Should We Diagnose Autosomal Dominant Alport Syndrome When There Is a Pathogenic Heterozygous *COL4A3* or *COL4A4* Variant?

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Several recent studies have reported a single pathogenic *COL4A3* or *COL4A4* mutation in up to 30% of individuals undergoing genetic testing for Alport syndrome, and have described this as an autosomal dominant (AD) disease.[1–7] However, the use of both AD and Alport syndrome in these circumstances is contentious. Clinicians who use Alport syndrome when there are heterozygous *COL4A3* or *COL4A4* variants consider that renal failure occurs often enough to justify this diagnosis. In addition, they say that affected individuals must be made aware of their risk of renal failure and the need for ongoing medical supervision. They further argue that the use of AD is consistent with X-linked and autosomal recessive (AR) inheritance for other Alport cases, and that the commonly used alternative, thin basement membrane nephropathy (TBMN) is a histological diagnosis

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for which there may be little evidence.

The panel behind the "Expert Guidelines for the Management of Alport Syndrome and Thin Basement Membrane Nephropathy" have not recommended the adoption of AD dominant Alport syndrome.[8] What is the reasoning behind this decision?

The genetics of Alport syndrome are complex. Inheritance is X-linked with pathogenic *COL4A5* variants in 85% of families, and AR is linked with 2 pathogenic variants in *COL4A3* or *COL4A4 in trans* (on opposite chromosomes) in the remaining 15%.[9] Ninety percent of men with X-linked Alport syndrome develop end-stage renal failure by the age of 40 years, but only 15% to 30% of women have renal failure by the age of 60 years.[8,10,11] Most men and women with recessive disease have renal failure by age 40 years.[12]

In contrast, individuals with heterozygous *COL4A3* or *COL4A4* variants typically have a thinned glomerular basement membrane (GBM) without lamellation, together with normal renal function, hearing,

and ocular examination, and are diagnosed with TBMN.[13] Many, but not all, have a benign course. They may represent the parents, siblings, and offspring of those with AR Alport syndrome, in which case they are considered the carriers of recessive disease. However, many others do not have family members with recessive Alport disease.

Individuals With Heterozygous *COL4A3* or *COL4A4* Mutations Do Not Have Alport Syndrome and Rarely Develop Renal Failure

Individuals with Alport syndrome develop progressive renal failure and have a lamellated GBM, with hearing loss, and also often lenticonus and retinopathy. They have a syndrome with the concurrent disease features of a lamellated GBM, renal failure, hearing loss, and retinopathy.

In contrast, heterozygous *COL4A3* or *COL4A4* mutations are usually only associated with hematuria. The penetrance of renal failure with heterozygous *COL4A3* or *COL4A4* variants is much less than the nearly 100% expected for men with X-linked Alport syndrome and all those with recessive disease.

Heterozygous *COL4A3* or *COL4A4* pathogenic variants occur in at least 1% of the population,[13] most of whom have normal or nearly normal renal function. In 1 nonhospital series of 61 middle-aged individuals with TBMN and presumed heterozygous *COL4A3* or *COL4A4* pathogenic variants, only 3 (5%) had impaired renal function, and none had end-stage disease.[14] The higher prevalence in other series may be because patients are derived from hospital cohorts with an ascertainment bias toward more severe disease.

Even within a family in which 1 member has a heterozygous *COL4A3* or *COL4A4* mutation and renal failure, other members with the same variant typically have persistently nearly normal renal function. There are few, if any, reports of renal failure occurring in members of consecutive generations (grandparent, parent, child) with the same variant. The term AD Alport syndrome implies that half the offspring, male and female, of the affected person develop Alport syndrome and renal failure, but this is rare.

In addition, most individuals diagnosed with AD Alport syndrome have not had a renal biopsy, so it is not known whether their GBM is lamellated. Renal failure and hearing loss occur inconsistently in people with heterozygous *COL4A3* or *COL4A4* variants and may have other explanations. There are no reports of lenticonus or central fleck retinopathy in such cases.

Furthermore, there is also little evidence that a heterozygous *COL4A3* or *COL4A4* mutation can itself produce a lamellated GBM, hearing loss, or ocular abnormalities without further complicating factors. *COL4A3* and *COL4A4* code for a collagen IV α3 or α4 chain, which together with the α5 chains, form the α3α4α5 heterotrimer. A single mutation in *COL4A3* or *COL4A4* results at worst (with a nonsense variant or a complex variant that produces a downstream nonsense change) in loss of the corresponding α chain, but the allele from the remaining chromosome is intact. Therefore, in the most damaging cases, there is a 50% reduction in collagen IV α3α4α5 that appears to produce GBM thinning but has not been reported to result in the typical lamellation of Alport syndrome.

Interestingly, although we and our colleagues described AD Alport syndrome in Bull terrier and Dalmatian dogs, these animals were highly inbred, and we were unable to identify a single heterozygous *COL4A3* or *COL4A4* mutation in affected dogs using multiple sequencing approaches.[15,16] There may well be additional variants in other genes that explain this disease.

AD Is Not Used for the Carrier State of Other Autosomal Recessively Inherited Diseases

A person with a heterozygous mutation in a gene for hemochromatosis is not reported as having AD hemochromatosis despite their risk of iron overload. They are often described as *carriers* or as having a heterozygous variant that in the homozygous or compound heterozygous state causes AR disease. Thus, using the term AD Alport syndrome for the carrier state of recessive disease is inconsistent with the practice for other genes.

There is also the issue that if we used AD Alport syndrome for the family members of a person with AR Alport syndrome who had a heterozygous *COL4A3* or *COL4A4* variant, then some family members would be diagnosed with AR and others with AD Alport syndrome. This would be confusing for the family and for their treating clinicians.

Renal Failure May Occur With Heterozygous *COL4A3* or *COL4A4* Pathogenic Variants Because of Additional Genetic and Nongenetic Factors

Next-generation sequencing has demonstrated even more complexity in the genetics of Alport syndrome. Combinations of variants include 2 *in cis* in *COL4A3* or *COL4A4*,[17] 1 in *COL4A3* plus 1 in *COL4A4*, and 1 in *COL4A3* or *COL4A4*, with an additional variant in another podocyte gene such as *NPHS2* or *MYH9*.[18,19]

Other nongenetic explanations for renal impairment with heterozygous *COL4A3* or *COL4A4* include secondary nongenetic focal segmental glomerulosclerosis,[13,20,21] superimposed IgA glomerulonephritis,[13,22] poorly controlled hypertension, diabetes, obesity, smoking, and nephrotoxic medications.[2] In general, these other causes of renal failure have not been excluded in patients with heterozygous mutations.

TBMN and Heterozygous Pathogenic *COL4A3* or *COL4A4* Variants

The expert guidelines panel recognized that the major advantage of using TBMN for individuals with heterozygous *COL4A3* or *COL4A4* variants was that this diagnosis and its implications are widely understood. They recognized that TBMN is not a wholly satisfactory term, because renal biopsies are rarely performed when this diagnosis is suspected. However, heterozygous *COL4A3* and *COL4A4* variants are consistently associated with a thinned GBM without the lamellation seen in X-linked and AR Alport syndrome. Thus, TBMN is an accurate description of the GBM appearance associated with heterozygous variants that does not change over an individual's lifetime.

We soon expect to be able to explain why some, but relatively few, heterozygous *COL4A3* or *COL4A4* mutations cause kidney failure. We hope then that the Alport community will develop more accurate terminology for these variants and the combinations that occur. In the meantime, it is preferable to describe them as *heterozygous pathogenic variants*, possibly adding that they are "consistent with the diagnosis of TBMN or the carrier state of AR Alport

syndrome.'' Otherwise, the use of AD Alport syndrome is likely to induce anxiety in many people who have a low risk of renal failure, and who may make important decisions based on this misinformation. Furthermore, confusion will ensue if the terminology is changed prematurely, and subsequent changes are necessary when the genetics are better understood. It is preferable to wait until we understand better why some individuals with heterozygous mutations develop kidney failure, and then have definitive recommendations about the terms to describe these variants and their risk more accurately.

DISCLOSURE

The author declared no competing interests.

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