STUDY OF THE COL4A3 GENE AND DESCRIPTION OF NEW MUTATIONS RESPONSIBLE FOR AUTOSOMAL DOMINANT ALPORT SYNDROME

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OBJECTIVES

Autosomal forms represent 20% of all cases of Alport syndrome (15% recessive and 5% dominant).
They are caused by mutations in the COL4A3 and COL4A4 genes, which encode alpha-3 and alpha-4 collagen chains.
Our objective is to find, in the patients diagnosed with autosomal Alport syndrome admitted in our hospital, mutations in the COL4A3 gene responsible for this disease.

METHODS

We analyze 8 families with a clinical diagnosis of autosomal Alport syndrome.
We carry out a search of mutations in the COL4A3 gene using direct DNA sequencing from the index patient after amplifying it with polymerase chain reaction and mutation analysis with CSGE-heteroduplex.

RESULTS

6 patients (75%) presented a dominant inheritance, one of them (12.5%) had a recessive inheritance, and another one (12.5%) had no previous family history of Alport syndrome.

We have found 16 mutations. 2 of them were pathogenic and responsible for the disease:
Mutation **c.345DelG; p.G115GFSX37** is the deletion of a Guanine in the position 345 of the COL4A3 gene, which produces a stop codon 37 codons later, which leads to the generation of a truncated protein and is responsible for the symptoms in this family. This mutation has not been described in the literature.

Mutation **c.4235G>T; p.G1412V** changes a Guanine with a Thymine in position 4235 of the gene, which generates a change of glycine with valine in the position 1412 of the protein, which has already been described as pathogenic. All other mutations can be classified as demographic polymorphisms; 7 of which have already been described and 7 are described in this study. They are intronic variants located far away from splicing areas, which means that they are not considered as pathogenic variants.

MUTATION	REFERENCE	MEANING
c.345 Del G; p.G115GFSX37	Our study	Frameshift
c.4235G>T; p.G1412V	Tazon Vega et al (2003)	Missense
c.127G>C; p.G43R	Heidet et al (2001)	Polymorphism
IVS5+73C>T	Voskarides et al (2007)	Polymorphism
c.422T>C; p.L141P	Longo et al (2002)	Polymorphism
c.485A>G; p.E162G	Heidet et al (2001)	Polymorphism
c.G976T; p.D326Y	Heidet et al (2001)	Polymorphism
c.1352A>G ; p.H451R	Heidet et al (2001)	Polymorphism
c.1721C>T; p.P574L	Heidet et al (2001)	Polymorphism
IVS 4-41 INSG	Our study	Polymorphism
IVS16+14T>C	Our study	Polymorphism
IVS 17+35T>G	Our study	Polymorphism
IVS30-66C>T	Our study	Polymorphism
IVS32+69 A>G	Our study	Polymorphism
IVS 39-4 Del TT	Our study	Polymorphism
IVS46-69C>T	Our study	Polymorphism

CONCLUSIONS

Mutation **c.345 Del G; p.G115GFSX37** is a deletion that generates a truncated protein. This is a pathogenic mutation responsible for an autosomal dominant Alport syndrome, which is described for the first time in this study.
We describe 7 intronic mutations classified as demographic polymorphisms because they are far away from splicing regions, which means that they have no effect on the resulting protein.