

DOUBLE HETEROZYGOSITY IN A PATIENT WITH MILD-MODERATE ALPORT SYNDROME

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INTRODUCTION

Alport syndrome (AS) is a rare genetic disease marked by microscopic hematuria and chronic kidney disease, and may also compromise vision and hearing. AS stems from mutations in the COL4A3, COL4A4 or COL4A5, disrupting the formation of the $\alpha 3$ - $\alpha 4$ - $\alpha 5$ chain in the collagen IV network. The disease manifests mainly through renal impairment, with persistent hematuria, proteinuria and progressive decline in renal function. Genotype-phenotype correlations are relatively evident, with etiologies involving autosomal dominant, autosomal recessive, X-linked, and even digenic inheritance patterns. Diagnosis relies on urinalysis, histological examination and genetic testing, aided by next-generation sequencing.

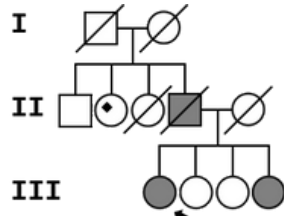
OBJECTIVE

1. To present a patient with two likely AS-related pathogenic variants, showing only renal dysfunction and a report of similar cases in the paternal family, but with varied clinical expression;
2. To discuss whether the variants found are both determinants of the patient's condition or if one of them may predominate.

CASE DESCRIPTION

A 49-year-old female sought a geneticist with slowly progressive proteinuria for 30 years. She is the eldest daughter of four children born to a non-consanguineous couple, reporting a similar condition in her father (deceased) and younger sister (see pedigree). Genomic analysis by exome sequencing revealed two heterozygous variants in the COL4A3 gene: the first, c.3325C>T (p.Pro1109Ser), a missense variant that affects a region with an important role in the structural stability of collagen; the second, c.3829G>A (p.Gly1277Ser), also missense, classified as likely pathogenic for Alport syndrome. The first variant has an uncertain significance because, although three individuals with membranous nephropathy, familial hematuria and Alport syndrome have been previously identified, it was also seen in a healthy individual (or asymptomatic for nephrological conditions).

The second alteration has already been deposited by a Brazilian group (ClinVar SCV002526416) as pathogenic or probably pathogenic for Alport syndrome at different levels of specification, including a case of autosomal dominant inheritance. The variants were screened in living relatives (mother and sisters), but the results are not yet available.



DISCUSSION

It is possible that both observed variants contribute to the patient's renal manifestation, given their relatively low frequency (0.42% and 0.03%) in ClinVar and the fact that they only appear heterozygous, never homozygous, in population databases. Furthermore, their dysfunctional impact on the $\alpha 3$ chain of collagen IV in the glomerular basement membrane has already been reported. However, conflicting insertions in the databases raised suspicions that one of them may not play a relevant role in this case, or even that the low severity of the condition is due to the combined action of both variants. It was recommended that the family analysis be expanded to better identify the role of each variant in this group.

REFERENCES

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