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A Newly Discovered Mutation in The *NOTCH2* Gene and Atypical Presentation of Alagille Syndrome

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ABSTRACT

Alagille syndrome (ALGS) is a rare multisystem genetic disorder that presents with various clinical features, including liver disease.

This disorder is caused by mutations in *JAG1* or *NOTCH2* gene. However, *NOTCH2* mutations are rarely found in Alagille patients. Little is known about the clinical and pathological profiles of patients with *NOTCH2* mutations in Alagille.

Herein, we present a patient diagnosed with atypical Alagille syndrome. Following sequencing, a novel variant in *NOTCH2*, NM_024408.4 (c.6143A>T, p. Asp2048VaL), was identified.

This report highlights the importance of genetic testing in the diagnosis of this condition and the need to increase suspicion of the disease in atypical young patient's presentation of ALGS.

Keywords: Alagille syndrome; *NOTCH2; JAG1*

INTRODUCTION

Alagille syndrome (ALGS), also known as arteriohepatic dysplasia, is a rare genetic disorder affecting multiple organs, with liver involvement being a common finding [1]. It is caused by mutations in the *JAG1* (ALGS type 1) or *NOTCH2* (ALGS type 2) genes and is inherited in an autosomal dominant pattern, with an incidence of 1: 30,000 per live births [2].

Up to 97% of the reported cases are caused by mutations in *JAG1*, with less than 1% of patients having *NOTCH2* mutations. Unclear relationships between genotypes and phenotypes, variable penetrance, and alterations in clinical presentations increase the difficulty in the diagnosis of ALGS syndrome with *NOTCH2* mutations. The clinical features of *NOTCH2*- related ALGS are not as typical as those of *JAG1*-related ALGS [1].

NOTCH2 is a protein-coding gene located on chromosome 1p12-p11.2 in humans. *NOTCH2* encodes *NOTCH2* protein, which is a member of the Notch family of transmembrane receptors.

NOTCH2 plays a crucial role in cell-to-cell communication and signaling. It is involved in multiple cellular processes including cell proliferation, differentiation, and death. The *NOTCH2* protein is particularly important

during embryonic development, where it regulates the formation of many different organs and tissues, including the liver, pancreas, heart, and eye.

Mutations in *NOTCH2* have been linked to several human diseases, including Alagille syndrome and Hajdu-Cheney syndrome [5].

The ALGS-related *NOTCH2* mutation was first identified in 2006 by McDaniell et al. A *NOTCH2*-deficient mouse model showed ALGS-like symptoms which prompted McDaniell et al. to screen *NOTCH2* variations in a cohort which did not have a *JAG1* mutation [6].

Alagille syndrome is the most common disorder associated with mutations in *NOTCH2*. Notably, individuals carrying mutations in *NOTCH2* have a lower penetrance of clinical features compared to those carrying *JAG1* mutations.

Skeletal anomalies and facial features are infrequently found in *NOTCH2* mutation-related individuals. Here, we present a case report of a patient diagnosed with atypical Alagille syndrome. Following sequencing, a novel variant in the *NOTCH2* gene (c. 6143A > T, p. Asp2048VaL) was identified.

CASE PRESENTATION

A 37-year-old male was evaluated at the Sheba Medical Center, Liver Diseases Center, for generalized itching and increased serum liver enzyme levels for 14 years.

The patient had no significant medical history, nor receiving medications. He did not consume alcohol and there was no family history of liver disease.

A clinical examination revealed no typical facial appearance of Alagille. The liver was not palpable, and no hepatosplenomegaly was observed. Laboratory investigations revealed elevated serum bilirubin (total bilirubin 4.1 mg/dL, direct bilirubin 0.6 mg/dL) and liver enzymes (aspartate aminotransferase (AST) 55 U/L; alanine aminotransferase (ALT) 103 U/L; alkaline phosphatase (ALP) 179 U/L; Gamma-glutamyltransferase (GGT) 127) levels (Figure 1, Figure 2)

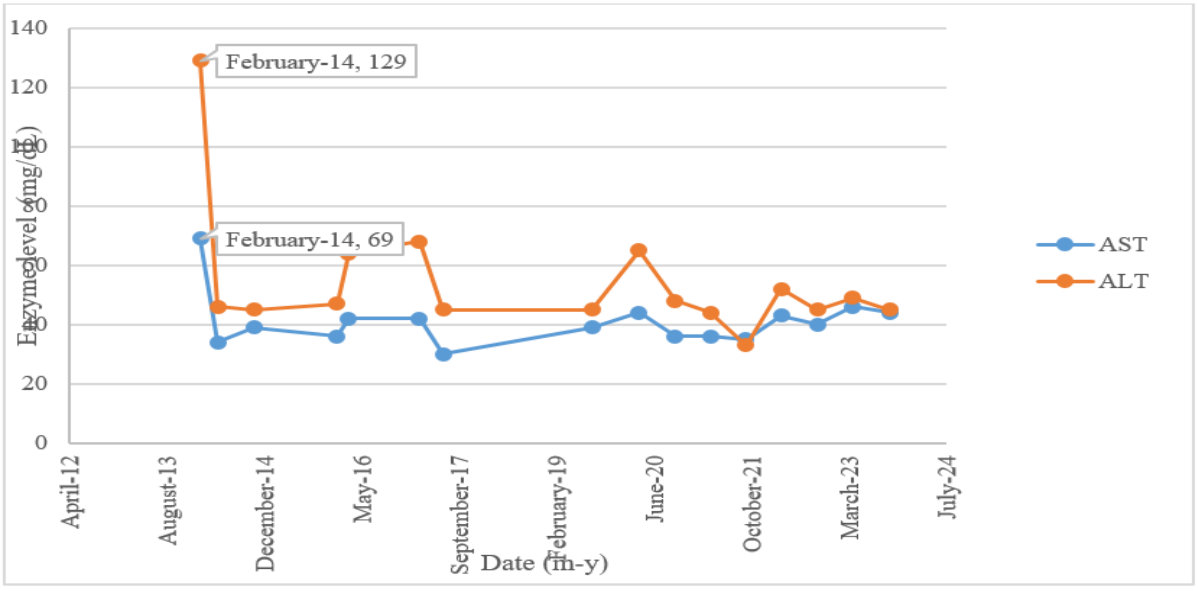

Figure 1: AST and ALT levels following treatment.

The labels indicate the initiation of Ursodeoxycholic acid.

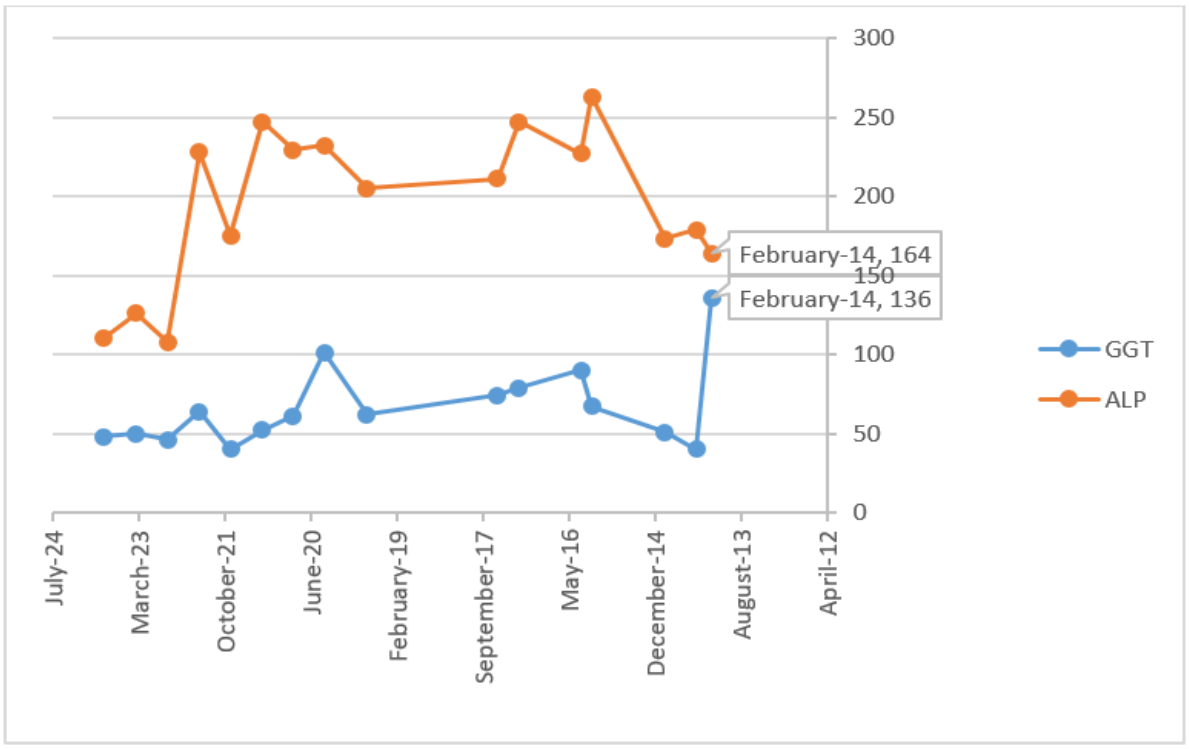

Figure 2: Cholestatic liver enzyme levels after URSO treatment. The labels indicate the initiation of Ursodeoxycholic acid**.**

Hematological disorders, including hemolysis or PNH, were ruled out, and indirect hyperbilirubinemia was attributed to Gilbert Syndrome. Preliminary workup had shown no evidence of infectious (viral hepatitis B and C), metabolic (Wilson's disease, Celiac and Alpha 1 Anti Trypsin deficiency, thyroid function abnormalities), nor immunological etiology
(ANA, AMA, ASMA, ALKM, and ANCA were negative, and immunoglobulins were within the normal range).

An abdominal ultrasound with Doppler study showed a normal liver, with no evidence of bile duct dilatation, and the gallbladder, spleen, kidneys, and pancreas were normal. The portal vein is patent.
Skeleton images revealed considerable flattening of the femoral heads on both sides with a smooth cortex border, and considerable thickening and narrowing of the femoral neck on both sides with subluxation of the hip joints, possibly due to epiphyseal dysplasia.
Radiography of the trunk demonstrated normal vertebrates with no evidence of “butterfly vertebrae.”
Echocardiography revealed an EF of 58%, with mild mitral and tricuspid valve regurgitation, with no signs of pulmonary hypertension.
An ophthalmological assessment detected posterior embryotoxon in the left eye, without other pathological findings.
Gastroscopy revealed no varices or portal hypertensive gastropathy. The magnetic resonance cholangiopancreatography results were normal.
Liver biopsy has shown no specific changes with minimal microvesicular steatosis and mild focal pericentral fibrosis. The quantitative hepatic copper content was within the normal range.

Further genetic testing was performed, which detected a rare heterozygous mutation in *NOTCH2* (c. 6143A > T, p. Asp2048VaL, 1:120459202), which has not been previously reported.

Parental genetic analysis revealed no mutations, confirming that the mutation was de novo. The patient was treated with ursodeoxycholic acid at 900 (mg/day) and bizafibrate at 200 (mg/day). Following treatment, the itching improved significantly, and a decrease in liver enzymes level AST 44 U/L, ALT 45 U/L (Figure 1), GGT 48 U/L, ALP 110 U/L (Figure 2) was noted.

Genetic studies

Genomic DNA was extracted from peripheral blood of the patient. Exonic sequences were enriched in the DNA sample using the IDT xGen Exome Research Panel V2.0 capture (Integrated DNA Technologies, Iowa, United States), and sequenced on a NovaSeq 6000 sequencing system (Illumina, San Diego, CA) as 100-bp paired-end runs. Data analysis including read alignment and variant calling was performed with DNAnexus software (Palo Alto, CA) using default parameters, with the human genome assembly hg19/GRCh37 as reference.

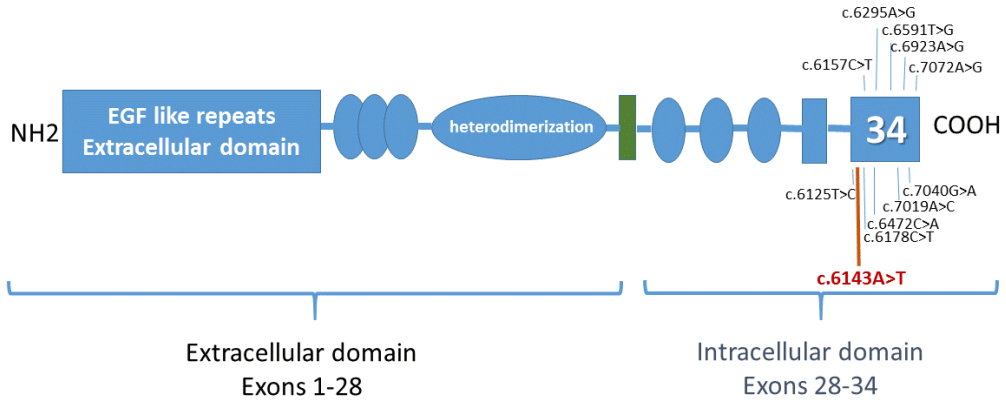

Figure 3: the position of previously known missense pathogenic variants in exon 34 in addition to the one identified in our patient.

DISCUSSION

Alagille syndrome is a rare genetic disorder that affects multiple organs, with liver involvement being common. The diagnosis is based on a combination of clinical features, laboratory findings, and imaging studies. Genetic testing is essential to confirm the diagnosis and identify the underlying genetic defects and to provide genetic counseling to the family.

In this report, we present a young patient with Alagille syndrome with an atypical presentation. Apart from the increased liver enzyme levels, his only clinical presentation (following an extensive workup) was posterior embryotoxon in his left eye. A novel pathogenic variant in *NOTCH2*

was identified. This variant has neither been previously reported in the literature in affected patients, nor in healthy individuals and thus expands the spectrum of known pathogenic variantss in Alagille syndrome.

The identified variant maps to exon 34 of the gene. Pathogenic loss-of-function variants in this exon are reported to be associated with Hajdu- Cheney syndrome [8].

In Figure 3. We mapped the position of previously known missense pathogenic variants in exon 34 in addition to the one identified in our patient show that in accordance with Li et al our patient has extrahepatic manifestation

A patient with atypical clinical features of Alagille syndrome responded well to medical therapy.

NOTCH2 plays an important role in multiple cellular processes.

As reported in a recent article about defining the pathogenicity of *NOTCH2* variants for the diagnosis of Alagille syndrome. This finding suggests that the presence of certain *NOTCH2* variants is strongly associated with Alagille syndrome type 2, indicating a disease-causing effect. Conversely, the absence of these variants in databases such as gnomAD can provide further evidence to support a suspected Alagille syndrome diagnosis [7].

The treatment options for Alagille syndrome are limited, and management is mainly supportive. Ursodeoxycholic acid and cholestyramine can help alleviate the symptoms of cholestasis, but liver transplantation may be required in severe cases. Our patient partially responded to the administration of ursodeoxycholic acid; however, following the introduction of bezafibrates, his itching resolved.

This case report highlights the importance of genetic testing in the diagnosis of this condition and the need to increase the suspicion of the disease in atypical young patient's presentation. There is a need for ongoing research to identify new mutations and improve our understanding of the pathophysiology of Alagille syndrome.

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