# Alagille Syndrome

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**KEYWORDS**

• *JAG1* • *NOTCH2* • Pediatric • Cholestasis • Liver transplant

**KEY POINTS**

- Alagille syndrome (ALGS) is a multisystem disorder with variable phenotypic penetrance caused by heterozygous mutations in 1 of 2 genes that are fundamental components of the Notch signaling pathway, *JAGGED1* (*JAG1*) and *NOTCH2*.
- Features of the syndrome include characteristic facies, bile duct paucity, chronic cholestasis, and abnormalities in cardiac, renal, vascular, skeletal, and ocular systems.
- Indications for transplantation include severe pruritus, liver synthetic dysfunction, portal hypertension, bone fractures, and growth failure.
- Genotype-phenotype correlation studies have not shown a link between mutation type and clinical manifestation or severity, leading to the hypothesis that a second gene could function to modify the effects of a *JAG1* or *NOTCH2* mutation. Several candidate genetic modifiers have been identified in animal and human studies.
- Current therapies for ALGS patients are supportive and focus on clinical manifestations. In the future, new therapeutic approaches may involve modulation of Notch pathway signaling, cell-based therapies, or correction of specific mutations in vitro or in vivo.

## INTRODUCTION

Alagille syndrome (ALGS) is an autosomal dominant, multisystem disorder with variable phenotypic penetrance that was first described in 1969 by Daniel Alagille. Initial diagnosis was based on the presence of intrahepatic bile duct paucity and at least 3 other clinical features: chronic cholestasis, cardiac disease, ocular abnormalities, skeletal abnormalities, and characteristic facial features. Although not currently included in the diagnostic criteria, patients also have a high prevalence of renal and

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