPS III subtypes (defined by the enzyme involved) and even among members of the same family. Death usually occurs in the second or third decade of life secondary to neurologic regression or respiratory tract infections.

Clinical correlation and, if necessary, family testing are recommended.

Tested by: M-K Lee M.T(20058) Confirmed by: Sae-Mi Lee M.D(1067) Chang-ahn Seol M.D(1037)

GC Genome

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS

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INCIDENTAL FINDINGS

No (Likely) Pathogenic Variant was identified in the 78 genes recommended by ACMG
* Investigation of 78 genes recommended by ACMG SF v3.1 (Genet Med.2022 June 17.)

METHODS

Genomic DNA was extracted from EDTA whole blood and all the exons of 5,870 genes were captured using Celemics G-Mendeliome DES Panel. Sequencing was performed on DNBSEQ-G400 (MGI) platform generating 2 × 100 bp paired-end reads. The DNA sequence reads were aligned to reference sequence based on public human genome build GRCh37/UCSC hg19. Using a in-house bioinformatics pipeline, data were filtered and analysed to identify sequence variants.

Sequence variants were classified based on the ACMG/AMP guidelines (Richards et al., 2015). Reported results are focused on pathogenic and likely pathogenic variants in genes related to the phenotype of proband, while variants of uncertain significance are only rarely reported at our discretion. Depending on the results of additional studies in the literature and databases, the classification of the variant may change. Variants that pass internal QC criteria are not validated by Sanger sequencing.

ANALYSIS STATISTIC

Mean depth of coverage	284.08X
% of > 10x	99.6%

LIMITATIONS

The absence of definitive pathogenic findings does not rule out the diagnosis of a genetic disorder as some genetic abnormalities may be undetectable with this test. It is possible that the genomic region where a disease-causing variant exists in the proband was not captured or sufficiently sequenced with low quality. Additionally, multifactorial disorders and some types of genetic disorders due to nucleotide repeat expansion/contraction, abnormal DNA methylation, and other mechanisms may not be detectable with this test. This test also cannot reliably detect mosaicism, chromosomal aberrations, and deletions/insertions of 20 bp or more. Some genes have inherent sequence properties (for example: repeats, homology, high GC content, rare polymorphisms) that may result in suboptimal data, and variants in those regions may not be reliably identified.

※ This test was developed and its performance characteristics determined by GC Genome. It has not been cleared or approved by the Korean Ministry of Food and Drug Safety (MFDS).

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