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Genetic heterogeneity of Alport syndrome

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Genetic heterogeneity of Alport syndrome. Forty-one families have been studied with stringent diagnostic criteria of Alport syndrome: proven renal disease with hematuria affecting at least two relatives, neural hearing loss in at least one affected individual, and evolution to renal failure in at least one affected individual. The proportion of affected offsprings of affected females does not significantly differ from the ratio expected for a dominant trait. The descendance of affected males shows a lack of affected males. In four families, with parental consanguinity and nonaffected parents, the findings agree with an autosomal recessive inheritance. Study of quantitative traits such as death or renal death among brothers, uncle-nephew pairs and whole families shows evident intra-familial resemblances. We conclude that Alport syndrome seems to be a heterogeneous state composed of a number of genetically distinct syndromes, with an autosomal dominant, an X-linked dominant, and an autosomal recessive form.

Hétérogénéité génétique du syndrome d'Alport. 41 familles ont été étudiées selon de stricts critères diagnostiques de syndrome d'Alport: néphropathie hématurique affectant au moins deux sujets par famille, surdité neurogène chez au moins un sujet atteint de néphropathie, et évolution vers l'insuffisance rénale chez au moins un sujet atteint. Les proportions de descendants malades de mères atteintes sont compatibles avec une transmission autosomique dominante. Dans la descendance des pères atteints, on note un déficit de mâles atteints. Dans quatre familles avec consanguinité parentale et parents indemnes, les données sont en faveur d'une transmission récessive autosomique. L'étude d'un trait quantitatif comme la mort ou la mort rénale parmi les frères, les paires oncle-neveu et les familles entières montre d'évidentes ressemblances intra-familiales. Nous concluons que le syndrome d'Alport semble être un ensemble hétérogène composé d'un certain nombre de syndromes distincts génétiquement, avec une forme autosomique dominante, une forme dominanate liée au sexe et une forme autosomique récessive.

Despite many studies, the genetics of Alport syndrome remains disputed. This familial disorder is characterized by progressive renal deterioration associated with hematuria and nerve deafness. One of the main difficulties in genetic study of the disease is its differential severity according to sex. In most cases affected males develop renal insufficiency in early adulthood and thus have few offspring; on the contrary, females generally are affected less severely.

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The familial distribution of the disease suggests that it is caused by an autosomal dominant gene, but many authors have noted deviations from the 1:1 ratio of affected to unaffected offsprings.

Various theories have been proposed to explain not only the anomalous proportions of normal and affected offspring but also the greater severity of the syndrome in males than in females.

From a historical point of view, three theories are prominent. In 1958 Perkoff et al [1] in a study of a large Utah kindred showing a decrease in affected sons and an increase in affected daughters suggested that the gene showed partial sex linkage (partial sex linkage refers to genes located on a homologous segment of the X and Y chromosomes). For statistical and biological reasons, this theory is no longer accepted as the mode of inheritance. Shaw and Glover [2] suggested that the distortion of the segregation ratios is caused by a tendency of the autosome carrying the gene to segregate preferentially with the X chromosome in spermatogenesis and with the X chromosome entering the oocyte rather than the polar body in oogenesis.

This hypothesis was supported by Cohen, Cassady, and Hanna [3], Mulrow et al [4], Fuhrmann [5], and McNeill and Shaw [6]. Preus and Fraser [7] found rather different ratios. They propose autosomal dominant inheritance with reduced penetrance in the sons of affected fathers. In affected mothers the unfavorable intrauterine environment increases the penetrance of the gene in both sons and daughters. Genetic heterogeneity may explain the observed segregation distortion: two dominant modes of transmission, one X-linked in some families, and one autosomal in others. This possibility has been raised by many authors [8–11].

On the other hand, the age at death of males with Alport syndrome suggests the existence of two genetic forms of the disease, one in which affected males die before 30 years of age and another in which they die later [12]. We studied 41 families in an attempt to re-evaluate current concepts of Alport syndrome.

Methods

The subjects studied belong to 41 well-documented families followed at the Departments of Nephrology and Pediatric Nephrology of the Necker-Enfants Malades Hospital. (This study includes families studied previously by Feingold and Bois [8], Grünfeld, Bois, and Hinglais [13], and Habib et al [14].)

Table 1. Segregation ratio for Alport syndrome according to sex of affected parent (probands not included)

Affected parents	Offspring sex	Affected N	Affected %	1:1 segregation χ^2	1:1 segregation P
Mothers[a] [59]	Sons	67	41.8	1.8	>0.10
	Daughters[b]	70	45.7	0.51	>0.40
Fathers[a] [20]	Sons	20	15.0	9.8	>0.01
	Daughters[b]	20	65.0	1.8	>0.10

[a] Affected mothers are either symptomatic or asymptomatic carriers, affected fathers are always symptomatic carriers (see **Results**).

[b] Among the 32 and 13 affected daughters, seven and four have isolated proteinuria without having an affected child. If these daughters are not counted, the proportions of affected daughters become 39.7 and 56.3%; these proportions do not differ from the 1:1 ratio.

Table 2. Correlation between relatives for age of death or renal death (affected males only)

Relationship	Correlation coefficient	Significance
Brothers (12 Sibships) 26 Individuals	0.66	$P < 0.01$
Uncle-nephew (31 pairs)[a]	0.76	$P < 0.001$
Whole family (15 Families) 45 Individuals	0.62	$P < 0.001$

[a] All the pairs are not independent.

Pedigrees were collected from hospital records and personal communication with physicians and families.

All the families included in this study fullfilled the following criteria: *(1)* proven renal disease with hematuria affecting at least two relatives; there are therefore two probands per family; *(2)* neural hearing loss in at least one affected individual; *(3)* progression to renal failure in at least one affected subject.

Segregation analysis

To examine genetic transmission of the disease, we classified the individuals into affected and unaffected and by sex and affected parent.

We defined a symptomatic carrier as one who has hematuria and/or renal failure and an asymptomatic carrier as one who shows no clinical evidence of renal disease but has an affected parent or sibling and at least one affected offspring. Females having proteinuria and an affected parent or sibling but with unaffected offspring are also classified as carriers. Probands belong only to the group of symptomatic carriers. The group of affected individuals refers to all types of carriers. The two probands of each kindred were not included in the analysis.

Genetic heterogeneity

"Genetic heterogeneity" was studied by intrafamilial resemblances in age at death or renal death. A high correlation (that is, 0.50 for siblings) of age at death in affected relatives suggests that patients were affected by more than one type of mutant gene. The theoretical background of this methodology was described by Haldane [15].

Intraclass correlation coefficients were computed for the age at death of brothers and all diseased males of the family. For uncle-nephew pairs the interclass correlation coefficient was calculated.

Results

Figure 1 shows the 41 pedigrees, with their main clinical manifestations.

Segregation analysis

The analysis concerns the first 37 pedigrees. Table 1 presents the segregation of the disease in the offspring of affected males and females. Twenty-five sibships were excluded from analysis because the affected parent could not be determined with certainty.

There is no distortion of the sex ratio (87 males vs. 90 females) and hence no evidence for prenatal loss of affected males as suggested by Graham [16].

The proportions of affected males (41.8%) and females (45.7%) among the offsprings of affected females do not differ significantly from the 1:1 ratio expected for a dominant disease. In the offsprings of affected males the proportion of affected females (65%) does not differ from the 1:1 ratio, but there is incomplete penetrance of the gene in females (Tishler [17]); the proportion of affected males differs significantly ($P < 0.01$).

Families with parental consanguinity (families 38, 39, 40, 41)

In four families with parental consanguinity (parents are first cousins), we observed in each sibship male and female patients with severe renal disease and nerve deafness, whereas parents and other relatives were unaffected. These findings agree with an autosomal recessive inheritance. Passwell et al [18] described a female offspring of a first-cousin marriage who presented nephritis, deafness, and Fanconi syndrome. The parents were unaffected.

Study of intrafamilial resemblance

Intrafamilial resemblance was studied in the first 37 families. Values of the correlation coefficients are given in Table 2. All are significant. They are similar to those reported by Tishler and Rosner [12]. The high correlations observed at death or renal death in affected relatives suggests that there are at least two genetically distinct diseases.

Discussion

The abnormal segregation in Alport syndrome suggested by Shaw and Glover [2] and confirmed by MacNeill and Shaw [6] is not supported by our data. Our findings agree well with those of Preus and Fraser [7]. The discrepancy between the many previous estimates of segregation ratio and those reported by Preus and Fraser [7] and our study is difficult to explain. It may be due to the use of different diagnostic criteria or whether probands are included in the statistical analysis.

The present results therefore suggest the two following hypotheses: *(1)* Alport syndrome is transmitted as an autosomal dominant trait with reduced penetrance in males who receive the mutant gene from their father; *(2)* Alport syndrome is genetically heterogeneous, including an X-linked dominant

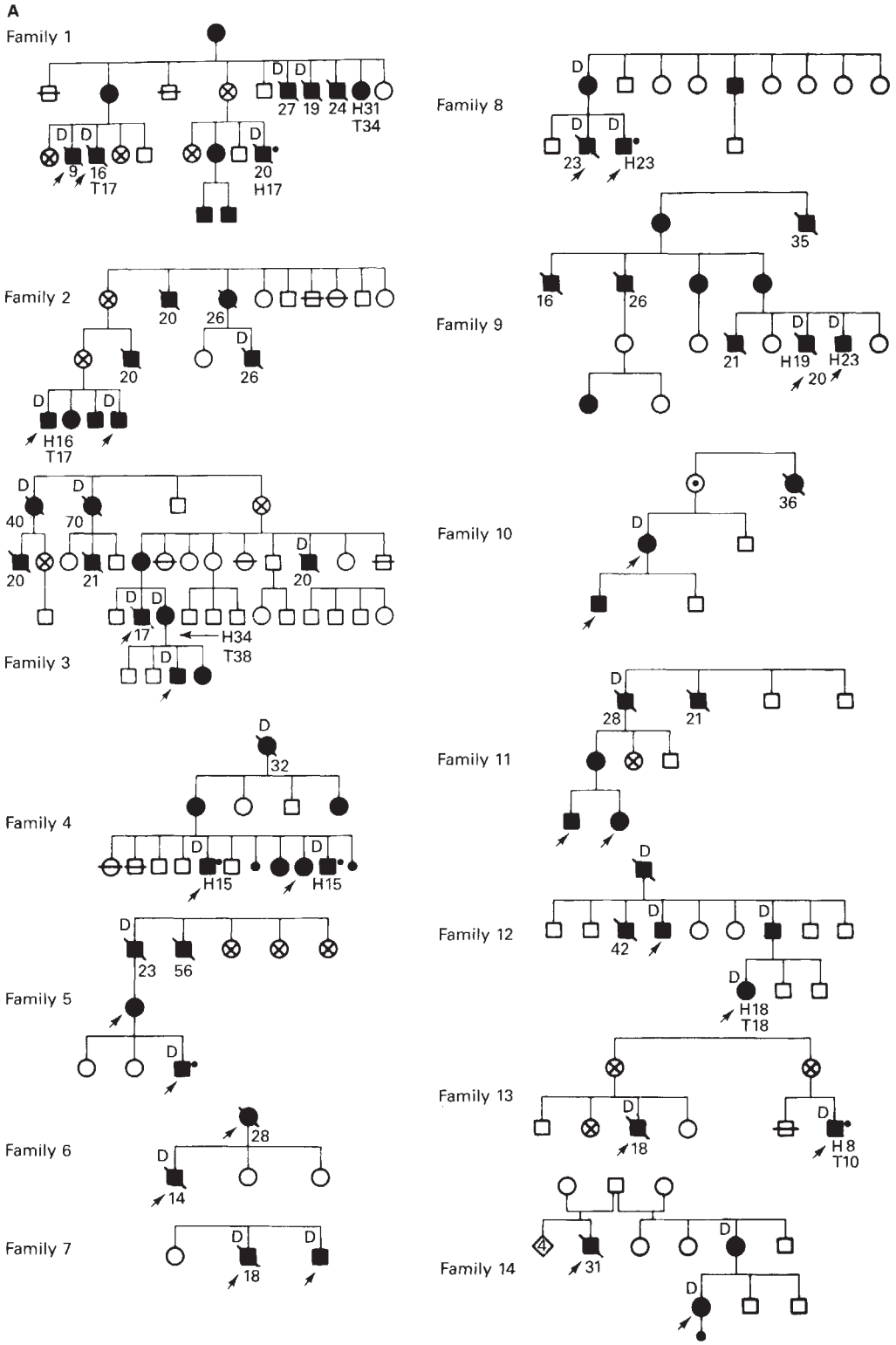

Fig. 1A. *Geneology of the 41 Alport pedigrees.* Symbols are: ⊗, isolated proteinuria; ■, hematuric nephropathy or renal insufficiency; ⊟ deceased in early childhood; D, deaf; ●, died in uremia, age—21 years; ■, hemodialysis, age—23 years; T24, transplantation, age—24 years; proband; ●, abortion; ◇, number of subjects (sex unknown); ⊙, carrier female; □•, bilateral anterior lenticonus; ♂♀, twins.

form and an autosomal dominant type, which explains the cases of male-to-male transmission.

The second hypothesis seems more realistic to us for the following reasons: *(1)* There are now a number of examples of clinically similar conditions which may be caused by mutations at more than one locus; *(2)* the first hypothesis does not explain

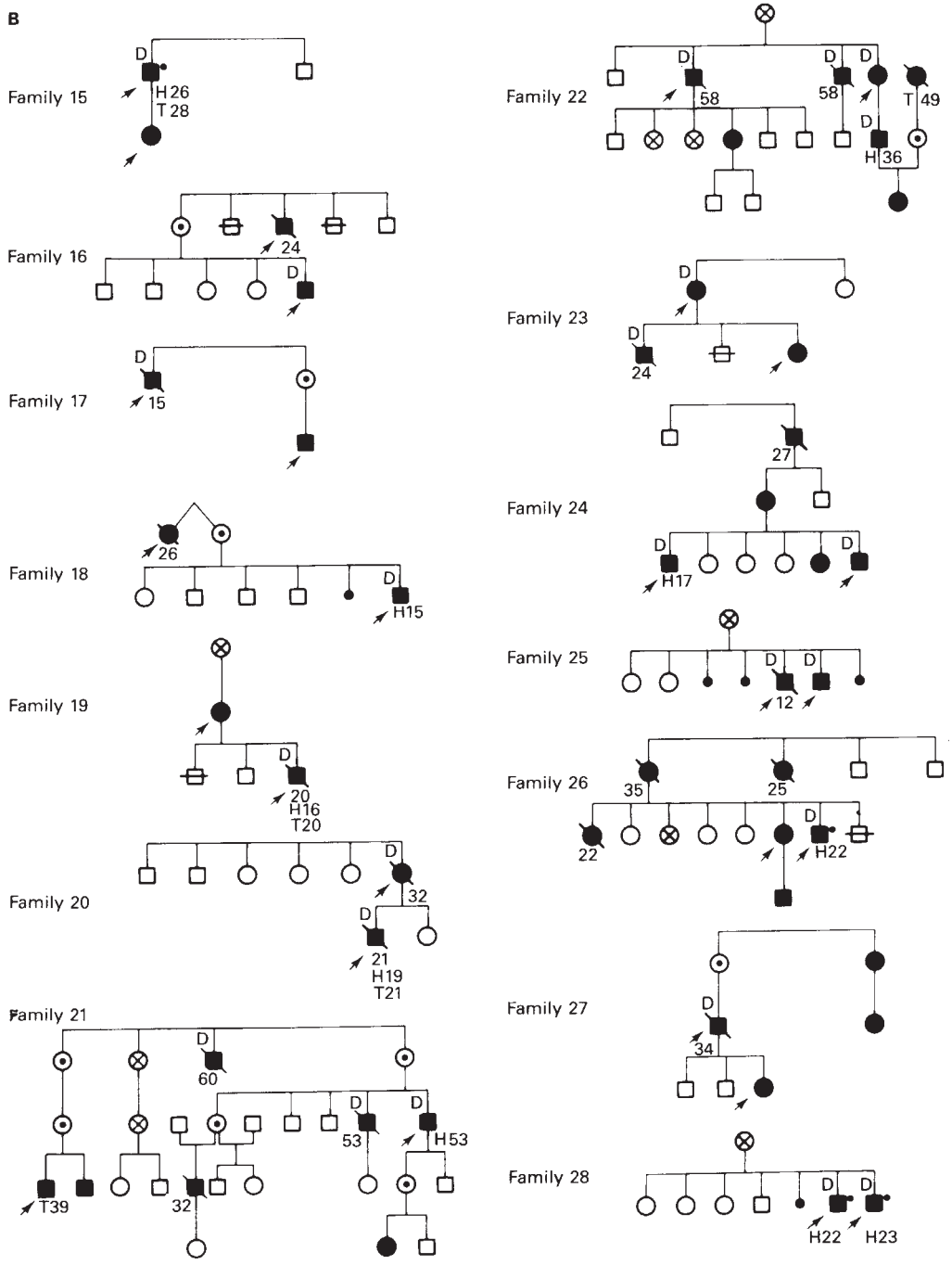

Fig. 1B See Figure 1A for explanation of symbols.

why the disease is more severe, yet penetrance is reduced in males; *(3)* the study of intrafamilial resemblances throughout a quantitative trait supports the hypothesis of genetic heterogeneity, but the exact relationship between the clinical forms of the disease and the two possible dominant forms (autosomal and X-linked) remains unknown.

Among the 37 families where the disease is caused by a dominant gene, only in three families is a male-to-male transmission observed, which excludes a sex-linked inheritance. In the 34 other families it is difficult to assign to each geneology an autosomal or a sex-linked mode of inheritance because affected fathers have no offspring (22 families) or have unaffected sons (12 families). In 15 families where affected males have offspring it is possible to estimate roughly the relative proportions of the X-linked and the autosomal forms. Let x and 1-x be these proportions and p be the proportion of the affected sons among those born to an affected father. It can be shown that

$$p = x.0 + (1-x).1/2$$

(in the sex-linked forms affected fathers have unaffected sons, and in the autosomal form, half of them are affected), if p equals

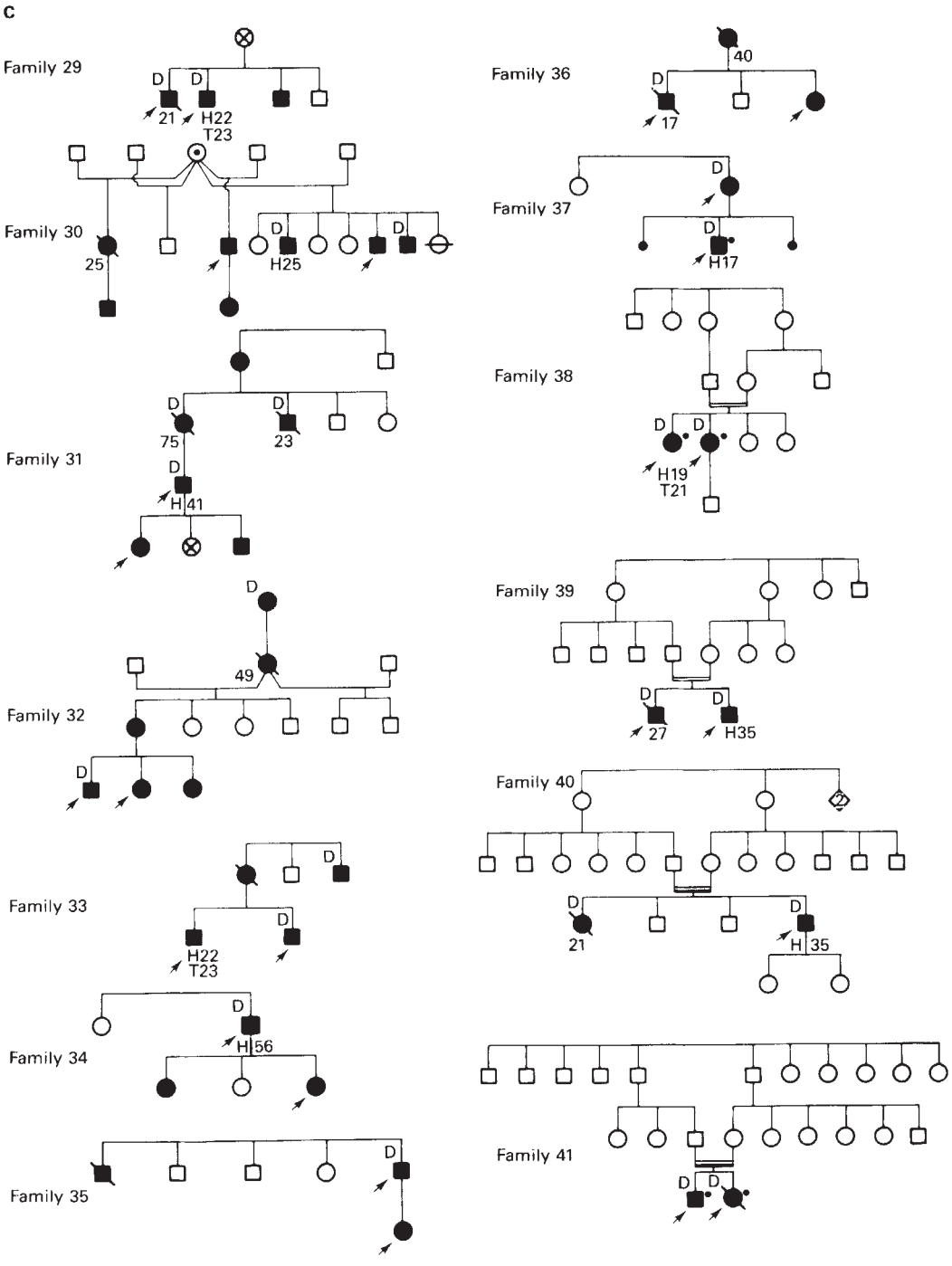

Fig. 1C See Figure 1A for explanation of symbols.

0.15 (Table 1), x equals 0.70. About two-thirds of the families have the sex-linked form and one-third the autosomal form. These estimations must be confirmed by other studies.

From this study we conclude that Alport syndrome is a heterogeneous state composed of a number of genetically distinct diseases: the existence of an autosomal dominant, an x-linked dominant, and an autosomal recessive form of Alport syndrome seems very likely. It should be noted that ultrastructural glomerular basement membrane changes were observed by Habib et al [14] in most patients regardless of the type of genetic transmission.

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