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PATIENT INFORMATION

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

* (YYYY-MM-DD)

CLINICAL INFORMATION

Symptoms	Intellectual disability, Atrial septal defect, Cryptorchidism

RESULT SUMMARY

Primary findings	Variant reported	**Additional findings**	No variant reported
Secondary findings	Variant reported		

PRIMARY FINDINGS

POSITIVE

A heterozygous likely pathogenic variant was identified in *NIPBL*. *NIPBL* is associated with autosomal dominant 'Cornelia de Lange syndrome 1 (OMIM: 122470)'. 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 de novo or inherited.

Cornelia de Lange syndrome 1 (OMIM: 122470)

Gene	Variant		Classification
NIPBL	Genomic Position	5-36985791-AGG-A (GRCh38)	Likely pathogenic
	cDNA	NM_133433.4:c.2612_2613del	
	Protein	NP_597677.2:p.Arg871ThrfsTer2	
	Zygosity	Heterozygous	
	Inheritance	Unknown	

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PRIMARY FINDINGS INTERPRETATION

NIPBL NM_133433.4:c.2612_2613del (NP_597677.2:p.Arg871ThrfsTer2)	
Population Data	The variant is not observed in the gnomAD v4.1.0 dataset.
Predicted Consequence / Location	Frameshift: predicted to result in a loss or disruption of normal protein function through nonsense-mediated decay (NMD) or protein truncation. Multiple pathogenic variants are reported downstream of the variant.
Segregation Data	None
Computation and Functional Data	None
Previously Reported Variant Data	None
Disease Association	Cornelia de Lange syndrome 1 (OMIM: 122470)
Validation	Not performed as the variant was considered high-quality
Variant Classification	Likely pathogenic

ADDITIONAL FINDINGS

No additional variants were identified, including variants of uncertain significance (VUSs) that could not be reported as primary findings due to limited evidence of pathogenicity, even though they may explain the patient's symptoms; pathogenic, likely pathogenic variants or VUSs that may partially explain the patient's symptoms, regardless of whether they fit the mode of inheritance; or variants associated with the family history provided by the healthcare provider, regardless of the patient's current symptoms.

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SECONDARY FINDINGS

Breast-ovarian cancer, familial 2 (OMIM: 612555) is an autosomal dominant, multifactorial disorder. Individuals with pathogenic variants in *BRCA2* (OMIM: 600185) have an increased risk for developing breast cancer and ovarian cancer (includes fallopian tube and primary peritoneal cancers) and other cancers such as prostate cancer, pancreatic cancer, and melanoma to a lesser extent. Genetic counseling and clinical management are warranted.

Breast-ovarian cancer, familial, 2 (OMIM: 612555)

Gene	Variant		Classification
BRCA2	**Genomic Position**	13-32362596-A-T (GRCh38)	Pathogenic
	cDNA	cDNA: NM_000059.4:c.7879A>T	
	Protein	NP_000050.3:p.Ile2627Phe	
	Zygosity	Heterozygous	
	Inheritance	Unknown	

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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
- MITOMAP (A human mitochondrial genome database): https://www.mitomap.org/MITOMAP

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NOTES

1. Results summary: Results are categorized into positive, inconclusive, and negative. A variant in a known disease gene that would fit the patient's phenotype is reported.

Category	Explanation
Positive	• AD or XL disease: one heterozygous or hemizygous P/LP variant is identified in a known disease gene. • AR disease: one homozygous P/LP variant or two P/LP (potential) compound heterozygous variants are identified in a known disease gene.
Inconclusive	• AD or XL disease: one heterozygous or hemizygous VUS is identified in a known disease gene. • AR disease: At least two heterozygous or one homozygous VUS are identified in a known disease gene. • AR disease: One heterozygous P/LP variant is identified in a known disease gene. • A P/LP variant(s) are identified in a GUS that has sufficient evidence of being a disease gene.
Negative	• No clinically significant variant that would fit the patient's phenotype well is identified.

Abbreviation: AD; autosomal dominant, AR; autosomal recessive, XL; X-linked, P; Pathogenic, LP; likely pathogenic, VUS; variant of uncertain significance, GUS; gene of uncertain significance.

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 can detect single nucleotide variants, and small insertions/deletions (<50 bp) with high accuracy in most of the genomic regions. If low level mosaicism variants on autosomes and sex chromosomes, 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.
3. The test results are based on the clinical information and family history provided in the test order. If the information provided is incorrect or insufficient, the test may not yield reliable results. If the test results have weak clinical correlations, additional testing may be required at the discretion of your medical provider. Whole exome sequencing test or Sanger sequencing test on the biological parents or other family members is recommended to confirm segregation of the variant(s).
4. Variant interpretation is based on currently available scientific and medical information that was publicly available at the time the results were reported. Therefore, the referenced data may not be current at the time of genetic counseling.
5. In case of a negative result with no significant variants reported, it does not rule-out the possibility of having a genetic condition. As new clinical/scientific information becomes available, variant classification may change and a new diagnosis can emerge. To ensure newly available information is promptly reflected in the variant interpretation for the reanalysis of the existing genomic data, 3billion performs automated daily reanalysis of the data as requested and inform the ordering medical provider if a new molecular diagnosis is identified or a variant is reclassified. The medical provider may also add new phenotypic information on the patient.
6. Physician consent for reanalysis is renewed on a 10-year cycle. After 10 years, when a physician renews the physician's consent for reanalysis, the reanalysis period will be extended for another 10 years.

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METHODS

Sequencing data was processed at 3billion starting from the FASTQ files. In total, 9,275,345,146 bases of sequence were generated and uniquely aligned to the Genome Reference Consortium Human Build 38 (GRCh38) and Revised Cambridge Reference Sequence (rCRS) of the mitochondrial genome, generating 78.68 mean depth-of-coverage within the 33,183,698 bases of the captured region, which is approximately 99.3% of the RefSeq protein coding region. Approximately 99.80% of the targeted bases were covered to a depth of ≥20x. Despite the insufficient coverage across 0.20% 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, 63,427 single nucleotide variants (SNV) and 11,789 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 v4.4.0, Genome Res. 2010;20:1297–303) and 3bCNV v2.1, an internally developed tool, for calling CNV (copy number variants) including aneuploidy based on the DOC information when appropriate control samples are available. It also incorporates Mutect2 v4.4.0 (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) in the context of the patient's phenotype, relevant family history and previous test results provided by the ordering physician. Only variants deemed clinically significant and relevant to the patient's clinical indications at the time of variant interpretation are reported. The VCF files and/or annotated small variant lists are available upon request.

ADDITIONAL MEMO

Ginecoid lipoid distribution, microorchidea, normal male karyotype (46, XY), high sexual horomone-binding globulin 23.7nmol/L (normal range 72-220nmom/L), high Bioavailable testosterone 26.5 (0.2 - 3.4), high Free testosterone 2.35pg (0.15-0.6pg), HbA1c: 6.1%

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DISCLAIMER

This research service was developed by 3billion for the purpose of analyzing and interpreting single nucleotide variants, small insertions and deletions, and structural variants from whole exome sequencing data generated by an external laboratory. The interpretation depends on the quality of the sequencing data. However, because the sequencing data is generated from an external laboratory, 3billion does not take responsibility for the quality of the sequencing data provided. 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