International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Foetal Brain Malformation Associated with Compound Heterozygous LAMB1 Variants: Case Report of Dandy Walker Syndrome

Priya Singh[1], Astha Pandey[2]

[1,2]Department of Biotechnology, Kanpur Institute of Technology, Rooma, Kanpur-208001(U.P.) India.

Abstract

Dandy Walker malformation (DWM) is a complex malformation involving the posterior fossa and cerebellum. Aim of this study represents chronic disorder DWM, is a rare condition with an estimated incidence of 1 in 350,000 live births in the united state. Hydrocephaly, a common finding, is seen in approximately 80% of cases. DWM is present in 4% to 12% of cases of hydrocephaly in infants. DWS is more frequent cerebral malformation where hypoplasia and upward rotation of the vermis cerebelli, occipital encephalocele a cystic enlargement of fourth ventricle and in total enlarged posterior fossa. *LAMB1* mutations are linked to lissencephaly 5 a severe neurodevelopmental defects and congenital brain defects. In Whole-exome sequencing we identified two likely compound heterozygous variants of *LAMB1* gene that are c.5225-8_5230del location intron 33-exon 34 and c.1364G>A; (p. Cys455Tyr) location exon 11, both classified as VUS but predicted to be detrimental. The phenotype overlaps with known *LAMB1*-related malformations, suggesting a potential pathogenic association. This case emphasizes the utility of prenatal WES and expands the clinical spectrum of *LAMB1* variants. It this report a foetus with severe posterior fossa malformations, including cerebellar vermis hypoplasia, enlarged cisterna magna, and a small occipital encephalocele detected on prenatal ultrasound.

Keywords: Dandy Walker Malformation, Whole-Exome Sequencing (WES), LAMB1 Gene.

Introduction

Congenital brain malformations constitute a heterogeneous group of structural abnormalities, which present at birth that can cause many developmental disruptions, hypoplasia enlarged cisterna magna at various embryonic or foetal stages.[1] Dandy Walker malformation (DWM) is a complex cerebral malformation involving the posterior fossa and cerebellum that cause various anomalies that are, hydrocephalus, and encephalocele, upward rotation of the vermis cerebelli, enlargement of fourth ventricle. It is a rare condition with an estimated incidence of 1 in 350,000 in united state Hydrocephaly, a common finding, is seen in approximately 80% of cases. DWM is present in 4% to 12% of cases of hydrocephaly in infants.[2] Diagnosis of DWM to those malformations with all of the following features: 1) a large median posterior fossa cyst widely communicating with the fourth ventricle, 2) a small, rotated, raised cerebellar vermis, 3) an upwardly displaced tentorium, 4) an enlarged posterior fossa, 5) antero-laterally displaced but apparently normal cerebellar hemispheres, 6) a normal brain stem. If any one of above mention criteria were not found, the malformation was considered distinct from Dandy-walker syndrome. Recent advances in prenatal imaging and next-generation sequencing, Whole exome or

genomic sequencing have improved diagnostic accuracy and enabled early identification of genetic variants contributing to developmental brain disorders.[3]

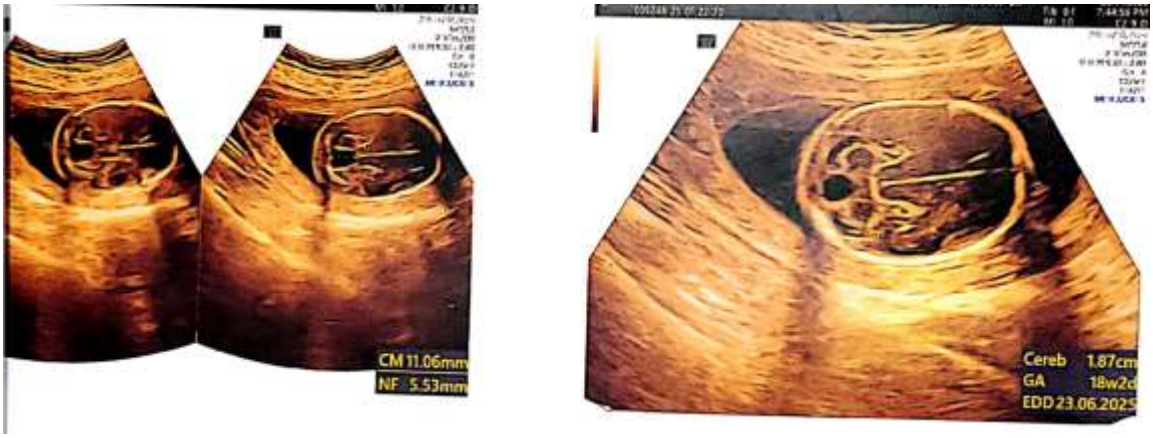
This case documents a foetal case where we analysed severe posterior fossa malformations and compound heterozygous *LAMB1* variants detected via Whole exome sequencing. Through comparison with previously published cases, the report aims to provide insights into the potential pathogenic role of these variants and contribute to the growing spectrum of *LAMB1*-related neurodevelopmental disorders.

Case Presentation

A 23 years old woman married non-consanguineously. Her first pregnancy antenatal scan showed vermian hypoplasia, enlarged cisterna magna (DW variant/malformation), mild coarse facies, prominent eyebrows, low set ears, high arched palate. Her second pregnancy antenatal USG level 2 scan (19 weeks 6 days+/- 1 week 3 days) showed occipital encephalocele(small), vermian hypoplasia, laterally bilateral nuchal thickness, mild bilateral clinodactyly, high arched palate, bilateral very low set ears. L2 showed small occipital encephalocele, dysplastic cerebellar vermis with mega cisterna magna (suggestive of dandy walker malformation). L2 showed enlarged cisterna magna measures “11.2 mm” with complete aplasia of vermis and trapezoid shaped GAP between the cerebellar hemi-spheres features (suggestive of dandy walker malformation)[Figure-1] Product of conception (POC) of woman is suspected to be affected with Ciliopathy or Cortical malformation defect, or Walker Warburg syndrome and has been evaluated for pathogenic gene variations.[14] In simple terms, presented for evaluation following abnormal findings detected in their first pregnancy first trimester ultrasound there was underdeveloped region seen in the ultrasound images of the foetus and that underdeveloped region continues to the second trimester ultrasound there is no development seen in the region so they go for termination of fetus. In their second pregnancy the same underdeveloped region was seen in first trimester and in routine second-trimester prenatal ultrasound. So they go for the genetic testing for the foetus and they demonstrated significant posterior fossa abnormalities, including cerebellar vermis hypoplasia, an enlarged cisterna magna measuring “11.2 mm”, and a small occipital encephalocele. There is report from a pregnancy where ultrasound scans showed serious brain and facial abnormalities in the foetus:

- Vermian hypoplasia: part of the cerebellum (brain) was underdeveloped.
- Enlarged cisterna magna and encephalocele: fluid-filled space and brain tissue bulging out at the back of the head.
- Facial and ear abnormalities, clinodactyly (curved fingers), and high-arched palate.

Figure-1: Ultrasound Scan Of 19th Week Pregnancy.[14]



The overall sensitivity rate of detection of congenital anomalies by USG approx 60%. Small well defined septated cystic lesion arising from a SK defect in occipital region s/o small occipital encephalocoele. Dysplastic cerebellar vermis with mega cisterna magna likely Dandy Walker Malformation. [Figure-1]

Genetic Findings

After evaluation, likely compound heterozygous variants of uncertain significance related to the given phenotype were detected [Table-1,2]. Genetic test results are reported based on the recommendations of American College of Medical Genetics and Genomics. [5,6,7]

Two rare changes in ***LAMB1*** were found.

Table-1: Description Of *LAMB1* Gene.[14]

Gene (Transcript)	Location	Variant	Zygosity	Disease	Inheritance	Classification
LAMB1 **(-) (ENST00000222399.11)**	Intron 33-Exon 34	c.5225-8_5230del	Likely compound Heterozygous	Lissencephaly 5 (OMIM#61519	Autosomal recessive	Uncertain Significance (PM2)
	Exon 11	c.1364G>A (p.Cys455Tyr)				Uncertain Significance (PM2, PP3)

Table-2: Description Of *LAMB1* Gene Variants

Gene	Change (Technical name)	Type	Meaning
LAMB1	c.5225-8_5230del	Deletion in intron-exon region	May affect how the gene is read or spliced
LAMB1	c.1364G>A (p.Cys455Tyr)	Missense mutation	Changes one amino acid (Cysteine → Tyrosine) in the protein

- The ***LAMB1*** **gene** helps form *laminin*, a protein important for building brain structure.
- Defects in this gene are known to cause **Lissencephaly-5 (LIS5)** — a severe brain formation disorder where the brain surface looks smooth and may lead to:[(4)]
  - Hydrocephalus (fluid buildup)
  - Seizures
  - Developmental delay

The features seen in the foetus (like brain malformation and encephalocele).

The *LAMB1* gene, located on chromosome 7q31.1, laminin is a family of extracellular matrix glycoprotein are the major no collagenous constitute of basement membrane that encodes laminin β1, a key component of the laminin heterotrimeric complex involved in basement membrane formation. Laminins are essential for maintaining extracellular matrix integrity, neuronal migration, radial glial scaffolding, and proper cortical layering during brain development. [12,13]

Lissencephaly 5 is caused by homozygous or compound heterozygous mutations in the LAMB1 gene. Lissencephaly-5 (LIS5) is an autosomal recessive brain malformation characterized by cobblestone

changes in the cortex, more severe in the posterior region, and subcortical band heterotopia. Affected individuals have hydrocephalus, seizures, and severely delayed psychomotor development.[4]

Variant Interpretation

Variant description: A likely compound heterozygous variant was detected in the LAMB1 gene.

Variant 1: A heterozygous 14 base pair deletion in intron 33-exon 34 boundary of the LAMB1 gene (chr7:g.107924082_107924095del; c.5225-8_5230del; ENST00000222399.11; Depth: 63x) was detected. This variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1), topmed and our internal databases. The reference region is conserved across species.

Variant 2: A heterozygous missense variant in exon 11 of the LAMB1 gene (chr7:g.107975239C>T; Depth: 79x) that results in the amino acid substitution of Tyrosine for Cysteine at codon 455 (p.Cys455Tyr; ENST00000222399.11) was detected. The observed variant lies in the 'Laminin EGF domain' domain of the LAMB1 protein (PF00053). The p. Cys455Tyr variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1) and topmed databases and has a minor allele frequency of 0.00060% in our internal database. The in-silico predictions of the variant are probably damaging by PolyPhen-2 and damaging by SIFT and MutationTaster2. The reference codon is conserved across species.

Test Methodology

Targeted gene sequencing: Selective capture and sequencing of the protein coding regions and clinically relevant in the genome is performed. Variants identified in the exonic regions and splice-site are generally actionable compared to variants that occur in non-coding regions. Targeted sequencing represents a cost-effective approach to detect variants present in multiple/large genes in an individual.

DNA extracted from blood was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean depth of >80-100X on Illumina sequencing platform. We follow the GATK best practices framework for identification of germline variants in the sample using sentieon. The sequences obtained are aligned to human reference genome (GRCh38) using BWA aligner and analyzed using sentieon for removing duplicates, recalibration and re-alignment of indels. Sentieon haplotype caller is then used to identify variants in the sample. The germline variants identified in the sample is deeply annotated using VariMAT pipeline. Gene annotation of the variants is performed using VEP program[9] against the Ensemble release 104 human gene model. In addition to SNVs and small Indels, copy number variants (CNVs) are detected from targeted sequence data using the Exome Depth method.[10] This algorithm detects CNVs based on comparison of the read-depths in the sample of interest with the matched aggregate reference dataset. Clinically relevant mutations in both coding and non-coding regions are annotated using published variants in literature and a set of diseases databases: ClinVar, OMIM, HGMD, LOVD, DECIPHER (population CNV) and SwissVar. Common variants are filtered based on allele frequency in 1000Genome Phase 3, gnomAD (v3.1 & 2.1.1), dbSNP (GCF_000001405.38), 1000 Japanese Genome, TOPMed (Freeze_8), Genome Asia, and our internal Indian population database (MedVarDb v4.0).[11, 14]

This is a laboratory developed test and the development and the performance characteristics of this test was determined by MedGenome.[14]

References

1. Bimal P. Chaudhari, Mai-Lan Ho, Congenital Brain Malformations: An Integrated Diagnostic Appro-

ach, Seminars in Pediatric Neurology, Volume 42,2022,100973,ISSN 1071-9091, https://doi.org/10.1016/j.spen.2022.100973. (https://www.sciencedirect.com/science/article/pii/S1071909122000213)

2. Reith W, Haussmann A. Dandy-Walker-Malformation [Dandy-Walker malformation]. Radiologe. 2018 Jul;58(7):629-635. German. doi: 10.1007/s00117-018-0403-7. PMID: 29797040.
3. Klein O, Pierre-Kahn A, Boddaert N, Parisot D, Brunelle F. Dandy-Walker malformation: prenatal diagnosis and prognosis. Childs Nerv Syst. 2003 Aug;19(7-8):484-9. doi: 10.1007/s00381-003-0782-5. Epub 2003 Jul 16. PMID: 12879343.
4. Amberger J, Bocchini CA, Scott AF, Hamosh A. McKusick's Online Mendelian Inheritance in Man (OMIM). Nucleic Acids Res. 2009 Jan;37(Database issue):D793-6. doi: 10.1093/nar/gkn665. Epub 2008 Oct 8. PMID: 18842627; PMCID: PMC2686440.
5. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID: 25741868; PMCID: PMC4544753.
6. Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, Raca G, Ritter DI, South ST, Thorland EC, Pineda-Alvarez D, Aradhya S, Martin CL. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med. 2020 Feb;22(2):245-257. doi: 10.1038/s41436-019-0686-8. Epub 2019 Nov 6. Erratum in: Genet Med. 2021 Nov;23(11):2230. doi: 10.1038/s41436-021-01150-9. PMID: 31690835; PMCID: PMC7313390.
7. McCormick EM, Lott MT, Dulik MC, Shen L, Attimonelli M, Vitale O, Karaa A, Bai R, Pineda-Alvarez DE, Singh LN, Stanley CM, Wong S, Bhardwaj A, Merkurjev D, Mao R, Sondheimer N, Zhang S, Procaccio V, Wallace DC, Gai X, Falk MJ. Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. Hum Mutat. 2020 Dec;41(12):2028-2057. doi: 10.1002/humu.24107. Epub 2020 Nov 10. PMID: 32906214; PMCID: PMC7717623.
8. Li H, Durbin R. Fast and accurate long-read alignment with Burrows-Wheeler transform. Bioinformatics. 2010 Mar 1;26(5):589-95. doi: 10.1093/bioinformatics/btp698. Epub 2010 Jan 15. PMID: 20080505; PMCID: PMC2828108.
9. Cunningham F, Allen JE, Allen J, Alvarez-Jarreta J, Amode MR, Armean IM, Austine-Orimoloye O, Azov AG, Barnes I, Bennett R, Berry A, Bhai J, Bignell A, Billis K, Boddu S, Brooks L, Charkhchi M, Cummins C, Da Rin Fioretto L, Davidson C, Dodiya K, Donaldson S, El Houdaigui B, El Naboulsi T, Fatima R, Giron CG, Genez T, Martinez JG, Guijarro-Clarke C, Gymer A, Hardy M, Hollis Z, Hourlier T, Hunt T, Juettemann T, Kaikala V, Kay M, Lavidas I, Le T, Lemos D, Marugán JC, Mohanan S, Mushtaq A, Naven M, Ogeh DN, Parker A, Parton A, Perry M, Piližota I, Prosovetskaia I, Sakthivel MP, Salam AIA, Schmitt BM, Schuilenburg H, Sheppard D, Pérez-Silva JG, Stark W, Steed E, Sutinen K, Sukumaran R, Sumathipala D, Suner MM, Szpak M, Thormann A, Tricomi FF, Urbina-Gómez D, Veidenberg A, Walsh TA, Walts B, Willhoft N, Winterbottom A, Wass E, Chakiachvili M, Flint B, Frankish A, Giorgetti S, Haggerty L, Hunt SE, IIsley GR, Loveland JE, Martin FJ, Moore B, Mudge JM, Muffato M, Perry E, Ruffier M, Tate J, Thybert D, Trevanion SJ, Dyer S, Harrison PW, Howe KL,

Yates AD, Zerbino DR, Flicek P. Ensembl 2022. Nucleic Acids Res. 2022 Jan 7;50(D1):D988-D995. doi: 10.1093/nar/gkab1049. PMID: 34791404; PMCID: PMC8728283.

10. Plagnol V, Curtis J, Epstein M, Mok KY, Stebbings E, Grigoriadou S, Wood NW, Hambleton S, Burns SO, Thrasher AJ, Kumararatne D, Doffinger R, Nejentsev S. A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. Bioinformatics. 2012 Nov 1;28(21):2747-54. doi: 10.1093/bioinformatics/bts526. Epub 2012 Aug 31. PMID: 22942019; PMCID: PMC3476336.
11. 1000 Genomes Project Consortium; Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR. A global reference for human genetic variation. Nature. 2015 Oct 1;526(7571):68-74. doi: 10.1038/nature15393. PMID: 26432245; PMCID: PMC4750478.
12. Rei Yasuda, Hirokazu Hashimoto, Mikiko Oka, Jung-Wan Mok, Marium Waqar, Brigitte Dauwalder, Oguz Kanca, Toshiki Mizuno, Shinya Yamamoto, Functional analysis of pathogenic variants in LAMB1 -related leukoencephalopathy reveals genotype–phenotype correlations and suggests its role in glial cells , Human Molecular Genetics, **34**, 11, (990-999), (2025).https://doi.org/10.1093/hmg/ddaf050
13. Sen, K., Kaur, S., Stockton, D. W., Nyhuis, M., & Roberson, J. (2021). Biallelic variants in LAMB1 causing hydranencephaly: a severe phenotype of a rare malformative encephalopathy. *American Journal of Perinatology Reports*, *11*(01), e26-e28.
14. MedGenome Labs Ltd, DNA TEST REPORT, 2025, MEDGENOME LABS- Order ID/Sample ID: 1187142/8945532.