Editorial

ALPORT SYNDROME: FROM GENES TO BEDSIDE

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Alport syndrome (AS) is an inherited disorder characterized by the familial occurrence in successive generations of progressive nephritis with hematuria and of neural hearing loss.[1] Male patients usually have severe renal disease with progressive renal failure occurring before the fourth decade, whereas most females tend to have a normal life span. The first symptoms, usually consisting of microscopic or macroscopic hematuria, occur in early life, especially in males. Hematuria may in rare cases be observed at birth. Other presenting symptoms of AS include proteinuria, edema, hypertension, deafness and renal failure. Hearing defects may not be present in all affected members of a family and are more frequent in male patients. However, the real incidence of hearing loss is difficult to evaluate in the absence of systematic audiological studies. Associated changes in other organs, such as eyes or smooth muscles, and cell types, such as platelets and granulocytes, are known to occur in some patients with AS. The disease follows an X-linked trait in approximately 80% of the cases, whereas autosomal recessive, autosomal dominant and uninformative pedigrees account for the remainder.[2]

Ever since the early descriptions of this disease by Guthrie and Hurst, the pathogenetic basis of AS has remained an enigma.[3,4] The first clues to an understanding of the pathogenesis of AS were provided by the advent of electron microscopy in the early 1970s, which helped to characterize the changes in glomerular basement membrane (GBM). Ultrastructural studies usually revealed variable thinning of the GBM in the early stages and regional thinning and thickening, frequently accompanied by splitting and lamellation, as the disease progresses (Figures 1 and 2). This in turn indicated that the genetic abnormality in AS was likely to be found in some gene or genes encoding proteins responsible for the structural integrity of GBM. In 1971, Kefalides demonstrated for the first time that GBM is composed of a unique type of collagen, which he referred to as type IV collagen.[5] This inspired Spear to suggest that AS might be caused by mutation in type IV collagen gene.[6] However, it was soon apparent that type IV collagen has a highly complex structure consisting of six genetically distinct α chains, instead of one, as was originally believed. In the mid-1980s, cDNA and genes for α1 and α2 collagen chains were cloned and the gene was assigned to chromosome 13.[7,8] This excluded these genes as possible candidates for being responsible for the most common X-linked form of AS. Attention was then focused on the novel α3(IV) and α4(IV) collagen chains. The α3(IV) collagen chain was found to contain the epitope for Goodpasture syndrome autoantibodies and it was noted that some of the AS patients lacked this antigen within the GBM.[12] These findings strongly favored the possibility that α3(IV) collagen was involved in the pathogenesis of AS. In 1988, the AS gene was localized to chromosome Xq 22-26, and it was speculated that this gene was responsible for the synthesis of Col α3(IV).[13-15] Subsequent developments, however, did not support this concept. In 1990, Hostikka et al. and Pihlajamiemi et al. reported the isolation of cDNAs for a novel α5(IV) collagen chain with genes located at Xq22-26.[16,17] This subsequently led to recognition of mutations in the Col 4A5 gene. To date, more than 100 mutations have been found in the Col 4A5 gene in patients with X-linked AS.[2,18] Major rearrangements of Col 4A5 are consistently associated with symptoms of classical AS, i.e., juvenile onset of end-stage renal disease, hearing loss, and a high rate of ocular lesions. Deletions of the 5' end of Col 4A5 and Col 4A6 cause AS with leiomyomatosis (Table 1). A large variety of mutations have been recognized. These include deletion, frameshift, nonsense, splice site and missense. Splice site and missense types of mutations tend to be associated with a higher age of onset of end-stage renal disease.[2] The mutations in AS result in

TABLE 1. *Genes known to be involved in the various genetic subtypes of AS.*

Disease	Gene	Location of gene	Age at ESRD
X-linked	Col 4A5	Xq22-26	Mostly juvenile
X-linked and with leiomyomatosis	Col 4A5 and Col 4A6	Xq22-26	All juvenile
Autosomal recessive	Col 4A3	2q35-37	All juvenile
Autosomal dominant	Col 4A4 (mutations not yet identified)	2q35-37	All juvenile

ESRD=end-stage renal disease.

abnormality in noncollagenous (NC1) domain of the corresponding α chains (Figure 3).

Mutations in Col 4A3 and Col 4A4 on chromosome 2q 35-37 have been described in Alport's patients with autosomal recessive disease. These mutations also give rise to abnormal NC1 domain of the α chains. These patients are either homozygous or compound heterozygotes for these mutations.[2] It has recently been shown that heterozygous mutations in Col 4A4 may be associated with benign familial hematuria syndrome. This concept was reinforced by the discovery of a family in which carriers of a Col 4A4 had the phenotype of familial benign hematuria, while the index case appeared to have features of AS.[1,19] These findings suggest that familial benign hematuria may indeed be a carrier of autosomal recessive AS. Although this seems to provide a long-suspected connection between the two conditions, the number of cases of familial benign hematuria with a proven link to AS is still extremely small and thus requires further confirmation.

The diagnosis of AS is usually based on clinical evaluation, meticulous investigation of the family members and electron-microscopic assessment of the basement membrane structure. It has recently been shown that immunohistochemical analysis of expression of α chains of type IV collagen in the basement membranes of kidney and skin can confirm suspected diagnosis of AS.[20] In X-linked forms of AS there is absence of α5(IV) in the skin and lack of staining not only for α5(IV), but also for α3(IV) and α4(IV) in the GBM. This is because absence or abnormality of one type of α chain interferes with incorporation of other α(IV) chains in the GBM. The autosomal recessive form of AS is characterized by absence of α3(IV), α4(IV) and α5(IV) in the glomerular basement membranes. There is, however, preservation of α5(IV) within the basement membranes of the tubules and Bowman's capsule. Alport syndrome is now considered to belong to a diverse group of collagen diseases such as osteogenesis imperfecta (Type I collagen), chondrodysplasia (Type II collagen), Ehlers-Danlos syndrome (Type III collagen) and epidermolysis bullosa (Type VII collagen).[21]

Renal transplantation is currently the treatment of choice for AS patients with end-stage renal disease and is known to have an excellent outcome. A rare but potentially devastating complication of renal transplantation in patients with AS is the development of anti-GBM nephritis. Luckily this complication occurs in no more than 5% of transplanted males.[1,22] It is due to the presence of normal epitopes of collagen IV α chains in the transplant, to which the recipient is not tolerant and therefore mounts an antibody response. Anti-GBM antibodies in these patients appear to have specificity for NC1 domain of α5(IV) or α3(IV). The latter seem to resemble Goodpasture antibodies. Most of the cases with post-transplant anti-GBM disease have a deletion in Col 4A5 gene as opposed to a missense mutation, which is generally seen in a majority of patients with X-linked AS.[18,22] The patients are generally young men with deafness and eye changes who have attained end-stage renal disease before the age of 30. In rare instances, anti-GBM disease may also develop in transplant recipients with autosomal recessive AS. This group may also include women.

Elucidation of the pathogenesis of AS is an excellent example of the power of molecular biology, which has had great impact on the diagnosis and management of this enigmatic disease complex. Thorough knowledge of the genetic basis of the disease in patients with AS is vital for proper management of the patient and for devising future strategies for simple and practical methods of determining the precise genotype and phenotype of these patients.

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