

Alport's syndrome and diffuse leiomyomatosis

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Abstract

In a few families and in isolated patients with Alport's syndrome (AS) (about 5%), with proven alpha5 chain of type IV collagen (COL4A5) gene mutation, the association with leiomyomatosis of the esophagus, tracheobronchial tree and female genitals has been reported. Diffuse leiomyomatosis is a rare clinical condition characterized by benign smooth – muscle - cell proliferation in the female genital tract, tracheobronchial tree, and especially the esophagus, in both males and females. This disease is clinically as severe in females as in males, whereas renal involvement is milder in females, just as in X-linked AS forms without leiomyomatosis. Affected females typically show clitoral hypertrophy, involvement of the labia majora and uterus. Some investigators have documented that the alpha5(IV) and alpha6(IV) chains of type IV collagen, which are usually expressed in the basement membrane of the smooth-muscle cells of the esophagus, are absent in leiomyomas from patients with Alport syndrome and diffuse esophageal leiomyomatosis. The mechanism involved in cell proliferation (causing leiomyomas) is not well understood.

Keywords

muscle cell proliferation, esophagus, tracheobronchial, female genitals, COL4A5-COL4A6 deletion

Disease name and synonyms

- Alport's syndrome and diffuse leiomyomatosis
- Diffuse leiomyomatosis with Alport's syndrome
- Leiomyomatosis, esophageal and vulval with nephropathy

Definition

In a few families and isolated patients with Alport's syndrome, with proven *COL4A5* gene mutation, the association with leiomyomatosis of the esophagus, tracheobronchial tree and female genitals has been reported.

Diffuse leiomyomatosis is a rare clinical condition characterized by benign smooth-muscle cell proliferation in the female genital tract, tracheobronchial tree and especially in the esophagus in both males and females.

Frequency

Diffuse leiomyomatosis concerns approximately 5% of patients with Alport syndrome.

History

The association of diffuse leiomyomatosis with typical Alport syndrome was first reported in 1982 by Gracia Torres and Guarner. Careful analysis of documented pedigrees failed to

disclose any male-to-male transmission, consistent with dominant X-linked inheritance.

Clinical description

Diffuse leiomyomatosis is clinically as severe in females as in males, whereas renal involvement is milder in females, just as in X-linked Alport syndrome forms without leiomyomatosis. Affected females typically show clitoral hypertrophy, and involvement of the labia majora and uterus.

Etiology

Some investigators have documented that type IV collagen $\alpha 5(\text{IV})$ and $\alpha 6(\text{IV})$ chains, which are usually expressed in the basement membranes of the smooth-muscle cells of the esophagus, are absent in leiomyomas from patients with Alport syndrome and diffuse esophageal leiomyomatosis.

The molecular basis of Alport syndrome with diffuse leiomyomatosis has been identified by the finding of deletions involving the 5' end of *COL4A5* and extending into the *COL4A6* genes.

It is possible that only the $\alpha 6(\text{IV})$ chain is critically involved for normal smooth muscle cell differentiation, but simultaneous mutation of both *COL4A5* and *COL4A6* genes is necessary for the development of diffuse leiomyomatosis.

Unresolved questions

It is well known that type IV collagen, in several cell types, including myocytes, contains cell-binding sites, within the triple helical and N and C termini. Therefore, the absence of $\alpha 5/\alpha 6$ chains may lead to abnormal morphogenesis and uncontrolled cell proliferation. However, the role of the *COL4A6* mutation in the development of this particular smooth-muscle cell tumoral process has not yet elucidated.

References

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