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Differential prevalence of extrahepatic clinical manifestations in patients with Jagged1 and *NOTCH2*-associated Alagille syndrome: Results from the International Multicenter GALA Study Group

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Background: Alagille syndrome (ALGS) is a phenotypically heterogeneous, autosomal dominant disorder, resulting from pathogenic variants in Jagged1 (*JAG1*) or *NOTCH2*. The natural history of liver disease in ALGS is highly variable and there are no known genotypic predictors of hepatic outcomes. The Global ALagille Alliance (GALA) Study Group has ascertained the largest genetically confirmed ALGS cohort to date, permitting exploration of *JAG1* and *NOTCH2* genotype-phenotype correlations.

Method: International multicentre retrospective study of children with ALGS, born between Jan-1997 and Aug-2019 with a pathogenic or likely pathogenic (LP) variant in *JAG1* or *NOTCH2.* Variants were classified according to the American College of Medical Genetics and Genomics criteria. Phenotypic differences were compared between *JAG1*-and-*NOTCH2*- ALGS patients and between those with a truncating, non-truncating or structural *JAG1* variant, using Chi-square test or Fisher's exact test. Transplant-free survival (TFS) and overall survival (OS) rates were analyzed using the Kaplan-Meier method.

Results: Among 845 genotyped ALGS patients, a pathogenic or LP variant in *JAG1* was identified in 97.5% (n=824) and a pathogenic or LP *NOTCH2* variant in 2.5% (n=21). Of *JAG1* variants, truncating were identified in 73% (n=604), non-truncating in 17% (n=137), and structural variants in 10% (n=83). The phenotypes of *JAG1*-ALGS patients were clinically indistinguishable with respect to liver involvement, including a history of neonatal cholestasis (NC) (82% vs. 81% vs. 82%, p=0.95) and presence of bile duct paucity (66% vs. 55% vs. 61%, p=0.27). Similarly, no significant differences in the prevalence of extrahepatic manifestations were identified (Table). Ten- and 18-year TFS in ALGS patients with a history of NC and either a truncating (n=473), non-truncating (n=110), or structural *JAG1* variant (n=62) were comparable (log-rank, *P*=0.24). OS rates at 10- and 18-years were ≥88% (log-rank, *P*=0.08). *JAG1*-and-*NOTCH2* ALGS patients were similar in terms of history of NC (90% vs. 82%, *P*=0.55), bile duct paucity (54% (n=7/13) vs. 64% (n=202/317, *P*=0.56), renal anomalies (28% vs. 36%, *P*=0.50) and vascular anomalies (27% vs. 32%, *P*=0.79). Those with a *NOTCH2* variant were significantly less likely to have characteristic facies (52% vs. 89%, *P*<0.001), an ECHO-confirmed cardiac anomaly (38% vs. 92%, *P*<0.001), posterior embryotoxon (13% vs. 52%, *P*=0.002), or butterfly vertebrae (0% vs. 43%, *P*<0.001). Ten- and 18-year TFS in patients presenting with NC were comparable between groups *(*59% and 74%; 49% and 61%, respectively; log-rank *P* =0.33). OS rates at 10- and 18-years were ≥88% in both groups (log-rank *P* =0.73).

Conclusion: We present the largest, comprehensive genetic analysis in ALGS. No phenotypic differences were observed between ALGS patients with a truncating, non-truncating or structural *JAG1* variant. The clinical heterogeneity in ALGS patients harbouring the same pathogenic variant further implicates genetic modifiers in defining the ALGS phenotype. *NOTCH2*-ALGS patients exhibit significantly reduced penetrance of extrahepatic features in comparison to *JAG1*-ALGS patients, however the natural history with respect to TFS and OS did not differ between groups.

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Table. Baseline clinical features for 824 children with ALGS with a pathogenic or likely pathogenic *JAG1* variant.

	***JAG1* pathogenic variants** (N=824)	***JAG1* Protein-truncating pathogenic variants** (N=604)	***JAG1* Non-protein-truncating pathogenic variants** (N=137)	***JAG1* Pathogenic structural variants** (N=83)	***P*-Value**
History of neonatal cholestasis	82% (n=645/789)	82% (n=473/578)	81% (n=110/135)	82% (n=62/76)	0.95
Bile duct paucity	64% (n=202/317)	66% (n=150/226)	55% (n=32/58)	61% (n=20/33)	0.27
Characteristic facies	89% (n=667/746)	89% (n=488/549)	89% (n=111/125)	94% (n=68/72)	0.34
ECHO-confirmed cardiac anomaly	92% (n=707/767)	92% (n=516/564)	94% (n=119/126)	94% (n=72/77)	0.44
Posterior embryotoxon	52% (n=355/679)	54% (n=266/492)	49% (n=56/115)	49% (n=35/72)	0.51
Butterfly vertebrae	43% (n=313/723)	44% (n=233/531)	51% (n=61/120)	49% (n=35/72)	0.28
Renal anomaly, any	36% (n=255/717)	36% (n=190/526)	32% (n=38/120)	39% (n=28/71)	0.54
Vascular anomaly, any	32% (n=107/336)	34% (n=80/239)	25% (n=15/60)	27% (n=10/37)	0.41