ORIGINAL ARTICLE

Consequences of *JAG1* mutations

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Background: Alagille syndrome (AGS) is a multi-system, autosomal dominant disorder with highly variable expressivity, caused by mutations within the *Jagged1 (JAG1)* gene.
Methods: We studied 53 mutation positive relatives of 34 AGS probands to ascertain the frequency of clinical findings in *JAG1* mutation carriers.
Results: Eleven of 53 (21%) mutation positive relatives had clinical features that would have led to a diagnosis of AGS. Seventeen of the 53 (32%) relatives had mild features of AGS, revealed only after targeted evaluation following the diagnosis of a proband in their family. Twenty five of the 53 (47%) mutation positive relatives did not meet clinical criteria, and two of these individuals had no features consistent with AGS at all. The frequency of cardiac and liver disease was notably lower in the relatives than in the probands, characterising the milder end of the phenotypic spectrum. The characteristic facies of AGS was the feature with the highest penetrance, occuring almost universally in mutation positive probands and relatives.
Conclusions: This study has implications for genetic counselling of families with AGS and *JAG1* mutations.

M any dominant genetic disorders manifest with variability of clinical features. This can lead to difficulties in establishing a diagnosis and to complicated counselling regarding the severity of the condition in future offspring. In diseases such as neurofibromatosis, Marfan syndrome, and tuberous sclerosis, severity may range from life threatening complications to benign findings, even within the same family. Establishing the diagnosis in a severely affected individual often leads to the identification of their mildly affected relatives, and it is not uncommon for a parent to be diagnosed subsequent to learning of their child's diagnosis.

Alagille syndrome (AGS; OMIM #118450) is a highly variable, multi-system, autosomal dominant disorder that primarily affects the liver, heart, eyes, face, and skeleton.[1–3] There is significant variability in the extent to which each of these systems is affected in an individual, if at all.[4 5] AGS has traditionally been diagnosed based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease (most often peripheral pulmonary stenosis), skeletal abnormalities (typically butterfly vertebrae), ocular abnormalities (primarily posterior embryotoxon), and characteristic facial features (broad forehead, deep set eyes, straight nose, pointed chin).[6] The clinical definition has been broadened to two of these major features if the individual has a positive family history.[7]

Prior to the introduction of a molecular diagnostic assay, identification of affected family members was based on pedigree analysis in combination with a targeted evaluation. Clinical evaluation of family members has sometimes been difficult to interpret because most of the major findings in AGS can also be seen in some percentage of the general population, or can be caused by other aetiologies. For example, there are many causes of elevated liver enzymes that are not related to AGS. Heart murmurs, many of which are considered benign, are very common in the general population. Posterior embryotoxon is found in 8–15% of the general population.[8] The true incidence of butterfly vertebrae in the normal population is unknown, but has been reported in both the general population and in association with other genetic syndomes.[9 10] Evaluation of the facial features

characteristic of AGS can be highly subjective, and are particularly difficult to recognise in adults.[11] In screening family members of affected individuals, subtle characteristics of AGS may be found, but frequently the individual does not meet the established clinical criteria needed to make the diagnosis. Although the presence of even a single clinical feature in combination with a family history can be highly suggestive, it is difficult to offer definitive genetic counselling in these cases. The availability of molecular carrier testing for many disorders including AGS has provided a tool for correctly identifying family members with an increased recurrence risk of passing the mutation to their offspring, regardless of their clinical phenotype. Molecular testing has now uncovered the most mildly affected individuals in the clinical spectrum of AGS.

AGS is caused by mutation or deletion of the *Jagged1* gene.[12 13] Jagged1 is a cell surface protein that functions as a ligand for the Notch transmembrane receptor. The Notch signalling pathway functions in many cell types throughout development to regulate cell fate decisions. Current screening techniques allow for the identification of mutations in 60–70% of individuals with AGS.[14] A minority (5–7%) of clinically defined cases result from a microdeletion in chromosome 20p.[15] There is no clear genotype–phenotype correlation in AGS.[12 16 17] Therefore, identification of a particular *JAG1* mutation does not offer any prediction of the severity of the disease. To date, studies regarding the clinical manifestations associated with *JAG1* have focused on documenting the frequency of findings in probands.[6 18]

The purpose of this study was to identify a cohort of *JAG1* mutation carriers, irrespective of their clinical phenotype, in order to determine the range and frequency of the clinical findings with these mutations. Relatives of mutation positive AGS probands were screened for the mutation and examined for the frequency and severity of clinical findings consistent with AGS. Probands were excluded from this analysis because their diagnosis was already established based on the presence of significant clinical features.

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Abbreviations: SSCP, single strand conformational polymorphism

MATERIALS AND METHODS

Our laboratory at the Children's Hospital of Philadelphia had screened 212 patients suspected of having AGS based on clinical criteria, for mutations in *JAG1*. All screening followed a protocol approved by the institutional review board. These studies identified 129 (61%) *JAG1* positive AGS probands.

To determine if the *JAG1* mutations were familial, we screened parental DNA samples. In 66/129 (51%) cases, DNA from both parents was available, in 14 (11%) cases only one parent was screened, and in 4 (3%) cases parental samples were not available but DNA from a family member other than a parent was screened. One individual was adopted and no screening of relatives was possible. Siblings were also screened whenever possible and additional family members were screened based on family history information. In 44/129 (34%) cases no parental or family samples were available for screening. A total of 53 mutation positive relatives were identified from 34 families. The mutation positive proband in each included family met classic clinical criteria for AGS.

Clinical information was obtained by direct examination of medical records, physician questionnaire, and family interviews. Families and/or referring physicians were asked about any history of liver and cardiac problems and if liver and cardiac evaluations had been performed on each family member. They were also questioned about any prior examinations for sub-clinical findings of AGS (eye examinations and spine *x* rays) and the results of any studies performed. When available, the records of all evaluations were reviewed. Individuals ascertained at the Children's Hospital of Philadelphia were seen by a dysmorphologist for evaluation of facial features. Individuals not seen at the Children's Hospital of Philadelphia were asked to send photographs to be reviewed by the same dysmorphologist. In all cases the dysmorphologist reviewing the facial features was blinded to the results of *JAG1* mutation testing.

DNA from all probands was screened for mutations in *JAG1* by single strand conformational polymorphism (SSCP) analysis, as previously described.[12] Primers for PCR analysis were designed to cover all exons as well as the intron–exon boundaries of *JAG1*. SSCP was performed and amplicons demonstrating band shifts were sequenced by the Nucleic Acid/Protein Core facility of the Children's Hospital of Philadelphia. Following identification of a mutation in the proband, family members were screened for the specific mutation by analysis of SSCP and/ or sequence analysis of the affected exon.

Chromosomes were studied by standard techniques, including G banding. In order to determine the presence of sub-microscopic deletions of chromosome 20p12, fluorescence in situ hybridisation was performed as previously described, using BAC probe 49D9, which contains the entire *JAG1* gene.[12]

RESULTS

Clinical data were collected and reviewed on 53 mutation positive relatives from 34 families. The cohort consisted of 30 parents, 16 siblings, and 7 other relatives. There were 22 males and 31 females. The age range of the relatives was 5 to 66 years. The mean age of the parents was 40 years and the mean age of the siblings was 13 years. The mean age of the probands was 14 years.

All relatives were found to have the same *JAG1* mutation or 20 p deletion as the one identified in the proband of that family. Three families had deletions and the remainder carried a mutation in *JAG1*. The deletions seen in the three patients were less than 3 Mb, and our data demonstrate that deletions of this size are not associated with clinical findings beyond those seen in AGS patients (Laufer-Cahana and

Spinner, unpublished data). Therefore, deletion and mutation carrying individuals cases were analysed in one cohort.

The majority (85%, n = 45) of the family members underwent three or more evaluations for manifestations of AGS. Evaluating the cohort as a whole, only 11 (21%) of 53 relatives had clinical features that would have been likely to lead to a diagnosis of AGS. These individuals had significant liver disease in association with other features and thus meet classic clinical criteria. These mutation positive relatives may have been diagnosed as probands on their own. In addition, another 17 (32%) relatives were also positive for at least three clinical features; however, it is unlikely that a diagnosis of AGS would have been reached in these individuals in the absence of a family history. Eight of these had asymptomatic or sub-clinical findings only (biochemical liver abnormalities, a heart murmur, eye findings, butterfly vertebrae, or characteristic facies). The presence of such features would not have caused an individual to present to a physician, and it is unlikely that a diagnosis of AGS would have been reached in the absence of their positive family history and a targeted clinical evaluation. The remaining 9 of the 16 had cardiac involvement but no overt liver disease and so would probably have not been evaluated for AGS in the absence of a positive family history. Therefore, although a total of 28 (53%) mutation positive relatives actually met criteria for AGS, only 11 would probably been diagnosed with AGS in the absence of their positive family history. Finally, there were two family members, who were evaluated for all major features of AGS and were found to have none of the five major clinical findings; one of these is a known mosaic. These individuals would never have been diagnosed with AGS in the absence of molecular testing. These results are summarised in table 1.

The frequency of clinical manifestations in this cohort of *JAG1* carriers is presented in table 2. The frequencies are compared with two other studies of clinical findings in AGS probands.[5 6 19] The probands in the current study were similar in clinical manifestations to others previously described, other than they appeared to have an increased frequency of intracardiac structural defects compared with other groups. Comparing probands with relatives, significant liver disease requiring treatment was present in only 31% of mutation positive relatives compared with 96 and 100% of probands. In addition, 25% of mutation carrying relatives had no evidence of cardiac disease at all compared with 2% of individuals in the proband studies.

The data were further evaluated in terms of age of the relatives (table 3). The frequency of clinical findings was determined separately for parents (mean age 40 years) and siblings (mean age 13 years). In comparison with the probands (mean age 14 years), the parents had a much lower frequency of significant liver disease (21% versus 97%). The siblings' frequency of liver disease was also lower (43%)

Table 1 Summary of clinical findings in mutation-positive relatives of AGS probands

JAG1 mutation positive individuals (probands = 34, relatives = 53)	Number
Relatives with clear clinical diagnosis of AGS*	11/53 (21%)
Relatives who met criteria on targeted evaluation	17/53 (32%)
Total relatives who met clinical criteria	28/53 (53%)
Relatives with 1 or 2 features of AGS	23/53 (43%)
Relatives with no features of AGS	2/53 (4%)
Total relatives who did not meet criteria	25/53 (47%)

*These individuals met classic criteria, namely liver disease in association with three of five clinical criteria.

Table 2 Clinical findings in *JAG1* mutation positive relatives of AGS probands, and the probands themselves, compared with clinical findings in two large studies of AGS probands with a clinical diagnosis of AGS

Clinical findings	Current study: relatives (53)	Current study: probands (34)	Current study: relatives and probands (87)	Emerick *et al*, 1999 (92)	Lykavieris *et al*, 2001 (163)
Liver disease, 42 relatives evaluated					
Cholestatic liver disease	31% (13/42)	97% (33/34)	61% (46/76)	96%	100%
Biochemical liver abnormalities only	24%(10/42)	3% (1/34)	14% (11/76)	4%	
No liver abnormalities	45% (19/42)	0% (0/34)	25% (19/76)		
Cardiac disease, 51 relatives evaluated					
PS/ PPS	41%(21/51)	82% (28/34)	58% (49/85)	67%	
Structural defect	31% (16/51)	47% (16/34)	38% (32/85)	24%	18%*
Murmur only	29% (15/51)	9% (3/34)	21% (18/85)	21%	
No cardiac anomalies	25% (13/51)	0% (0/34)	15% (13/85)	2%	6%*
Eye findings, 31 relatives evaluated					
Eye findings	71% (22/31)	75% (21/28)	73% (43/59)	78%	84%*
Vertebral anomalies, 19 relatives evaluated					
Butterfly vertebrae	26% (5/19)	64% (18/28)	49% (23/47)	51%	79%*
Facial features, 46 relatives evaluated					
Facies	91% (42/46)	97% (31/32)	94% (73/78)	96%	97%*

PS (pulmonary stenosis)/PPS (peripheral pulmonary stenosis–stenosis at any level in the pulmonary tree
Structural defect: intracardiac structural defects, such as tetralogy of Fallot and valvar pulmonary stenosis, excludes lone peripheral pulmonary stenosis
Eye findings: typically posterior embryotoxon
*Unpublished data from Lykavieris, taken from Crosnier *et al* (2000).

than the probands, but double that of the parents. Both siblings and parents had similar frequencies of structural cardiac disease.

DISCUSSION

The availability of genetic testing for AGS provides a tool for identifying individuals with *JAG1* mutations within a family in the absence of any overt or asymptomatic findings. This study highlights the enormous variability in clinical findings associated with *JAG1* mutations. Mutation positive relatives in this study varied from having fully expressed AGS to no detectable findings at all. To date, most studies have described the frequency of findings in probands who meet

Table 3 Frequency of clinical findings in mutation-positive relatives divided into parents and siblings, compared with proband data

Clinical findings	Relatives: parents (30)	Relatives: siblings (16)	Probands (34)
Liver disease			
Cholestatic liver disease	21% (5/24)	43% (6/14)	97% (33/34)
Biochemical liver abnormalities only	21% (5/24)	36% (5/14)	3% (1/34)
No liver abnormalities	58% (14/24)	21% (3/14)	0% (0/34)
Cardiac disease			
PS/ PPS	31% (9/29)	53% (8/15)	82% (28/34)
Structural defect	34% (10/29)	33% (5/15)	47% (16/34)
Murmur only	34% (10/29)	20% (3/15)	9% (3/34)
No cardiac anomalies	28% (8/29)	27% (4/15)	0% (0/34)

PS (pulmonary stenosis)/PPS (peripheral pulmonary stenosis): stenosis at any level in the pulmonary tree.
Structural defect: intracardiac structural defect, such as tetralogy of Fallot, excludes peripheral pulmonary stenosis alone.
Eye findings: typically posterior embryotoxon.

the full clinical criteria[6 18 19] and therefore represent the more severe end of the *JAG1* mutation phenotype. Previous data based on probands alone suggested that the frequency of clinically important liver disease was >96% and the frequency of pulmonary tree stenosis was 67%. This study reveals that the frequencies of serious disease in a more unselected population are much lower. If the relatives' data are considered alone, the frequency of liver disease is only 31% and pulmonary tree stenosis occurs in only 41%. Even if the probands and relatives are analysed as a group, thus including the more severe end of the spectrum, these frequencies are still lower compared with previous proband data, at 61% and 58% respectively (table 2).

Comparing the relatives with the probands in our cohort reveals that the frequency of serious clinical findings in relatives is strikingly lower for significant liver disease (31% *v* 97%) and pulmonary tree stenosis (41% *v* 82%). In addition, far more patients in the relatives cohort had a cardiac murmur only (29% *v* 9%) or no cardiac abnormality at all (25% *v* 0%). Cardiac and hepatic manifestations are the two features of AGS with most impact on mortality and morbidity,[6 19] and the penetrance of these manifestations is less severe in the unselected mutation carrier cohort. However, it is noteworthy that the relatives and probands in the current study as a whole appear to have an increased frequency of intracardiac structural disease compared with previous studies. This may reflect a difference in categorising structural heart disease or may, in fact, indicate a modifier effect in our population.

In further delineating the full spectrum of clinical manifestations associated with *JAG1* mutations, two important objectives are achieved. Firstly, a milder end of the spectrum is identified and although these individuals may not have previously come to attention on clinical grounds, they do require appropriate genetic counselling. Furthermore,

the genetic counselling offered to all *JAG1* carriers can now be modified based on the results of this study. The risk of cardiac or hepatic disease in a *JAG1* mutation carrier is not as high as was previously determined based on proband data alone. The true risk of clinically significant disease associated with a *JAG1* mutation is much lower and likely to be intermediate between the frequencies seen for probands and relatives alone. The true frequency in an unselected population of *JAG1* mutation carriers may well be closer to the data shown here for proband and relative groups combined (table 2).

This study includes two individuals with no detectable features of AGS and a third case with only facial features (all three had complete evaluations for AGS). These three cases were parents of probands. One of these cases is mosaic for a deletion in chromosome 20, and has been previously reported.[20] The other individual with no features also had normal clinical evaluations for the major features of AGS, but carried the identical mutation in *JAG1* as their affected child. Studies are underway to determine if he might also be mosaic. These individuals might manifest additional features of AGS on more detailed investigation, such as renal anomalies or vascular abnormalities and therefore it is not yet clear whether possession of a *JAG1* mutation can be truly silent.

This study is limited by incomplete evaluations in all the mutation positive relatives. Only 85% underwent three or more evaluations, and therefore the frequency of manifestations may be underestimated (table 4). However, it is expected that serious manifestations would be unlikely to be under-reported. Another limitation is that this cohort is not truly unselected. It is possible that mutation positive relatives may also carry or be exposed to modifiers that lead to expression of phenotypic features. In a truly unselected population there may be more clinically unaffected individuals. In ideal circumstances, individuals would be drawn from the general population, screened for mutations in *JAG1*, and then the frequency of manifestations determined from this totally unselected population. However, this would be impractical in view of the relatively low carrier rate. The existence of individuals with isolated heart disease and *JAG1* mutations[21 22] does suggest a need for wider screening.

The cohort of relatives is also inherently biased in that it predominately consists of parents, who have reached reproductive age and therefore represent the mildest end of the spectrum. Table 3 demonstrates that the older parental cohort does have milder liver involvement. However, both the parents (mean age 40 years) and siblings (mean age 13 years) have similar frequencies of structural cardiac disease, which is surprising considering the impact of cardiac disease on survival. In an effort to reduce the age bias in the relatives cohort, deceased siblings and other deceased relatives were included wherever possible, to include the younger, more severely affected individuals.

Current screening techniques allow for the identification of mutations in 60–70% individuals with AGS.[14] In cases in which a molecular diagnosis cannot be established, it is recommended that the parents of the proband undergo a complete clinical evaluation including liver enzyme studies, cardiac evaluation, ophthalmology evaluation, spine *x* rays, and evaluation of facial features. In the context of a positive family history, the identification of any finding is highly suggestive that the person could be a mutation carrier. It was interesting to find that the most frequent sub-clinical feature seen in our cohort was the facial features. It has recently been demonstrated that the facies in AGS are specific for the condition and not related to cholestasis, as had previously been suggested.[11] However, these facial features can be subtle and often difficult to evaluate, particularly in adults. Therefore it is essential that the evaluation of facies is performed by a practitioner familiar with the evolving facial phenotype.

This study broadens the spectrum of clinical manifestations associated with *JAG1* mutations by identifying mutation carriers with mild or undetectable clinical features. Within our cohort of relatives, the majority of mutation carriers did not have clinically significant liver disease, clearly showing that a *JAG1* mutation does not always lead to the classical clinical presentation of AGS. This suggests a need to re-define the syndrome based on molecular findings as well as in clinical terms. The frequency of serious liver and cardiac disease associated with a *JAG1* mutation is lower than previously thought and genetic counselling can now be offered to families with a more realistic and optimistic picture. Finally, the identification of mild and severely affected mutation positive individuals within a family sharing the same mutation in *JAG1* forms the basis for future studies exploring the role of modifiers on the AGS phenotype.

ACKNOWLEDGEMENTS

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Table 4 Percentage of mutation positive relatives evaluated for each major clinical feature of AGS

Diagnostic test	Relatives who had diagnostic test
Liver function tests	77% (41/53)
Echocardiogram	94% (50/53)
Opthalmological assessment	58% (31/53)
Spinal *x* rays	36% (19/53)
Dysmorphology assessment	83% (44/53)

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