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CASE REPORT

Clinical exome sequencing (carrier screening) identifies the gene *INPPL1* in a sporadic case of opsismodysplasia

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ABSTRACT

Introduction and aim. This study presents a case of opsismodysplasia in a family, characterized by skeletal dysplasia and neurological complications in two consecutive neonates.

Description of the case. Genetic analysis revealed that the father carries a likely benign/variant of uncertain significance (VUS) in exon 14 of the *INPPL1* gene (c.1706C>T, p.Thr569Met), while the mother carries a pathogenic variant in exon 15 (c.1809del, p.Trp604GlyfsTer17). These variants follow an autosomal recessive inheritance, confirming carrier status. Additionally, the father is a carrier of a likely pathogenic variant in the *CYP17A1* gene (OMIM*609300), specifically in exon 6 (c.1040G>A, p.Arg347His, heterozygous), affecting 17,20-lyase activity and associated with isolated 17,20-lyase deficiency. Targeted sequencing and Sanger validation elucidated the genetic basis of the condition, emphasizing the importance of genetic testing and counselling in families with a history of genetic disorders. The detected variants in the INPPL1 gene disrupt SHIP2 protein function, contributing to the observed abnormalities.

Conclusion. This study underscores the significance of early genetic diagnosis for reproductive counselling and timely intervention. Further research into opsismodysplasia's genetic mechanisms may lead to improved management and therapies for affected individuals. Overall, this case highlights the critical role of genetic analysis in diagnosing and managing rare genetic disorders, offering insights into personalized care and family planning.

Keywords. exome sequencing, *INPPL1* gene, opsismodysplasia, rare skeletal dysplasia

Introduction

Recurrent pregnancies resulting in offspring with congenital anomalies pose significant clinical challenges and necessitate thorough investigation to elucidate the underlying etiology.[1] We present a case of two consecutive pregnancies with offspring exhibiting similar skeletal deformities and neurological anomalies, despite uneventful antenatal periods and negative prenatal screenings.[2]

Opsismodysplasia (OMIM#258480) is a rare genetic disorder characterized by severe skeletal abnormalities and distinct facial features. It is primarily caused by homozygous or compound heterozygous mutations in the inositol polyphosphate phosphatase like 1 (*INPPL1*) gene (OMIM*600829) located on chromosome 11q13.[3] First described by Zonana et al. in 1977 and later designated under its current name by Maroteaux in 1984, opsismodysplasia presents a complex array of clinical manifestations, posing significant challenges to affected individuals and their caregivers.[4] Individuals with opsismodysplasia often exhibit facial dysmorphism, in-

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cluding microcephaly, delayed ossification, a prominent brow, enlarged fontanels, and flattened vertebrae. Additionally, they may display distinct craniofacial features such as a depressed nasal bridge, diminutive nose, forward-facing nasal openings (anteverted nares), elongated philtrum, and increased distance between the eyes (hypertelorism), accompanied by protruding eyes (exophthalmos). These facial characteristics contribute to the clinical diagnosis of opsismodysplasia.[5]

Beyond facial features, individuals with opsismodysplasia typically present with skeletal abnormalities such as rhizomelic micromelia, characterized by extremely short long bones, as well as abbreviated hands and feet. Other skeletal manifestations include slender thorax, profound platyspondyly, and delayed bone maturation, often leading to significant functional impairment. Respiratory infections are a common concern, with fatalities resulting from respiratory failure documented within the initial years of life. However, extended survival has also been reported, underscoring the variable clinical course of the disorder.

Radiographic examinations play a crucial role in the diagnosis of Opsismodysplasia, revealing characteristic skeletal abnormalities such as abbreviated long bones, delayed epiphyseal ossification, pronounced platyspondyly, and metaphyseal cupping. Additionally, distinctive abnormalities in the metacarpals and phalanges are often observed, further aiding in the clinical assessment of affected individuals.

The recurrence of similar congenital anomalies in two consecutive pregnancies despite negative prenatal screenings underscores the complexity of this case. The absence of identifiable genetic or environmental factors highlights the limitations of current diagnostic modalities in elucidating rare and multifactorial conditions. The presence of periventricular leukomalacia in the first child and underdeveloped gyration with corpus callosum aplasia in the second child suggests a potential neurological basis for the observed anomalies.

Aim

This study presents a case of opsismodysplasia in a family, characterized by skeletal dysplasia and neurological complications in two consecutive neonates.

Description of the case

A detailed family history was taken to identify patterns of inheritance and assess the likelihood of the disorder being passed on. However, the family's medical history did not reveal any notable anomalies. The first child, a female born in April 2015 via Lower Segment Cesarean Section (LSCS) in PrayagRaj, Uttar Pradesh, India, presented with global developmental delay, microcephaly, tented upper lip, cortical thumbs, bilateral congenital talipes equinovarus, overlapping fingers, retrognathia, hypotonia, and respiratory difficulties. Imaging studies revealed periventricular leukomalacia on MRI, indicative of cerebral white matter injury. Despite extensive investigations including karyotyping, biochemical assays, and TORCH screenings, the underlying cause remained elusive. Tragically, the child succumbed to complications after 35 days of life.

The second child, a male born in 2023, exhibited similar skeletal deformities including acyanotic heart disease with an atrial septal defect (ASD) of 3.5 mm. Imaging studies revealed a small brain with underdeveloped gyration and corpus callosum aplasia on MRI, consistent with neurological abnormalities observed in the first child. Despite negative prenatal screenings and unremarkable antenatal evaluations, the child experienced respiratory difficulties and passed away after 30 days of life.

Investigations

Extensive investigations were conducted for both children, encompassing karyotyping, biochemical assays including complete blood count, renal and liver function tests, erythrocyte sedimentation rate, ultrasound imaging, and TORCH screenings. Additionally, imaging studies including X-rays and MRI were performed to assess skeletal and neurological abnormalities.

An Indian family presenting with a clinical diagnosis of Opsismodysplasia was enrolled in this Case study, comprising parents and affected siblings. Ethical approval was obtained from the Institutional Ethical Committee at Banaras Hindu University. The research methodology involved targeted sequencing, specifically capturing and sequencing the protein-coding regions of the genome or genes. This approach enhances the identification of mutations within exonic regions, which are typically more clinically actionable compared to variations in non-coding regions.

Sample collection and DNA extraction

Blood samples were collected from the family members (parents), and genomic DNA was extracted using Pure Link Genomic DNA mini-Kit (Cat No. K1820-01) standard protocols. The DNA samples were isolated for targeted gene capture using a custom capture kit.

Sequencing and data analysis

Sequencing of the captured libraries was performed on the NextSeq 1000 and 2000 Systems Illumina platform, achieving a mean coverage of >80-100X. The obtained sequences were aligned to the human reference genome (GRCh37/hg19) using the BWA program and analyzed using Picard and GATK version 3.6 to identify variants relevant to the clinical indication.[6,7]

Variant annotation and filtering

Gene annotation of the identified variants was conducted using the VEP program (Version 102.0) against the En-

sembl release 87 human gene model. Clinically relevant mutations were annotated using published variants in literature and databases such as ClinVar, OMIM, GWAS, HGMD, and SwissVar. Common variants were filtered based on allele frequency in population databases including 1000 Genome Phase 3, ExAC, EVS, dbSNP147, 1000, an internal Indian population database. Genetic variations that are present in a significant proportion of the general population, usually with a minor allele frequency (MAF) above a certain threshold (e.g., >1%).[8,9]

Variant interpretation

Non-synonymous and splice site variants found in the clinical exome panel consisting of 8332 genes were utilized for clinical interpretation. Silent variations that did not result in any change in amino acid in the coding region were not reported. The effect of non-synonymous variants was assessed using multiple algorithms such as PolyPhen-2, SIFT, Mutation Taster2, Mutation Assessor, and LRT.[9-12]

Validation and clinical interpretation

Validation of identified variants by Sanger sequencing 3500 Series Genetic Analyzers with BigDye™ Terminator v3.1, was recommended to rule out false positives. It was advised to sequence the variants in both affected and unaffected family members to validate their significance (Tables 1 and 2). Genetic counseling was also recommended for further guidance and interpretation of the genetic findings.[13,14]

Table 1. Sanger sequencing analysis results for father's *INPPL1* gene

Gene name	*INPPL1* (Exon 15)
Variation detected in NGS	chr11:71943374C>T (HET); c.1706C>T; p.Thr569Met
Sanger validation result	Present (Heterozygous)

In the Table 1, the Sanger sequencing analysis results for the father's INPPL1 gene are provided. The detected variation corresponds to a substitution of cytosine with thymine at nucleotide position 1706 in exon 15 of the INPPL1 gene, resulting in the amino acid change from threonine to methionine at codon 569 (p.Thr569Met). The Sanger validation confirms the presence of this variant in a heterozygous state.

Table 2. Sanger sequencing analysis results for mother's *INPPL1* gene

Gene name	*INPPL1* (Exon 15)
Variation detected in NGS	chr11:71943766delC (HET); c.1809del; p.Trp604GlyfsTer17
Sanger validation result	Present (Heterozygous)

In the Table 2, the Sanger sequencing analysis results for the mother's INPPL1 gene are outlined. The detected variation corresponds to a deletion at nucleotide position 1809 in exon 15 of the INPPL1 gene, resulting in a frameshift mutation leading to the substitution of tryptophan at codon 604 with glycine and a premature termination codon (p.Trp604GlyfsTer17). The Sanger validation confirms the presence of this variant in a heterozygous state.

NGS result and variant confirmation

NGS analysis identified a heterozygous missense variation in exon 14 of the INPPL1 gene (chr11:71943374C>T), resulting in the amino acid substitution of Methionine for Threonine at codon 569 (p.Thr569Met; ENST00000298229, Table 3). The variant lies in the catalytic domain of the SHIP2 protein, and missense mutations in this domain have been reported to inactivate the phosphatase function of the protein. This variant was detected in the father of the patient. Based on the evidence, this INPPL1 variation was classified as a likely benign variant, warranting correlation with the clinical symptoms Figures 1 and 2.[15]

Table 3. Pathogenic variant identified in the mother and likely benign/VUS variant in father of the patient are presented, the patient's father carries a likely benign/VUS variant in exon 14 (c.1706C>T, p.Thr569Met), while the patient's mother carries a pathogenic variant in exon 15 (c.1809del, p.Trp604GlyfsTer17), these variants follow an autosomal recessive mode of inheritance

Disease	Patient's father	Patient's mother
Opsismodysplasia (OMIM#258480)	Carrier	Carrier
	Mode of Inheritance: AR	Mode of Inheritance: AR
	Gene: *INPPL1* (OMIM*600829)	Gene: *INPPL1* (OMIM*600829)
	Exon 14, c.1706C>T, p.Thr569Met	Exon 15, c.1809del, p.Trp604GlyfsTer17
	Classification: likely benign	Classification: pathogenic
Isolated 17,20-lyase deficiency (OMIM#202110), 17-alpha-hydroxylase/17,20-lyase deficiency (OMIM#202110) Mode of inheritance: AR	Carrier Gene: *CYP17A1* (OMIM*609300) Exon 6, c.1040G>A, p.Arg347His, Heterozygous Classification: likely pathogenic	Non-carrier

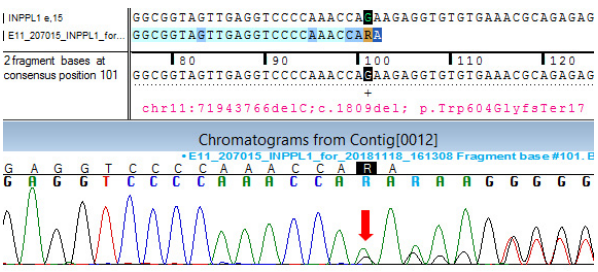

Fig. 1. The figure depicts the sequence chromatogram and alignment illustrating the observed variation in exon 15 of the *INPPL1* gene (chr11:71943766delC; c.1809del; p.Trp604GlyfsTer17), the variation is identified in a heterozygous state in the mother

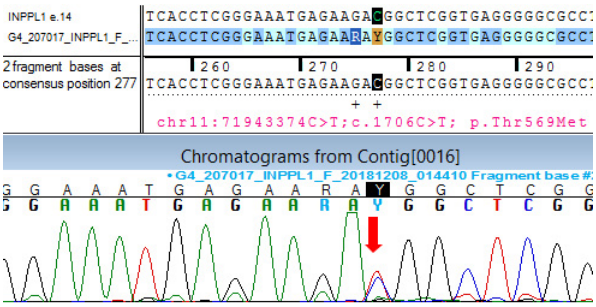

Fig. 2. The figure displays the sequence chromatogram and alignment, highlighting the variation identified in exon 14 of the *INPPL1* gene (chr11:71943374C>T; c.1706C>T; p.Thr569Met), this variation was detected in a heterozygous condition in the father of the patient

ACMG classification of p.Trp604GlyfsTer17 mutation

The p.Trp604GlyfsTer17 mutation identified in exon 15 of the INPPL1 gene is classified as likely pathogenic according to ACMG guidelines. This classification is supported by strong evidence including the presence of a frameshift resulting in a premature termination codon (PVS1), absence from control populations (PM2), and multiple lines of computational evidence supporting a deleterious effect (PP3, PM4, Table 4).

Table 4. Variant interpretation based on prediction tools and ACMG classification

Variant	Prediction tools SIFTa mutation taster (pathogenicity)	ClinVar	ACMG classification
c.1706C>T (p.Thr569Met) in INPPL1 exon 14	Likely benign	Likely benign	Variant of uncertain significance (VUS)
c.1809del (p.Trp604GlyfsTer17) in INPPL1 exon 15	Pathogenic	Pathogenic	PVS1, PM2, PP3, PM4

c.1706C>T (p.Thr569Met) in INPPL1 exon 14: ClinVar support the Likely Benign pathogenicity of the c.1706C>T (p.Thr569Met) variant, and it is classified as likely benign in the Leiden Open Mutation Database. Multiple in-silico analysis tools, such as SIFT (Sorting Intolerant From Tolerant) and Mutation Taster, support a likely benign or VUS classification, indicating that ACMG PP3 is not met. While the PM2 criterion is fulfilled due to the variant's extreme rarity (GMAF=0.00060), the PM1 criterion is not applicable as there is no evidence of a mutational hotspot.

c.1809del (p.Trp604GlyfsTer17) in INPPL1 exon 15: Predicted as pathogenic by various tools and supported by ClinVar. ACMG classification includes PVS1 (null variant in a gene where loss of function is a known mechanism of disease), PM2 (absent from controls), PP3 (multiple lines of computational evidence), and PM4 (protein length changes due to frameshift).

Discussion

The presented case involves a family with two consecutive neonates affected by Opsismodysplasia, a rare genetic disorder characterized by skeletal dysplasia and neurological complications. Genetic analysis revealed that the patient's father carries a likely benign/variant of uncertain significance (VUS) in exon 14 of the *INPPL1* gene (c.1706C>T, p.Thr569Met), while the patient's mother carries a pathogenic variant in exon 15 of the *INPPL1* gene (c.1809del, p.Trp604GlyfsTer17). These variants follow an autosomal recessive mode of inheritance, confirming the parents' carrier status for this condition and this variant requires further confirmation due to its unclear classification.

Additionally, the father was found to be a carrier of a likely pathogenic variant in the *CYP17A1* gene (OMIM*609300), specifically in exon 6 (c.1040G>A, p.Arg347His, heterozygous), which affects 17,20-lyase activity. Isolated 17,20-lyase deficiency is primarily associated with mutations in the *CYP17A1* gene, which encodes for the enzyme cytochrome P450 17α-hydroxylase/17,20-lyase. This enzyme plays a crucial role in steroid hormone biosynthesis, specifically in the production of glucocorticoids and sex steroids. The identification of pathogenic variants to clinically significant variants and subsequent validation by Sanger sequencing provides valuable insights into the genetic basis of opsismodysplasia in this family. The variants detected in the *INPPL1* gene, particularly in exon 14 and exon 15, are known to disrupt the function of the SHIP2 protein, leading to the characteristic skeletal and neurological abnormalities observed in opsismodysplasia.[17-22]

The detection of these variants underscores the importance of genetic testing and counselling in families with a history of genetic disorders.[18] By identifying carrier status in parents, healthcare providers can offer informed reproductive counselling to mitigate the risk of passing on genetic conditions to future offspring. Additionally, early detection of genetic disorders allows for timely intervention and management strategies to improve patient outcomes.[19,20]

Conclusion

In conclusion, the genetic analysis of this family with opsismodysplasia revealed likely pathogenic variants in the *INPPL1* gene, confirming carrier status in both parents. The identification of these variants highlights the role of targeted sequencing and Sanger validation in diagnosing rare genetic disorders and providing valuable genetic counselling to affected families. Moving forward, further research into the genetic mechanisms underlying Opsismodysplasia may lead to the development of targeted therapies and improved management strategies for affected individuals.

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Declarations

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The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

Author contributions

Conceptualization, S.R. and R.S.; Methodology, A.A. And S.M.; Software, A.A. And S.M.; Validation, R.S., S.R. and A.A.; Formal Analysis, R.S.; Investigation, S.R.; Resources, R.S.; Data Curation, S.M.; Writing – Original Draft Preparation, A.A.; Writing – Review & Editing, R.S., S.R. and A.A.; S.M.; Visualization, S.R.; Supervision, R.S.; Project Administration, R.S.; Funding Acquisition, S.R.

Conflicts of interest

There are no conflicts of interest.

Data availability

The detailed datasets analyzed during the current study are available with the corresponding author. In the future, it will be made available on reasonable request. Data are however available from the authors upon reasonable request.

Ethics approval

The studies involving human participants were reviewed and approved by the Ethics Committee of the Institutional Ethical committee before starting the study (No. Dean/2022/EC/3827).

References

1. Krakow D, Vriens J, Camacho N, et al. Mutations in the gene encoding the calcium-permeable ion channel TRPV4 produce spondylometaphyseal dysplasia, Kozlowski type and metatropic dysplasia. *Am J Hum Genet*. 2009;84(3):307-315. doi: 10.1016/j.ajhg.2009.01.021
2. Robertson SP, Twigg SR, Sutherland-Smith AJ, et al. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. *Nat Genet*. 2003;33(4):487-491. doi: 10.1038/ng1119
3. Stenson PD, Mort M, Ball EV, et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. *Hum Genet*. 2017;136(6):665-677. doi: 10.1007/s00439-017-1779-6
4. Scott RM. Opsismodysplasia: Another lethal skeletal dysplasia among the bent bone dysplasias. *Am J Med Genet Part A*. 2004;126A(1):33-36.
5. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics*. 2009;25(14):1754-1760. doi: 10.1093/bioinformatics/btp324
6. McKenna A, Hanna M, Banks E, et al. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res*. 2010;20(9):1297-1303. doi: 10.1101/gr.107524.110
7. Picard. Broad Institute. http://broadinstitute.github.io/picard/. Accessed July 20, 2024.
8. Van der Auwera GA, Carneiro MO, Hartl C, et al. From FastQ data to high confidence variant calls: the Genome Analysis Toolkit best practices pipeline. *Curr Protoc Bioinformatics*. 2013;43(1110):11.10.1-11.10.33. doi: 10.1002/0471250953.bi1110s43
9. MacArthur J, Bowler E, Cerezo M, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res*. 2017;45(D1):D896-D901. doi: 10.1093/nar/gkw1133
10. McLaren W, Pritchard B, Rios D, Chen Y, Flicek P, Cunningham F. Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor. *Bioinformatics*. 2010;26(16):2069-2070. doi: 10.1093/bioinformatics/btq330
11. Yates AD, Achuthan P, Akanni W, et al. Ensembl 2020. *Nucleic Acids Res*. 2020;48(D1):D682-D688. doi: 10.1093/nar/gkz966
12. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*. 2018;46(D1):D1062-D1067. doi: 10.1093/nar/gkx1153
13. Amberger JS, Bocchini CA, Schiettecatte F, Scott AF, Hamosh A. OMIM.org: Online Mendelian Inheritance in Man (OMIM®), an online catalog of human genes and genetic disorders. *Nucleic Acids Res*. 2015;43(Database issue):D789-D798. doi: 10.1093/nar/gku1205
14. Landrum MJ, Lee JM, Benson M, et al. ClinVar: public archive of interpretations of clinically relevant variants. *Nucleic Acids Res*. 2016;44(D1):D862-D868. doi: 10.1093/nar/gkv1222
15. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536(7616):285-291. doi: 10.1038/nature19057
16. Okada Y, Momozawa Y, Sakaue S, et al. Deep whole-genome sequencing reveals recent selection signatures linked to evolution and disease risk of Japanese. *Nat Commun*. 2018;9(1):1631. doi: 10.1038/s41467-018-03274-0
17. Nagasaki M, Yasuda J, Katsuoka F, et al. Rare variant discovery by deep whole-genome sequencing of 1,070 Japa-

nese individuals. *Nat Commun*. 2015;6:8018. doi: 10.1038/ncomms9018

18. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods*. 2010;7(4):248-249. doi: 10.1038/nmeth0410-248
19. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc*. 2009;4(7):1073-1081. doi: 10.1038/nprot.2009.86
20. Schwarz JM, Rödelsperger C, Schuelke M, Seelow D. MutationTaster evaluates disease-causing potential of sequence alterations. *Nat Methods*. 2010;7(8):575-576. doi: 10.1038/nmeth0810-575
21. Reva B, Antipin Y, Sander C. Predicting the functional impact of protein mutations: application to cancer genomics. *Nucleic Acids Res*. 2011;39(17):e118. doi: 10.1093/nar/gkr407
22. Greenblatt MS, Brody LC, Foulkes WD, et al. Locus-specific databases and recommendations to strengthen their contribution to the classification of variants in cancer susceptibility genes. *Hum Mutat*. 2008;29(11):1273-1281. doi: 10.1002/humu.20889