3billion

Report date: N/A

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Comprehensive Genetic Screening for Your Newborn

NEWBORN DETAILS

Unique ID	[Unique ID]	**Physician**	[Physician]	**Sample type**	DBS
3billion ID	[3billion ID]	**Department**	Obstetrics & Gynecology	**Collected on**	yyyy-mm-dd
DOB* / Sex	yyyy-mm-dd / Male	**Institution**	[Institution]	**Ordered on**	yyyy-mm-dd
Ethnicity	Latino/Admixed American			**Accessioned on**	yyyy-mm-dd

* (YYYY-MM-DD)

RESULT SUMMARY

DETECTED

A homozygous pathogenic variant was identified in the *ALDH7A1* gene. The *ALDH7A1* gene is associated with Epilepsy, early-onset, 4, vitamin B6-dependent (OMIM: 266100). As this variant has never been reported in other patients, clinical correlation is recommended. Parental testing is also recommended to check if the variant is {italic::de novo} or inherited.

Epilepsy, early-onset, 4, vitamin B6-dependent (OMIM: 266100)

Gene	Variant		Classification
ALDH7A1	Genomic Position	5-126552059-C-G (GRCh38)	Pathogenic
	cDNA	NM_001182.5:c.1279G>C	
	Protein	NP_001173.2:p.Glu427Gln	
	Zygosity	Homozygous	
	Inheritance	Unknown	

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RESULT INTERPRETATION

ALDH7A1 NM_001182.5:c.1279G>C (NP_001173.2:p.Glu427Gln)	
Population Data	The variant is observed at an extremely low frequency in the gnomAD v4.1.0 dataset (total allele frequency: 0.051%).
Predicted Consequence / Location	Missense variant
Segregation Data	None
Computation and Functional Data	Functional studies provide moderate evidence of the variant having a damaging effect on the gene or gene product (PMID: 16491085, 22784480). In silico tool predictions suggest damaging effect of the variant on gene or gene product [REVEL: 0.94 (>=0.6, sensitivity 0.68 and specificity 0.92); 3Cnet: 0.97 (> 0.75, sensitivity 0.96 and precision 0.92)].
Previously Reported Variant Data	The same nucleotide change resulting in the same amino acid change has been previously reported as pathogenic/likely pathogenic with strong evidence (ClinVar ID: VCV000017994 / PMID: 16491085 / 3billion dataset). Different missense changes at the same codon (p.Glu427Asp, p.Glu427Gly) have been reported as pathogenic/likely pathogenic with strong evidence (ClinVar ID: VCV000204865, VCV000944165 / PMID: 19128417).
Disease Association	Epilepsy, early-onset, 4, vitamin B6-dependent (OMIM: 266100)
Validation	Not performed as the variant was considered high-quality
Variant Classification	Pathogenic

MEDICAL IMPLICATIONS & ACTION PLAN

1. **Disease Summary**
   - Cause: A genetic form of epilepsy caused by a defect in Vitamin B6 metabolism, leading to excessive neuronal hyperexcitability.
   - Key Symptoms: Seizures that do not respond to standard anti-epileptic drugs (refractory seizures), persistent episodes of convulsions, and excessive irritability without a known cause.
2. **Benefits of Early Intervention**
   - Initiating Vitamin B6 therapy before symptom onset or immediately after the first seizure can prevent irreversible brain damage and support normal neurodevelopment.
3. **Follow-up Management & Confirmatory Testing**
   - Additional Confirmatory Testing: Final diagnosis is established by measuring alpha-aminoadipic semialdehyde (α-AASA) and pipecolic acid levels in blood or urine.
   - Specialist Consultation: Upon detection, immediate consultation with a pediatric neurologist is required to determine the initiation of prophylactic Vitamin B6 (Pyridoxine) therapy.
   - Long-term Management: If confirmed, lifelong Vitamin B6 supplementation is necessary, along with regular developmental monitoring to ensure healthy growth.

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LIST OF GENES

The 595 genes included in this test provide comprehensive coverage across all clinical specialties, including Metabolism, Immunology, Endocrinology, Hematology, Neurology, Gastroenterology, Nephrology, ENT/Dental, Cardiovascular, Medical Genetics, Pulmonology, Oncology, Ophthalmology, and Dermatology.

For the complete list of genes and associated conditions, please [click here].

RESOURCES

- Online Mendelian Inheritance in Man®:This report contains information from the Online Mendelian Inheritance in Man® (OMIM®) database, which has been obtained under a license from Johns Hopkins University. This report does not represent the entire, unmodified OMIM® database, which is available in its entirety at http://omim.org/downloads.
- gnomAD (genome Aggregation Database): gnomad.broadinstitute.org
- ClinVar (National Center for Biotechnology Information ClinVar Database): ncbi.nlm.nih.gov/clinvar
- HGVS (Human Genome Variation Society): varnomen.hgvs.org
- HGMD (The Human Gene Mutation Database) Professional

REFERENCES

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NOTES

1. Results summary: Results are categorized into detected and not detected.

Category	Explanation
Detected	• AD or XL disease: one heterozygous or hemizygous P/LP variant is identified within the curated gene list. • AR disease: one homozygous P/LP variant or two P/LP (potential) compound heterozygous variants are identified within the curated gene list.
Not Detected	• No clinically significant variant

2. Variant Classification: A variant is classified according to the ACMG guideline (PMID 25741868) using the type of evidence including population data, computational and predictive data, functional data, segregation data, de novo data, and allelic data.

RECOMMENDATIONS

1. Genetic counseling is warranted to review the test results and interpretation.
2. This test is designed for newborn screening purposes. A 'Detected' result does not necessarily constitute a definitive diagnosis of the associated disorder, nor does a 'Not Detected' result 100% exclude the possibility of a condition (potential for false negatives). If clinical symptoms or a relevant family history are present, a comprehensive clinical evaluation by a specialist and additional confirmatory testing (e.g., biochemical assays) may be required regardless of the test results.
3. This test can detect single nucleotide variants, small insertions/deletions (<50 bp) and large (>=3 consecutive exons) copy number variants with high accuracy in most of the genomic regions. If low level (<20%) mosaicism variants on autosomes and sex chromosomes, small (<3 consecutive exons) copy number variants (CNVs), structural variants (SVs) including inversions and translocations, or low heteroplasmic level mitochondrial genome variants are suspected, it is recommended to perform other tests specifically designed to detect these types of variants. Variants in regions of high sequence homology, such as pseudogenes, may be difficult to detect. Intronic variants, epigenetic factors, or variants in regulatory regions called by being near coding exons may not be interpretable.
4. Variant interpretation is based on currently available scientific and medical information that were publicly available at the time the results were reported. Therefore, the referenced data may not be current at the time of genetic counseling.

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METHODS

Genomic DNA was extracted from DBS specimen using standard protocol. Exome capture was performed using xGen Exome Research Panel v2, supplemented with xGen human mtDNA panel and xGen Custom Hyb Panel v1 (Integrated DNA Technologies, Coralville, Iowa, USA). Sequencing was performed using NovaSeq X (Illumina, San Diego, CA, USA). In total, 11,458,836,111 bases of sequence were generated and uniquely aligned to a modified version of the Genome Reference Consortium Human Build 38 (GRCh38), in which falsely duplicated regions of chromosome 21 were masked to N's based on the masking file developed in collaboration with the GRC (Genome Reference Consortium) (Nat Biotechnol. 2022;40:672-680) and Revised Cambridge Reference Sequence (rCRS) of the mitochondrial genome, generating 168.58 mean depth-of-coverage within the 34,212,647 bases of the captured region, which is approximately 99.3% of the RefSeq protein coding region. Approximately 99.40% of the targeted bases were covered to a depth of ≥20x. Despite the insufficient coverage across 0.60% of the bases (see below for details), these metrics are consistent with high quality exome sequencing data and deemed adequate for analysis. Gene or exon level depth-of-coverage (DOC) information is available upon request. In total, [[snp]] single nucleotide variants (SNV) and [[indel]] small insertions and deletions (INDEL) were identified. Sequencing data analysis and variant interpretation were performed using 3billion's proprietary system, EVIDENCE v4.2 (Clin Genet. 2020;98:562-570). EVIDENCE incorporates bioinformatics pipeline for calling SNV/INDEL based on the GATK best practices (GATK v3.8, Genome Res. 2010;20:1297-303), Manta (Bioinformatics. 2016;32:1220-2) for structural variant calling including CNV (copy number variants) based on paired-end information, and 3bCNV v23.0818, an internally developed tool, for calling CNV including aneuploidy based on the DOC information. It also incorporates Mutect2 (Genome Res. 2010;20:1297–303) for calling lower level heteroplasmic SNV/INDEL in the mitochondrial genome, ExpansionHunter v5.0.0 (Bioinformatics. 2019;35:4754–6) for calling repeat expansion variants, MELT v2.2.2 (Genome Res. 2017;27:1916–29) for calling mobile element insertion variants, AutoMap v1.2 (Nat Commun. 2021;12:518) for detecting regions of homozygosity (ROH). Variant Effect Predictor v104.2 (VEP, Ensembl, Genome Biology 2016;17:122) is used for variant annotation. Variants were prioritized based on the guideline recommended by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (Genet Med. 2015;17:405-424, Genet Med. 2020:22:245-257, and Hum Mutat. 2020;41:2028-2057). Only variants deemed clinically significant and relevant to the patient's clinical indications at the time of variant interpretation are reported. Based on internal studies validating the accuracy of the SNVs and INDELs called with high quality scores, only low quality variants are confirmed by Sanger sequencing. SVs with breakpoints identified were attempted to be confirmed by Sanger sequencing.

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DISCLAIMER

This test was developed by 3billion for the purpose of identifying single nucleotide variants, small insertions and deletions, and structural variants from the [exome/genome] sequence. This laboratory is certified under the College of American Pathologists (CAP#: 8750906) and Clinical Laboratory Improvement Amendments (CLIA#: 99D2274041) as qualified to perform high complexity clinical laboratory testing.Assay validation and clinical validation were performed following the Korea Institute of Genetic Testing Evaluation, the American College of Medical Genetics and Genomics (ACMG) Technical Standards and Guidelines Section G (https://www.acmg.net/PDFLibrary/Standards-Guidelines-Clinical-Molecular-Genetics.pdf) and the CAP Next Generation Sequencing (NGS) Worksheets (Santani A et al. J Mol Diagn. 2019 May;21(3):369-374; https://www. cap.org/member-resources/precision-medicine/next-generation-sequencing-ngs-worksheets). This test is designed for newborn screening purposes only and is not intended as a standalone diagnostic tool. If low-level mosaicism or variants within regions that are incompletely sequenced due to technical difficulties with amplification, sequencing, or alignment are suspected, it is recommended to perform appropriate testing specifically designed to detect such variants. This report may not be copied or reproduced except in its totality.

ACCREDITATIONS AND CERTIFICATIONS

CAP License #	CLIA ID #
8750906, AU-ID# 2052626	99D2274041

This case has been comprehensively reviewed by our clinical team of physicians, geneticists and informaticists.
Report electronically signed by:

Go Hun Seo, M.D, Ph.D.
Chief Medical Officer & Laboratory Director