BACKGROUND

Opsismodysplasia is an autosomal recessive osteochondrodysplasia disorder characterized by a severe delay in bone maturation. This leads to rhizomelic micromelia with small hands and feet, relative macrocephaly, and craniofacial dysmorphism including frontal bossing, short nose with anteverted nares and depressed nasal bridge, long philtrum, and abnormal ears. Typical radiological signs include very delayed appearance of ossification centers, severe platyspondyly, and short tubular bones with flared metaphyses.

Since the first case description by Zonana et al in 1977, diagnosis of opsismodysplasia was based on clinical features, radiological findings, and histology.\(^1\)\(^{-13}\) In 2013, the *INPPL1* (inositol polyphosphate phosphatase-like 1) gene encoding the SHIP2 protein (for src homology 2 domain-containing inositol phosphatase 2) was reported to be the genetic cause in most patients with this disorder. In some cases with a clinical diagnosis of opsismodysplasia, no *INPPL1* pathogenic

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**CASE REPORT**

Prenatal-onset *INPPL1*-related skeletal dysplasia in two unrelated families: Diagnosis and prediction of lethality

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**Abstract**

This report describes two patients with *INPPL1*-related skeletal dysplasia diagnosed prenatally. A literature review is conducted to find out if high-lethality is associated with particular pathogenic variants in *INPPL1* gene. Prediction of lethality in the prenatal setting has an impact on perinatal management. Some frameshift variants in *INPL1* gene are uniquely observed in lethal cases; however, more patients are needed to confirm the correlation.

**KEYWORDS**

*INPPL1* gene-related phenotype, opsismodysplasia, prenatal whole exome sequencing, Schneckenbecken dysplasia, skeletal dysplasia
variant has been found suggesting genetic heterogeneity of this disease.\textsuperscript{14-16} Initially, this condition was thought to be lethal but it is now clear that the outcome is more variable from stillbirth to survival into adulthood.\textsuperscript{12,17,18}

In postgenomic era, with the decrease in cost of whole exome sequencing (WES) and the availability of tests in clinical molecular diagnostic laboratories, genetic tests become more accessible and utilized by many clinicians to confirm the diagnosis of many genetic disorders including rare skeletal dysplasia. Prenatal-WES has become an important diagnostic tool in cases with abnormal ultrasound findings suggesting a severe, potentially lethal, osteochondrodysplasia. Diagnostic results will predict pregnancy outcome and influence perinatal management. Here we describe two fetuses from two unrelated families with novel pathogenic and likely pathogenic variants in the \textit{INPPL1} gene. Also, a focused minireview is conducted to find out if there are specific variants in \textit{INPPL1} gene that are predictors of high lethality in the prenatal setting.

2 \hspace{1em} \textbf{CASE REPORTS}

2.1 \hspace{1em} \textbf{Case A}

A 35-year-old woman, Gravida 6 Para 4 plus 1 abortion and 3 living healthy children, is married to her first cousin and both are of Saudi descent. She is a known case of stable Crohn’s diagnosed at age of 29 years, underwent ileal resection at the age of 30 years, and has remained in remission on Humira 40 mg every 2 weeks. Due to her chronic illness, she was seen in a high-risk pregnancy clinic for prenatal care at the gestational age of 12 weeks plus 5 days. Previous obstetrical history and family history were remarkable for previous neonatal death in the neonatal intensive care unit (NICU) at the age of 1 week due to cardiopulmonary compromise secondary to skeletal dysplasia of unknown etiology (Figure 1).

Current pregnancy measurements of nuchal translucency (NT) scan were within normal limits (CRL of 63 mm, NT of 2 mm; at 72 centiles suggestive for low risk for Trisomies).

A morphology scan at the gestational age of 19 weeks plus 6 days showed a single alive fetus with significant shortening of all long bones, a small bell-shaped chest, and decreased bone echogenicity. Femoral length/abdominal circumference (FL/AC) ratio was 0.09 (lethal if < 0.16). Thoracic circumference/abdominal circumference (TC/AC) ratio was 0.60 (lethal if < 0.60). There were no apparent bowing of long bones or fractures on ultrasound. It was suspected that the fetus has autosomal recessive skeletal dysplasia with borderline indices of lethality. Amniocentesis at the gestational age of 22 weeks was performed for genomic investigations. Single nucleotide polymorphism array (SNP array) was normal. Prenatal trio whole exome sequencing (WES) was performed in a clinical genomic diagnostic laboratory and revealed homozygous (c.1563dup; p.I522Yfs*30) pathogenic variant in \textit{INPPL1} gene (NM_001567.3). Thus, the fetus was diagnosed prenatally with opsismolaysia and parents were carriers of this variant.

\textbf{FIGURE 1} Family pedigrees
Pregnancy was complicated by preterm premature rupture of membrane (PPROM) at the gestational age of 27 weeks and 2 days. She was admitted to the hospital and received antibiotics as per PPROM protocol. High and low vaginal swabs were negative. Patient was evaluated on daily basis and had no signs of chorioamnionitis. Because of the variability of opsismodysplasia prognosis in literature, the fetus was treated with full care so the mother received a full course of dexamethasone at the gestational age of 28 weeks plus 4 days for fetal lung maturity. She was discharged home at the gestational age of 30 weeks and planned for elective C-section delivery at term. Two weeks later, she developed labor-like pain and breathing difficulty due to significant polyhydramnios. A baby boy was born via elective C-section at the gestational age of 33 weeks plus 2 days. APGAR scores were 4 and 6 at 1 and 5 minutes, respectively. Birthweight was 1.86 kg (10-50th percentile). Head circumference was 33 cm (>90th percentile). Length was 28 cm (<3rd percentile). The baby was immediately intubated and required high-frequency mechanical ventilation. On examination, he had dysmorphic features and physical signs in keeping with severe skeletal dysplasia (Figure 2). Blood test revealed normal levels of phosphate 2.86 mmol/L (1.8-3.8 mmol/L), corrected calcium 2.3 mmol/L (2.1-2.55 mmol/L), magnesium 0.79 mmol/L (0.7-1 mmol/L), and alkaline phosphatase 86 U/L (83-248 U/L). Babygram revealed significant shortening of long bones with flared metaphyses, handlebar clavicles, and small iliac bones with medial projection of ilia (Figure 3). Head ultrasound was normal. Abdominal ultrasound showed mild hydronephrosis and ascites. Echocardiogram showed moderate size atrial septal defect, abnormal tricuspid valve with moderate regurgitation, and moderate size of patent ductus arteriosus (2.7 mm) shunting from left to right. Given the poor cardiorespiratory status of baby in context of apparently lethal skeletal dysplasia, parents opted for withdrawal of care and baby died at age of 12 days.

2.2 | Case B

A 29-year-old healthy woman, Gravida 2 para 0 plus 1 terminated pregnancy (TOP), is married to her 37-year-old first cousin and both are of Syrian descent. Previous obstetrical and family history was remarkable for TOP at the gestational age of 6 months due to abnormal ultrasound findings suggestive of skeletal dysplasia, no postmortem investigations so diagnosis remained unknown (Figure 1). Current pregnancy history was remarkable for fever and cold symptoms in the first-trimester relieved by paracetamol. Medications during pregnancy included dydrogesterone 10 mg twice a day for 2 months for possible low lying placenta, folic acid supplement, and prenatal vitamins. Patient had a morphology scan at the gestational age of 18 weeks plus 3 days which showed a single alive fetus with a thick nuchal fold of 10 mm, frontal bossing, small nose, and flat profile. Chest was small with short ribs and narrow intercostal space in addition to pulmonary hypoplasia. There was a remarkable shortening of long bones with wide metaphyseal ends but normal bone echogenicity. Femoral length/abdominal circumference (FL/AC) ratio and thoracic circumference/abdominal circumference (TC/AC) ratio were not measured. There was no apparent bowing of long bones or fractures.

Amniocentesis was performed for SNP array which was normal. Couple opted for TOP at the gestational age of 19 weeks. Postmortem investigations included limited autopsy for external examination, babygram, and skin biopsy.

FIGURE 2 Examination of the newborn (case A) shows short limbs with small trident hands and feet, and craniofacial dysmorphism including hypertelorism, depressed nasal bridge, short nose with anteverted nares and depressed nasal bridge, long philtrum, and low set deformed ears. Chest appears narrow and abdomen is protuberant. There are peripheral edema and puffy eyelids
for DNA extraction. External examination showed a female fetus with apparent facial dysmorphism: hypertelorism, depressed nasal bridge, small upturned nose, long philtrum, small mouth, low set deformed ears, and nuchal edema. There was a forehead ruptured edematous bulge likely a subcutaneous cystic lesion. There were obvious short limbs mainly rhizomelic, short hands and feet, and the abdomen was protuberant. Babygram showed shortening of all long bones with flared metaphyses and small square iliac bones, a small chest with horizontal short ribs, and platyspondyly (Figure 4). WES revealed a homozygous (c.310C>T; p.Gln104*) likely pathogenic variant in \textit{INPPL1} gene (NM_001567.3) which indicates the diagnosis of opsismodysplasia. Parents declined carrier tests.

3 | DISCUSSION

The \textit{INPPL1} gene encodes SHIP2 protein that plays an important role in chondrocytes during endochondral ossification and differentiation. Variants in \textit{INPPL1} gene have been reported to be the genetic cause in several cases of opsismodysplasia and one case of Schneckenbecken dysplasia (see Table 1). Presence of \textit{INPPL1} mutation-negative cases of opsismodysplasia and known molecular defects in \textit{SLC35D1} gene causing Schneckenbecken dysplasia should suggest genetic heterogeneity of both disorders. The underlying molecular interaction has to be determined for full understanding of the overlap between them. Both disorders are classified under the severe spondylodysplastic dysplasia group and radiologically distinguished by peculiar snail-shaped iliac wings in Schneckenbecken dysplasia. Also, they share similarities at the histopathological level thus considered as allelic disorders with variable prognosis ranging from perinatal lethal outcome in Schneckenbecken dysplasia case to nonlethal form in majority of opsismodysplasia cases.
| Location | Nucleotide change | Protein change | Protein domain | Zygosity (n = number of cases) | Onset of skeletal features (n = number of cases) | Outcome/Lethality (n = number of cases) | Additional nonskeletal features (n = number of cases) | References |
|----------|------------------|----------------|----------------|-------------------------------|--------------------------------|--------------------------------------|-----------------------------------|------------|
| Exon 1   | c.35dup          | p.Ala13Argfs*62| SH2            | 0                             | Prenatal                       | Lethal                               |                                   |            |
| Exon 1   | c.24,39del       | p.Gly9Trpfs*13 | SH2            | 0                             | Prenatal (1)                   | Nonlethal (2)                       | Hypophosphatemia (2)             |            |
| Exon 1   | c.94,121del      | p.Glu32Metfs*77| SH2            | 3                             | Prenatal (3)                   | Lethal (3)                          | -                                 |            |
| Intron 1 | c.183-8G>A       | 6 nucleotide insertion between Leu61 and Tyr62 | -               | 1                             | Postnatal                        | Nonlethal                           | -                                 |            |
| Exon 2   | c.276,280del     | p.Gln93Profs*3 | SH2            | 0                             | Unknown                        | Nonlethal                           | -                                 |            |
| Exon 2   | c.310C>T         | p.Gln104*      | SH2            | 1                             | Prenatal                       | TOP                                  | -                                 | This study |
| Intron 4 | c.519-3A>G       | -              | -              | 1                             | Prenatal                        | Nonlethal                           | -                                 |            |
| Exon 5   | c.545C>A         | p.Ser182*      | -              | 1                             | Postnatal                       | Nonlethal                           | Hypophosphatemia                  |            |
| Exon 6   | c.753G>C         | p.Gln251His    | -              | 0                             | Prenatal (1)                   | Nonlethal (2)                       | Hypophosphatemia (2)             |            |
| Exon 7   | c.768,769delAG   | p.Glu258Alafs*45| -             | 2                             | Prenatal                       | Nonlethal (3)                       | Hypophosphatemia (1; HTZ)         |            |
| Exon 10  | c.1150,1151del   | p.Lys385Glyfs*80| Catalytic      | 0                             | Prenatal (2)                   | Lethal (1)                          | Ventriculomegaly (1)              |            |
| Exon 10  | c.519-3A>G       | p.Arg401Trp    | Catalytic      | 0                             | Prenatal (1)                   | Nonlethal (1)                       | -                                 |            |
| Exon 12  | c.1328delinsTA   | p.Thr443Ilefs*23| Catalytic      | 0                             | Prenatal (2)                   | TOP (2)                             | -                                 |            |
| Exon 13  | c.1563dup        | p.1522Yfs*30   | Catalytic      | 1                             | Prenatal                       | Lethal                              | ? Schneckenbecken dysplasia form | This study |
| Exon 14  | c.1687,1691del   | p.Thr563Glyfs*3 | Catalytic      | 0                             | Prenatal                       | Lethal                              | -                                 |            |
| Exon 15  | c.1845dupT       | p.Ile616Tyrfs*14| Catalytic      | 3                             | Prenatal                       | TOP (3)                             | -                                 |            |
| Intron 16| c.1951 + 1G>A    | -              | -              | 1                             | Postnatal/Childhood            | Nonlethal                           | -                                 |            |
| Exon 17  | c.1976C>T        | p.Pro659Leu    | Catalytic      | 4                             | Postnatal (4)                  | Nonlethal (4)                       | Hypophosphatemia responded to pamidronate (2) Cardiac (2) Hypoplastic kidney (2) |            |
| Exon 17  | c.1975C>T        | p.Pro659Ser    | Catalytic      | 0                             | Unknown                        | Nonlethal                           | -                                 |            |

(Continues)
| Location   | Nucleotide change       | Protein change | Protein domain | Zygosity (n = number of cases) | Onset of skeletal features (n = number of cases) | Outcome/Lethality (n = number of cases) | Additional nonskeletal features (n = number of cases) | References |
|------------|-------------------------|----------------|----------------|-------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------------------|------------|
| Exon 17    | c.1960_1962delGAG       | p.E654del      | Catalytic      | HMZ 1                          | Prenatal                                      | Nonlethal                              | -                                               | 16         |
| Exon 18    | c.2071C>T               | p.Arg691Trp    | Catalytic      | HMZ 1                          | Prenatal                                      | Unknown                                | -                                               | 14         |
| Exon 18    | c.2064G>T               | p.Trp688Lys    | Catalytic      | HTZ 0                          | Prenatal                                      | TOP (2)                                | -                                               | 15         |
| Exon 19    | c.2164T>A               | p.phe722Ile    | Catalytic      | HTZ 0                          | Prenatal                                      | Nonlethal                              | TOP (1)                                         | 15         |
| Exon 19    | c.2327-1G>C             | -              | Catalytic      | HTZ 0                          | Prenatal                                      | Lethal (1)                             | Ventriculomegaly (1)                            | 22         |
| Exon 19    | c.2231 C>G              | p.Tyr777*      | Catalytic      | HTZ 0                          | Prenatal                                      | TOP (2)                                | -                                               | 17         |
| Intron 21  | c.2415 + 1G>A           | -              | -              | HTZ 1                          | Prenatal                                      | Nonlethal                              | Hypophosphatemia (1; HTZ)                       | 14, 20     |
| Exon 24    | c.2719C>T               | p.Arg907*      | SH3 binding    | HTZ 1                          | Prenatal                                      | Nonlethal                              | -                                               | 15         |
| Exon 25    | c.2845C>T               | p.Arg949*      | SH3 binding    | HTZ 1                          | Prenatal                                      | Nonlethal                              | -                                               | 15         |

Abbreviations: HMZ, Homozygous; HTZ, Heterozygous; Lethal, death in first year of life; Nonlethal, survived beyond first year of life; TOP, termination of pregnancy.

*Compound HTZ genotypes: (c.768_769del/c.2415+1G>A), (c.768_769del/c.2415+1G>A), (c.35dup/c.1687_1691del), (c.24_39del/c.753G>C), (c.276_280del/c.1975C>T), (c.1201C>T/c.2164T>A), (c.1328delinsTA/c.2064G>T), (c.1150_1151delGA/c.2327-1G>C), (c.2231 C>G/c.115delG).
For previously reported cases (n = 37) of opsismodysplasia during pregenomic era (prior 2013), that is, without known molecular cause, outcomes were nonlethal (survived beyond first year of life) in sixteen (n = 16), lethal (deceased in first year of life) in nine (n = 9) cases, terminated pregnancy in seven (n = 7), and unknown outcome in five (n = 5) cases. In postgenomic era, additional 34 cases with known genotype were reported in the literature and here we add our two patients. The spectrum of 29 variants in the thirty-six (n = 36) cases against outcomes is summarized in Table 1. Excluding cases with outcome of termination of pregnancy (n = 11), it is observed that the majority of INPPL1 skeletal dysplasia cases were nonlethal in seventeen (n = 17), lethal in seven (n = 7) cases, and unknown in one (n = 1) case. Out of seven lethal cases, five cases (n = 5/7) had homozygous frameshift variants [c.94_121del (n = 3), c.1563dup (n = 1), c.2415+1G>A (n = 1)] in INPPL1 gene; and two cases (n = 2/7) were compound heterozygous for variants that lead to a premature stop codon in amino acid sequence [c.35dup/c.1687_1691del (n = 1); and c.1150_1151delGA/c.2327-1G>C (n = 1)].

On the other hand, most of other frameshift variants observed in nonlethal cases were either coupled with missense variants in compound heterozygous status or located at the downstream end of the gene, for example, [HMZ c.2719C>T; and HMZ c.2845C>T] thus mitigating the impact of mutation in phenotype outcome. This might suggest that high lethality could be correlated with pathogenic variants resulting in a complete lack of expression or abolished catalytic function of SHIP2 protein; however, larger number of cases with similar genotypes is needed. Also, functional studies are essential for stronger evidence of correlation because there are two homozygous frameshift variants (c.768_769delAG; and c.545C>A) that are located between SH2 domain and catalytic domain of SHIP2 protein but still observed with nonlethal outcome.

Of note, hypophosphatemia has been reported as an occasional clinical feature in some cases of opsismodysplasia with clinical improvement upon treatments with oral phosphate replacement and pamidronate infusions. It seems from our review that hypophosphatemia, which appears in nonlethal cases, is age-dependent as observed in older survivors of whom younger siblings lacked phosphate wasting nephropathy thus long-term monitoring of phosphate in survivors should be considered.

Our cases were called to be a prenatal genetic diagnosis of opsismodysplasia due to pathogenic/likely pathogenic variants in INPPL1 gene as provided in clinical molecular reports. In case A, full perinatal care was provided due to potential survivability. In case B, the pregnancy was terminated according to parents’ decision. In light of this review, it seems that case A had postnatal radiological findings that mimic Schneckenbecken dysplasia because of the handlebar clavicles and medial projection from the ilia; thus, it is consistent with the observed lethal outcome in such dysplasia.

To avoid the confusion caused by the names of skeletal dysplasia and their different outcomes, we agree that INPPL1-related skeletal dysplasia should be viewed as one entity that has the two extremes where Schneckenbecken dysplasia-like phenotype represents the lethal end and opsismodysplasia to be the nonlethal form clinically. This would help the healthcare providers at least to have a better understanding of prognosis and planning for perinatal management.

4 Conclusion

Two more cases with novel pathogenic variants in INPPL1 gene are added to the literature in this review. Prediction of lethality is difficult to determine in prenatal-onset skeletal dysplasia especially with borderline lethality indices measured in prenatal ultrasound. Based on this review, certain frameshift variants in INPPL1 gene are uniquely observed in lethal cases; however, further evidence is needed to confirm the correlation. To summarize this review:

- Schneckenbecken dysplasia and Opsismodysplasia are allelic disorders caused by pathogenic variants in INPPL1 gene with lethal outcomes in Schneckenbecken dysplasia and nonlethal prognosis in Opsismodysplasia.
- Correlation of genotype with high lethality has clinical implications in perinatal management. Further genotype-phenotype correlation studies coupled with functional studies are needed to establish a stronger evidence of correlation between the observed frameshift variants in INPPL1 gene and the high risk of lethal outcome.

Acknowledgments

We thank families for their valuable permission to contribute in this publication. Also, sincere appreciation to Pathology and Laboratory Medicine Department at King Faisal Specialist Hospital and Research Centre-Jeddah branch for facilitating the genetic tests performed in case A and Molecular diagnostic Laboratory at International Medical Centre-Jeddah (IMC) in case B. Published with written consent of the patient.

Conflict of Interest

None declared.

Author Contribution

ISA: initiated this research project, supervised progress, performed the literature review, extracted and analyzed genetic data, and wrote the manuscript. RMI: participated in manuscript writing of case A. FJ and GFH: contributed in manuscript editing and critically reviewed clinical data of Case A.
FT: contributed in manuscript editing and critically reviewed clinical data of Case B. AE: obtained family’s consent and family pedigree and prepared the figures.

ETHICAL APPROVAL
An informed consent for publication was obtained from the families. Publication of this article is approved by institutional review board (IRB) of King Faisal Specialist Hospital and Research Centre-Jeddah branch (IRB 2020-CR-22).

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Abumansour IS, Iskandarani RM, Edrees A, Javed F, Taher F, Hakeem GF. Prenatal-onset INPPL1-related skeletal dysplasia in two unrelated families: Diagnosis and prediction of lethality. Clin Case Rep. 2021;9:e04079. https://doi.org/10.1002/ccr3.4079