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Case Report

Variable Expression of a Novel *JAG1* Frameshift Mutation in a Vietnamese Family with Alagille Syndrome

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Abstract

Background: Alagille Syndrome (ALGS) is an autosomal dominant multisystem disorder primarily associated with mutations in the *JAG1* gene, exhibiting variable expressivity and incomplete penetrance.

Methods: We describe a Vietnamese family of four members, including two affected siblings and an asymptomatic father, all carrying the same *JAG1* c.1456dup (p.Arg486LysfsTer5) mutation.

Results: The siblings exhibited classical ALGS features including neonatal cholestasis, facial dysmorphisms and cardiac defects, while the father remained phenotypically normal. The mother tested negative for the mutation.

Conclusion: This case illustrates the intrafamilial variability and incomplete penetrance of ALGS, emphasizing the role of genetic screening in familial counseling and disease management.

Keywords: Alagille Syndrome; *JAG1* Mutation; Frameshift Variant; Intrafamilial Variability; Asymptomatic Carrier; Genetic Counseling

Introduction

Alagille Syndrome (ALGS) is a complex, autosomal dominant multisystem disorder primarily caused by mutations in the *JAG1* gene, which encodes a ligand in the Notch signaling pathway critical for embryonic development and cell fate determination across multiple organ systems [1]. The classical phenotype of ALGS includes neonatal cholestasis due to bile duct paucity, congenital heart defects (most commonly peripheral pulmonary stenosis), skeletal anomalies such as butterfly vertebrae, distinctive facial features and ocular findings such as posterior embryotoxon [2].

A defining characteristic of ALGS is its highly variable expressivity and incomplete penetrance, even among individuals carrying the same pathogenic variant within a single family [3]. This phenotypic diversity complicates diagnosis, management and genetic counseling. In this report, we describe a Vietnamese family harboring a novel *JAG1* frameshift mutation. Notably, two affected siblings display classical ALGS features, while their father-who carries the same pathogenic variant-remains clinically asymptomatic. This case contributes to the understanding of intrafamilial variability and supports the critical role of comprehensive genetic evaluation and family screening.

Case Presentation

Family History and Background

The family originates from Long An province, Vietnam, comprising four individuals: two affected daughters, a clinically

unaffected father and a mother without the *JAG1* mutation. No prior family history of liver, cardiac or skeletal anomalies was reported before the diagnosis (Fig. 1, Table 1).

Patient 1 (Older Sister)

A term-born female (birth weight: 2.5 kg) presented at 3 months of age with persistent jaundice and characteristic facial features. Laboratory findings showed elevated liver enzymes (AST 442.57 U/L, ALT 526.37 U/L, GGT 895.46 U/L) and hyperbilirubinemia (total bilirubin 171.8 μmol/L, direct 99.5 μmol/L). Echocardiography revealed mild bilateral pulmonary artery branch stenosis and spinal radiographs showed a butterfly vertebra at T7. Genetic testing identified a heterozygous *JAG1* c.1456dup mutation. She received treatment with ursodeoxycholic acid, fat-soluble vitamins, calcium and vitamin D. At her latest follow-up in March 2025, bilirubin levels had normalized, although GGT remained elevated (GGT 1073.69 U/L).

Patient 2 (Younger Sister)

A preterm-born female (36 weeks gestation, 2.3 kg) presented with jaundice and anemia. Laboratory investigations revealed AST 485.17 U/L, ALT 448.95 U/L, total bilirubin 184 μmol/L, direct 110 μmol/L and GGT 344.89 U/L. Echocardiography demonstrated pulmonary artery stenosis and a patent ductus arteriosus. She experienced recurrent episodes of anemia requiring multiple blood transfusions.

She carried the same *JAG1* c.1456dup mutation. Management included ursodeoxycholic acid, multivitamins, calcium, iron supplementation and vitamin C. At her most recent evaluation, hyperbilirubinemia persisted (total bilirubin 287.63 μmol/L, direct 160 μmol/L), although anemia had improved.

Father

The father tested positive for the heterozygous *JAG1* c.1456dup mutation but exhibited no clinical manifestations. Comprehensive assessments-including liver function tests, echocardiography, skeletal imaging and ophthalmologic examination-were within normal limits. He remains asymptomatic to date.

Mother

Genetic screening revealed no *JAG1* mutation. The mother is phenotypically normal with no signs of liver, cardiac, skeletal or ocular involvement.

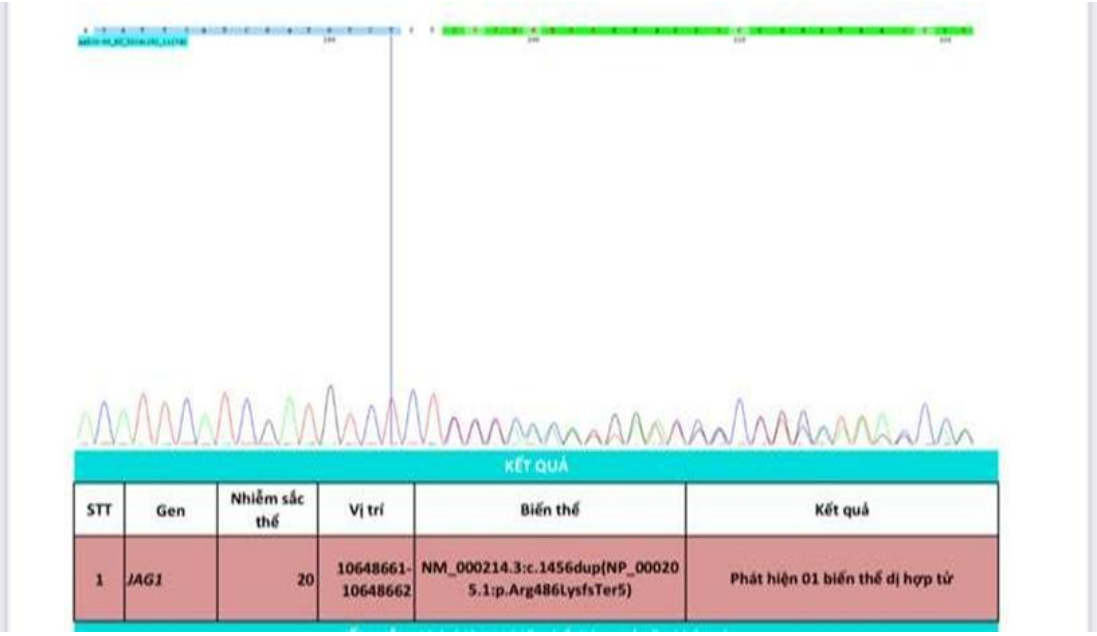

Figure 1: Genetic analysis result. Sanger sequencing demonstrating the heterozygous frameshift mutation c.1456dup (p.Arg486LysfsTer5) in exon 12 of the *JAG1* gene in both daughters and the asymptomatic father.

Characteristics	Patient 1 (Older Sister)	Patient 2 (Younger Sister)	Father	Mother
Gender	Female	Female	Male	Female
Age of Symptom Onset	3 months Present	1.5 months Present	None Absent	None Absent
Jaundice	Absent	Present (multiple	Absent	Absent
Anemia GGT (U/L)	895.5	transfusions) 344.9	Normal	Normal
Total Bilirubin (μmol/L)	171.8	184	Normal	Normal
Direct Bilirubin (μmol/L)	99.5	110	Normal	Normal
Liver Enzymes (AST/ALT U/L)	442.6 / 526.4	485.2 / 448.9	Normal	Normal
Cardiac Abnormalities	Mild branch pulmonary artery stenosis	Pulmonary artery stenosis + PDA	None	None
Skeletal Abnormality: Butterfly Vertebra	Present (T7)	Absent	Absent	Absent
Typical Facial Features	Present	Present	Absent	Absent
Ophthalmologic Examination	Normal	Normal	Normal	Normal
Genetic Testing Results	*JAG1* c.1456dup (heterozygous)	*JAG1* c.1456dup (heterozygous)	*JAG1* c.1456dup (heterozygous)	Negative
Clinical Manifestations	Prominent	Prominent	None	None

Table 1: Summary of clinical and genetic characteristics of family members.

Discussion

The present case exemplifies the significant variability in phenotypic expression associated with *JAG1* mutations, a hallmark of Alagille syndrome. The *JAG1* c.1456dup (p.Arg486LysfsTer5) variant identified in this family is a frameshift mutation located in exon 12-a known mutational hotspot. It is predicted to introduce a premature stop codon, leading to nonsense-mediated mRNA decay and a truncated, likely non-functional protein. While this variant has not been previously reported in Vietnamese cohorts, its predicted pathogenicity aligns with findings in other truncating *JAG1* variants linked to ALGS [1].

The most striking observation in this family is the complete absence of clinical symptoms in the father, despite carrying the same heterozygous mutation found in his affected daughters. This finding underscores the phenomenon of incomplete penetrance in autosomal dominant disorders and raises important questions regarding the molecular mechanisms underlying such disparity.

Previous studies have postulated the influence of genetic modifiers, epigenetic changes and conenvironmental exposures as potential contributors to phenotype modulation in ALGS. Tsai, et al., reported that modifiers of the Notch pathway or other interacting genes may influence disease severity, although conclusive markers remain elusive [4]. Moreover, Turnpenny and Ellard emphasized the role of complex transcriptional regulation and network interactions in modulating Notch signaling output, potentially accounting for variable tissue-specific effects [3].

From a clinical perspective, the presence of an asymptomatic mutation carrier has significant implications for family counseling. It reinforces the necessity of genetic testing for at-risk individuals, regardless of symptomatology and supports ongoing monitoring, particularly in early developmental stages. Moreover, documenting novel variants-such as c.1456dup-enhances global mutation databases and supports diagnostic accuracy in diverse populations. This case emphasizes the importance of genetic screening, early diagnosis and long-term monitoring, even for asymptomatic carriers, to ensure optimal management and genetic counseling.

Conclusion

We present a family with a novel *JAG1* frameshift mutation demonstrating significant intrafamilial phenotypic variability in Alagille syndrome. The presence of an asymptomatic mutation carrier stresses the necessity for family-based genetic investigations and underscores the complexity of genetic counseling in autosomal dominant disorders with incomplete penetrance.

Conflict of Interests

The authors have no conflict of interest to declare.

Ethics Approval and Consent to Participate

Not applicable for this case report.

Consent for Publication

Written informed consent was obtained from the parents for publication.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed.

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References

1. Kamath BM, Spinner NB. *JAG1* mutations in Alagille syndrome. Human Mutation. 2003;21(5):512-19.
2. Tsai EA, Gilbert MA, Grochowski CM. ALGS phenotype severity and modifier genes. American J Medical Genetics Part A. 2016;170(5):1218-24.
3. Turnpenny PD, Ellard S. Alagille syndrome: Pathogenesis, diagnosis and management. European J Human Genetics, 2012;20(3):251-7.
4. Li L, Krantz ID. Spectrum of *JAG1* mutations in Alagille syndrome. Human Mutation. 1997;10(5):368-75.