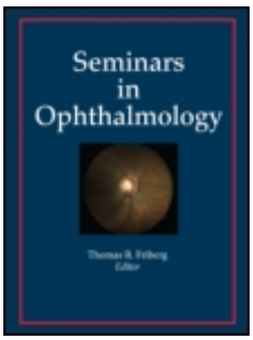

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The Genetics and Ocular Findings of Alagille Syndrome

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ABSTRACT Alagille syndrome is an autosomal dominant disorder caused by mutations in the *JAG1* gene. The *JAG1* gene encodes a ligand for the Notch receptor and thus is part of a critical signaling pathway during development. The ophthalmologist can play an important role in the diagnosis of Alagille syndrome by identifying the characteristic ocular findings. These include a posterior embryotoxon, optic disc drusen, angulated retinal vessels, and a pigmentary retinopathy. Despite recent advances in the genetics of Alagille syndrome, the correlations between genotypes and phenotypes remain incompletely defined.

KEYWORDS Alagille, *JAG1*, Notch, posterior embryotoxon

INTRODUCTION

The first descriptions of Alagille syndrome (AGS, OMIM 118450) were made in 1973 by Watson and Miller, who named it arteriohepatic dysplasia, and in 1975 by Daniel Alagille.[1,2] AGS is one of the familial intrahepatic cholestatic syndromes and is quite rare with a conservative estimate of its frequency reported at 1:70,000 live births.[3] In addition to cholestasis, the other major features that were initially described include cholestatic facies, vertebral anomalies, and cardiac abnormalities.[2] Additional systemic features may include renal abnormalities, mental retardation, and endocrine abnormalities. The first description of the ocular findings of AGS, including the syndrome's association with a posterior embryotoxon, was made by Riely et al.[4] in 1979. These ocular findings enable the ophthalmologist to play a critical role in the diagnosis of AGS when a patient presents with neonatal cholestatic jaundice of unclear etiology. Since these early reports, the disease causing gene has been identified and ocular and systemic features have been further delineated.

GENETICS

The inheritance pattern of AGS is autosomal dominant with low penetrance and highly variable expression. The disorder has been mapped to band 20p12 based upon studies of patients with cytogenetically visible deletions or translocations of chromosome 20.[5] Although there initially were considerations that the syndrome could be caused by deletion of multiple contiguous genes, it has been demonstrated that mutations in the *Jagged1* (*JAG*1) gene are responsible for

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AGS.[3,6] Locating the gene for AGS was a landmark discovery that enabled one to confirm a clinical diagnosis of AGS with genetic data. While patients with large cytogenetically visible deletions can have other features such as developmental delay and hearing loss,[6] the main features of AGS can be attributed to mutations in *JAG1*. Over 230 different mutations have been reported.[7] Consistent with its dominant inheritance, AGS is caused by haploinsufficiency of *JAG1*; one wild type allele is not sufficient to rescue the phenotype.[3] It has also been proposed that there could be a dominant negative effect if mutant JAG1 proteins are produced.[8]

The *JAG1* gene encodes one of several possible ligands for the Notch receptor. The Notch family of receptors plays critical roles in development as the Notch signaling pathway activates genes that inhibit cellular differentiation along particular developmental pathways.[3] Notch signaling is critical for multiple cell lineages and is conserved across multiple species.[3,6] At least five human Notch ligands and four receptors are reported and have been implicated in other human diseases besides AGS.[9] Mutations in *Notch1* have been found in patients with T-cell acute lymphoblastic leukemias, and mutations in *Notch 3* have been found in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).[3,6] All Notch receptor ligands share a common structure that includes an amino-terminal extracellular conserved DSL domain (Delta-Serrate-Lag-2–named after the Notch ligands in *Drosophila* and *C.elegans*), a variable number of EGF-like repeats, and a single transmembrane domain.[6] As expected, the cytoplasmic domain is unique for each ligand.

Studies that localized the expression of *JAG1* found that it is widely expressed. *JAG1* is expressed in multiple adult human tissues including the heart, placenta, lung, skeletal muscle, kidney, pancreas, stomach, thyroid gland, spinal cord, lymph node, trachea, adrenal gland, and bone marrow.[10] Boyer examined the expression of *JAG1* in a 23-week-old human fetus and found that it is expressed in the spleen, aorta, kidney, lung, skeletal muscle, and liver.[8] Using in situ hybridization, Bao and colleagues examined the ocular expression of *Jagged* as well as other Notch pathway genes in the rat eye.[11] They found *Jagged* expression in the neural retina, ciliary body, and the lens. Together, these studies show that this Notch ligand is expressed both in tissues known to be involved in AGS as well as other tissues. The clinical significance of expression in tissues not known to be involved in AGS is unclear. However, multiple factors beyond gene expression determine the activity of a Notch ligand or receptor.[12] These include post-translational modifications such as ubiquitylation of Notch ligands and glycosylation of Notch receptors.[12]

While there have been advances in the genetic understanding of AGS, the relationships between genotypes and phenotypes are still poorly understood. Investigations using animal models have demonstrated the complexity of the Notch signaling pathway. Mice that are homozygous for a null allele mutation of the *Jag1* gene die during embryogenesis, while mice that are heterozygous for the null allele were found to have anterior segment defects such as an iris coloboma or corneal opacities.[13] However, the heterozygous mice did not show other characteristics associated with human AGS. Mice doubly heterozygous for a *Jag1* null allele and a *Notch2* hypomorphic allele exhibit multiple characteristics of AGS including abnormalities at the bile ducts, heart, and kidneys.[14] Based on these findings, it has been proposed that *Notch2* is a genetic modifier of *Jag1*.[14] Interestingly, a study examining mosaic flies with one to three wild-type *Notch* alleles demonstrated a correlation between cell fates and the number of copies of *Notch*.[15] These studies suggest that the Notch signaling pathway is quite sensitive to the level of Notch receptor stimulation and that varying concentrations of JAG1 has significant effects on development. Along these lines, it has recently been reported that mutations in *NOTCH2* have been found in AGS patients that did not have an identifiable *JAG1* mutation.[16] Thus, it is worthwhile to consider looking for mutations of the Notch receptor if one sees a patient with clinical AGS but without a demonstrable *JAG1* mutation.

The environment is potentially another determinant of phenotype. Li et al.[3] studied four unrelated families expressing clinical AGS and found a vast range of phenotypes even among family members with the same *JAG1* mutations. Kamath reported monozygotic twins with the same mutation in exon 6 of the *JAG1* gene but different phenotypes.[17] One twin had only mild liver involvement while the other twin had severe liver involvement requiring transplantation. In this report, it is unclear how the ophthalmic exam varied as its description was limited to stating that each twin had an anterior chamber defect.

OCULAR FINDINGS: ANTERIOR SEGMENT

Good visual acuities are found in most patients with AGS despite a myriad of possible ocular findings. Wells et al.[18] reported eight patients from two different families that all had visual acuities of at least 20/40 except for one patient that had anisometropic amblyopia in the right eye. Hingorani et al.[19] reported the largest series of patients to date and found that the visual acuities of 22 unrelated patients were at least 20/30 except for one patient with strabismic amblyopia of the left eye. While this patient with amblyopia was the only patient with a tropia that was reported by Hingorani, strabismus has been observed in some other AGS patients as well.[20,21] Refractive errors in AGS patients have also been examined, and there is no clear association with a particular degree of refractive error.[19] High myopia has been reported in several patients[20,21] but not in larger case series.[18,19,22]

The ophthalmologist can play a critical role in diagnosing AGS when a patient presents with neonatal cholestasis. Identification of a posterior embryotoxon is the key feature. Riely et al.[4] were the first to note the presence of a posterior embryotoxon in patients with major systemic findings of AGS. They examined five patients with this disorder and found that all of them had bilateral posterior embryotoxon. Hingorani reported the largest series of ocular findings in AGS and found that 21 of 22 (95%) unrelated patients had a posterior embryotoxon.[19] It has been said that gonioscopy may be necessary to visualize the embryotoxon in some patients (E. Cotlier, personal communication). While a posterior embryotoxon is a major feature of AGS patients, one must note that 8–15% of the normal population may have a posterior embryotoxon.[23] A measurement of the diameter of the cornea may also contribute to the diagnosis. In the series reported by Hingorani, 9 patients had corneal diameter measurements and the average was 10.28 millimeters.[19] Wells et al. found that 4 of the 8 patients they examined had small corneal diameters.[18]

The presence of Axenfeld's anomaly does not often accompany the posterior embryotoxon. While Puklin found that 3 of 5 patients had iris strands to the posterior embryotoxon,[21] only 1 of the 22 patients reported by Hingorani had this finding.[19] High intraocular pressures are not associated with AGS and the intraocular pressures were normal in the single patient of Hingorani. Nonspecific iris changes seem to be more common than Axenfeld's anomaly. Abnormal irides were seen in all six patients reported by Brodsky[22] and 10 of the 21 patients examined by Hingorani.[19] Most of these patients had irides that were characterized by radial iris strands and hypoplastic stroma, but usually without sites that transilluminate light.[19,22] Thus, posterior embryotoxon, small corneal diameters, and iris stromal hypoplasia are the significant anterior segments findings, and the posterior embryotoxon is the most important of these findings. Other anterior segment abnormalities that have been reported but have a more tenuous association with AGS include keratoconus, corectopia, band keratopathy, and corneal pannus.[20,22,24] Lens opacities are infrequent. Puklin reported 1 patient with bilateral posterior subcapsular cataracts at the age of 31.[21] Hingorani found that 2 of their 22 patients had lens opacities described as unilateral lenticular haziness in one patient and bilateral dot-like sutural opacities in another patient.[19]

OCULAR FINDINGS: POSTERIOR SEGMENT

Optic nerve head abnormalities, abnormal vessels, and pigmentary retinopathy are characteristic of the fundus in AGS. In 1981, elevated optic discs in patients with AGS were reported.[20,21] Romanchuk and colleagues described one patient with bilateral optic disc elevation that was stable for a decade. They postulated that the disc appearance was due to proliferated glial tissue as buried disc drusen were not seen on exam or by fluorescein angiography.[20] These elevated optic discs have been referred to as pseudopapilledema since elevated intracranial pressure is not typically associated with AGS. This case without drusen contrasts to the report by Nischal et al.[25] that strongly suggests that disc drusen may be the cause of many of the elevated, abnormal appearing optic discs in AGS. In this paper, it is reported that all but one of twenty unrelated children with AGS had ultrasound evidence of disc drusen in one eye and 80% of the patients had bilateral disc drusen. The authors pointed out that the use of ultrasound to detect disc drusen can be considered to help diagnose a child with AGS. While this report shed light on a common cause of abnormally elevated discs in AGS, caution is in order; disc drusen may not completely explain all elevated discs. Narula et al.[26] have

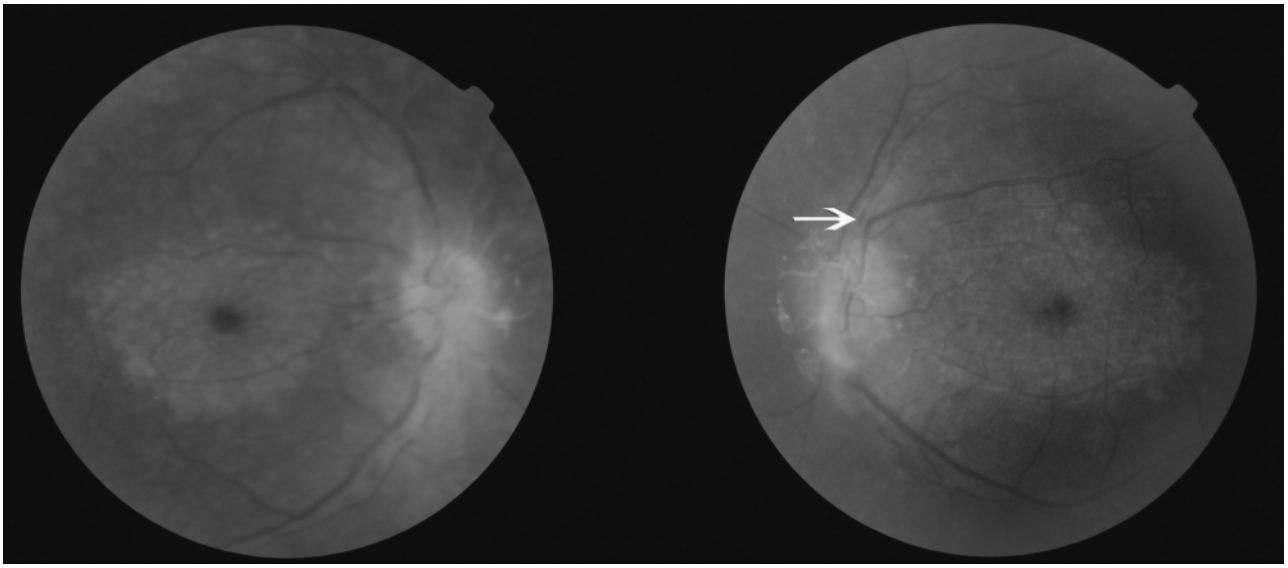

FIGURE 1 **Fundus photos of a 16-year-old girl with Alagille syndrome. This patient has a bull's eye maculopathy and sclerotic vessels around the optic discs. Note the abnormally angulated vessel in the left eye (arrow). This patient has been followed from the ages of 4 to 17 years, and the appearance of the macula has not changed significantly. Her visual acuities have been stable and are 20/38 in each eye.**

recently reported three patients with AGS who had idiopathic intracranial hypertension, including one child that required lumboperitoneal shunting. Thus, elevated intracranial pressure should be carefully considered in an AGS patient with elevated optic nerve heads, especially if disc abnormalities or visual loss is progressive. Other optic disc abnormalities that have been reported but seem to have a looser association include optic disc pit, ovoid discs, temporal crescent, and small or absent cups.[19,22,27]

Vascular anomalies are typically visible on fundoscopy whereas the vascular anomalies in other parts of the body cannot be visualized directly. Hingorani noted that there were either tortuous vessels or abnormal branching patterns in 6 of 21 patients.[19] Abnormal pulmonary arteries are common, and abnormalities of the intracranial vessels, aorta, renal, celiac, superior mesenteric, and subclavian arteries are also reported.[28] These systemic vasculature abnormalities can be a cause of significant morbidity and even mortality. We have seen a patient with AGS with bilateral renal artery stenosis that led to dangerously uncontrolled hypertension. As shown in her fundus photos (Figure 1), there are abnormal vessels including a retinal vessel that takes an abnormally angulated course.

The appearance of the pigmentary retinopathy of AGS is variable. Hingorani reported that 16 of 21 patients had pigmentary changes.[19] Twelve of 21 patients had a diffuse hypopigmentation of the fundus while other patients had peripapillary hypopigmentation or a speckling or granularity of the RPE in the peripheral retina. Maculopathy is reported but uncommon. Brodsky described one six-week-old patient with AGS who had well-circumscribed oval areas of reddish-brown discoloration in the macula.[22] In their report of 8 patients within two different families, Wells noted that 4 patients had a maculopathy characterized by pigment clumping, granularity, and deep yellow deposits at the level of the RPE.[18] As demonstrated in Figure 1, we have seen one patient that presented with a bull's eye maculopathy as well as a granular appearance of the peripheral RPE. This patient has been followed from the ages of 4 to 17 and has maintained a visual acuity of 20/38 in each eye. Johnson has reported histologic findings of AGS patients with a pigmentary retinopathy.[29] These histologic findings included disruption of the photoreceptor outer and inner segments, melanin pigment deposits within the inner nuclear layer and nerve fiber layer, and atrophy and hyperplasia of the RPE. In the past, it was proposed that the pigmentary retinopathy in AGS is due to deficiency in vitamins A and E secondary to cholestatic jaundice and malabsorption of fat-soluble vitamins. However, Hingorani and colleagues found normal serum levels of vitamins A and E in all 21 patients that they tested.[19] While not as frequent, chorioretinal folds are another fundus abnormality that has been reported.[18–20,22]

TABLE 1 **Reports of ERGs and Visual Fields**

	Romanchuk[20]	Puklin[21]	Wells[18]	Tanino[30]
Related patients?	Father and two offspring	Not related	2 pedigrees	3 siblings
Ages (years)	34, 4, 1.5	31, 23, 23, 20	48, 43, 26, 25, 13, 11	14, 11, 9
Retina	Pigmentary Retinopathy	Pigmentary retinopathy**	Pigmentary retinopathy	Retino-choroidal degeneration
Optic nerves	Enlarged, elevated	Peripapillary atrophy	Diffuse thickening	Patients 1 and 2 with crescent deformities. Patient 3 with eccentric deformity.
Number of patients with ERG	3	4	6	3
ERG	Normal*	One patient with decreased B wave amplitudes and normal implicit times for both scotopic and photopic conditions. Other patients were normal.**	Three patients with decreased photopic B wave amplitudes. Two of these three patients with decreased scotopic B wave amplitudes. Other patients were normal.	Reduced amplitudes of the single flash ERG for all patients.
Number of patients with visual fields	1	3	1	3
Goldmann visual fields	Enlarged blind spots	One patient with constricted fields. Other patients were normal.	Enlarged blind spots	Patient 1 with enlarged blind spot OS. Patients 2 and 3 with constriction.

*One patient had subnormal A and B waves at 7 months but had a normal ERG at 19 months. This patient received vitamin A supplementation during the intervening time, but it is unclear if the change in the ERG results was age related.
**One patient had posterior staphylomas OU with a refraction of −29.00 + 9.00X90 OD and −26.25+4.25X20 OS. This patient had decreased B wave amplitudes under scotopic conditions that were attributed to the myopia.

As previously stated, patients with AGS may retain a good visual acuity even with a prominent maculopathy. This raises an interesting question as to the functional significance of the pigmentary retinopathy despite the report of disruption of photoreceptor outer and inner segments.[29] There is a paucity of information about electroretinographic responses and visual fields in AGS. Table 1 summarizes the reports of electroretinograms (ERGs) and visual fields in AGS patients. Indeed, reports of electrophysiologic data seem to be equivocal and some have suggested that ERGs tend to be normal or only mildly abnormal despite the presence of the pigmentary retinopathy.[19–22] Puklin reported a 31-year-old man that had a pigmentary retinopathy, generalized constriction of Goldmann visual fields, and ERG b-wave responses with decreased amplitudes but normal implicit times in both scotopic and photopic conditions.[21] In this same report, two other patients with perhaps equally impressive signs of pigmentary retinopathy had normal visual fields and ERGs. Similarly, Wells and colleagues found some patients with abnormal ERGs and others with normal ERGs.[18] From these papers, there is no clear correlation between the extent of the pigmentary retinopathy and abnormal ERGs. In the patient with the bull's eye maculopathy (Figure 1), we have found constricted visual fields and markedly attenuated ERG responses with increased implicit times in both scotopic and photopic conditions (Fulton, unpublished data). Thus, as with other features of AGS, the severity of the retinopathy may vary widely and in an individual patient may be better delineated by perimetry and electroretinography. At present, it is uncertain as to whether ERG and visual field abnormalities are progressive.

CONCLUSION

The ophthalmologist can play a critical role in the diagnosis of AGS. Identification of posterior embryotoxon, disc drusen, and angulated retinal vessels contribute to the diagnosis. Perimetry and electroretinography should be considered as retinopathy may also be a feature. Despite the breadth of potential ocular abnormalities, many patients retain good visual acuities. Advances in genetics over the past 10 years have demonstrated the role of the Notch signaling pathway in AGS, and in many patients mutations in *JAG1* may be found. Correlations between genotypes and phenotypes remain to be defined and are an objective for future clinical and animal research.

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