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Alport syndrome Up To Date and development of gene targeted therapy

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Alport syndrome (AS) is a progressive hereditary renal disease that is characterized by sensorineural hearing loss and ocular abnormalities. It is divided into three modes of inheritance, namely, X-linked Alport syndrome (XLAS), autosomal recessive AS (ARAS), and autosomal dominant AS (ADAS). XLAS is caused by pathogenic variants in *COL4A5*, while ADAS and ARAS are caused by those in *COL4A3*/*COL4A4.* Diagnosis is conventionally made pathologically, but recent advances in comprehensive genetic analysis have enabled genetic testing to be performed as a first-line diagnosis of AS. Because of these advances, substantial information about the genetics of AS has been obtained and the genetic background of this disease has been revealed, including genotype–phenotype correlations and mechanisms of onset in some male XLAS cases that lead to milder phenotypes of late-onset end-stage renal disease (ESRD). There is currently no radical therapy for AS and treatment is only performed to delay progression to ESRD by using nephron-protective drugs. However, angiotensin-converting enzyme inhibitors can remarkably delay the development of ESRD (Figure 1). Recently, some new drugs for this disease have entered clinical trials or been developed in laboratories. And we are also developing a novel gene targeted therapy of "exon skipping therapy" and showed clinical-pathological findings of the XLAS model mouse was remarkably improved by this therapy. In this lecture, I will review the diagnostic strategy, genotype–phenotype correlation, molecular mechanisms of disease onset and treatment of AS including exon skipping therapy.

Figure 1. ACEI/ARB treatment in Male X-linked Alport syndrome