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Whole Genome Sequencing Germline Testing Report

LAB ID	**SPEC1378**	Specimen type	**Blood**
Name	**Baby of M.T.M. Perera**	Collection date	**12/09/2025**
Age | Gender	**3 days | Male**	Report date	**24/09/2025**
Indication	**Suspecting mitochondrial disease**	Referred by clinician	**Dr. Vindya Subasinghe**

Executive Summary

Two heterozygous variants, one pathogenic and one of uncertain significance, were identified in the *VARS2* gene, which are associated with Combined Oxidative Phosphorylation Deficiency 20

Clinical History

The proband, Baby of M.T.M. Perea, was referred for evaluation of suspected mitochondrial disease. He was born at 36+1 weeks of gestation by emergency caesarean section for antepartum haemorrhage, with intrauterine growth restriction. Postnatally, he developed respiratory distress with poor respiratory effort requiring ventilatory support. On examination, there are no dysmorphic features or neurocutaneous manifestations. Investigations revealed fluctuating lactate levels with mildly deranged liver function tests and transiently elevated creatine kinase. Coagulation profile showed mild prolongation of INR. Echocardiography demonstrated a small PDA and OS-ASD. Brain and renal ultrasound were unremarkable. Whole Genome Sequencing has been requested to investigate the underlying genetic etiology.

Results

The baby of M.T.M. Perea is heterozygous for a pathogenic and a variant of uncertain significance in the *VARS2* gene, which is associated with Combined Oxidative Phosphorylation Deficiency 20. The variants were confirmed to be compound heterozygous by phasing.
Additionally, he carries a heterozygous pathogenic variant in the *LRRC23* gene and a heterozygous likely pathogenic variant in the *DALRD3* gene.

Implications of Results

Presence of variants in the *VARS2* gene in the compound heterozygous state is consistent with a diagnosis of Combined Oxidative Phosphorylation Deficiency 20 (MIM:612802).

The *VARS2* gene encodes one of the mitochondrial aminoacyl-tRNA synthetases (mt-aaRSs) (1).
Only a few patients with *VARS2*-related deficiency have been described in the medical literature, and reported phenotypes are highly variable. Clinical manifestations may appear at any age and demonstrate significant heterogeneity.

Pathogenic variants in *VARS2* are most commonly associated with encephalomyopathy or cardiomyopathy, leading to chronic disability and poor prognosis. Patients with Combined Oxidative Phosphorylation Deficiency 20 may present with

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structural brain abnormalities, hypotonia, psychomotor delay, seizures, feeding difficulties, severe lactic acidosis, hypertrophic cardiomyopathy, and abnormal findings on cranial MRI (2).

Recurrence risk: The parents of the baby have a 25% chance of having another child affected by Combined Oxidative Phosphorylation Deficiency 20, given the high likelihood that they are each carriers of one of the identified variants.

Recommended Action

Genetic counselling is recommended for the family to understand the genetic findings and their implications.

Genomic Findings

Phenotype associated germline variants:	2
Incidental actionable germline variants:	0
Incidental germline variants:	0
Incidental germline variants (carrier status):	2
Copy number/structural variants:	0
Germline variants associated with Hereditary Cancer Syndromes:	0
Mitochondrial DNA variants:	0

Phenotype Associated Germline Variants

Gene/ Transcript/ Variant Type	Variant	Zygosity	Associated Condition/ Inheritance	Classification/ Attributes
VARS2 NM_020442.6 splice acceptor variant	**c.874-2A>G** 6:30917693 Intron 9	Heterozygous	Combined oxidative phosphorylation deficiency 20 Autosomal Recessive	**Pathogenic** Attributes: PVS1, PM1, PM2_P, PM3
VARS2 NM_020442.6 missense variant	**c.1102C>A** p.Pro398Thr 6:30919785 Exon 12	Heterozygous	Combined oxidative phosphorylation deficiency 20 Autosomal Recessive	**Uncertain significance** Attributes: PM2_P, PM3, PP3

Incidental Germline Variants (Carrier Status)

Gene/ Transcript/ Variant Type	Variant	Zygosity	Associated Condition/ Inheritance	Classification/ Attributes
LRRC23 NM_001135217.2 stop gained	**c.376C>T** p.Arg126Ter 12:6906548 rs1289377349 Exon 4	Heterozygous	Spermatogenic failure 92 Autosomal Recessive	**Pathogenic** Attributes: PVS1, PM2_P, PM3_P

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DALRD3 NM_001009996.3 frameshift deletion	**c.1192_1193delAA** p.Lys398Glufs*8 3:49016294 rs1188297461 Exon 9	Heterozygous	Developmental and epileptic encephalopathy 86 Autosomal Recessive	**Likely pathogenic** Attributes: PVS1, PM2_P

Quality Metrics

DNA QC metrics:

Total Reads:	923,734,114	Percentage genome covered (>10x):	94.29%
Average Unique Coverage (Count):	42.63x		

Methodology

Quality Assessment:

The variant classification system used in this report is based on joint consensus recommendations of the American College of Medical Genetics and Association for Molecular Pathology for evaluation of pathogenicity of sequence variants.

Assay method:

The test is performed using a comprehensive whole-genome next-generation sequencing (WGS) approach. Briefly, the extracted nucleic acid from patient blood samples that qualify for quality check is subjected to library preparation using a commercially available kit (Illumina DNA PCR Free Kit) as instructed by the manufacturer (Illumina, Inc.). Libraries that passed the quality check at this stage are normalized, pooled, and sequenced on Illumina Next Generation Sequencing Platform (Illumina NovaSeq X-Plus).

Variant Calling and Annotation:

Alignment, post-processing, and default quality-filtered variant calling were executed on the Illumina DRAGEN Bio-IT platform developed by Illumina Inc., USA. The analysis was facilitated by the 'Dynamic Read Analysis for GENomics' (DRAGEN) v4.2.4 pipeline using the GRCh38 (hg38) human reference genome. Generated VCF files were annotated using VarSeq 2.5.0. Following are the sources and versions of databases used: 1 kg Phase 3, ClinVar 2023-04-06 v2, Golden Helix CancerKb, Genome Asia 100 K variant frequencies, gnomAD Exome variant frequencies 2.1.1 v2, gnomAD Genomes (coding subset) variant frequencies 3.1.2 v2, NHBLBI ESP6500SI-V2-SSA137 exome variant frequencies 0.0.30, RefSeq Genes 110, Sift and polyphen2 missense predictions 2021-04-21.

Variant Assessment:

Variants after annotation were assessed and filtered based on the following criteria- Present in < 1% of the known germline population databases, Read Depth (DP) > 10, Genotype Qualities (GQ) > 20, Variant not reported to be Benign, Likely Benign, Conflicting. The final filtered variants were classified based on the ACMG/AMP guidelines. For SNVs, variants with Read Depth (DP) > 10 were considered.

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Limitations

This report was generated using the materials and methods described above, which required the use of various reagents, protocols, instruments, software, databases, and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases, and/or other items may compromise the quality or accuracy of the Report.

The Report has been created based on or incorporates references to, various scientific manuscripts, references, and other sources of information, including without limitation manuscripts, references, and other sources of information that were prepared by third parties that describe correlations between certain genetic mutations and particular diseases (and/or certain therapeutics that may be useful in ameliorating the effects of such diseases). Such information and correlations are subject to change over time in response to future scientific and medical findings. Genelabs Medical makes no representation or warranty of any kind, expressed or implied, regarding the accuracy of the information provided by or contained in such manuscripts, references, and other sources of information. If any of the information provided by or contained in such manuscripts, references, and other sources is later determined to be inaccurate, the accuracy and quality of the Report may be adversely impacted. Genelabs Medical is not obligated to notify you of any impact that future scientific or medical research findings may have on the Report.

The Report must always be interpreted and considered within the clinical context, and a physician should always consider the Report along with all other pertinent information and data that a physician would prudently consider prior to providing a diagnosis to a patient or developing and implementing a plan of care for a patient. The Report should never be considered or relied upon alone in making any diagnosis or prognosis. The manifestation of many diseases is caused by more than one gene variant, a single gene variant may be relevant to more than one disease, and certain relevant gene variants may not have been considered in the Report. In addition, many diseases are caused or influenced by modifier genes, epigenetic factors, environmental factors, and other variables that are not addressed by the Report (or that are otherwise unknown). This Report is based on a next-generation sequencing assay that does not distinguish between somatic and germline variants. If a germline variant is in question, further testing may be recommended. As such, the relevance of the Report should be interpreted in the context of a patient's clinical manifestations. The Report provided by Genelabs Medical is provided on an "AS IS" basis. Genelabs Medical makes no representation or warranty of any kind, expressed or implied, regarding the Report. In no event shall Genelabs Medical be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the Report, your reliance on the Report, or any defect or inaccurate information included within the Report. Medical knowledge annotation is constantly updated and reflects the current knowledge at the time.

This test is designed currently to identify exclusively the single nucleotide variants (SNVs), multi-nucleotide variants (MNVs), and short insertions and deletions (Indels). The test will not be able to identify copy number variations/gene amplifications, alternately spliced variants, intronic variants, gene fusions, or genomic-level mutations such as microsatellite instability or tumor mutation burden.

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Disclaimer

The tests are carried out in the lab with the presumption that the specimen belongs to the patient named or identified in the bill/test request form.
The test results relate specifically to the sample received in the lab and are presumed to have been generated and transported per specific instructions given by the physicians/laboratory.
The reported results are for information and are subject to confirmation and interpretation by the referring doctor.
Some tests are referred to other laboratories to provide a wider test menu to the customer.
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References

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**** End of Report ****