ANDROGEN INSENSITIVITY WITHOUT AN ANDROGEN RECEPTOR MUTATION: RESULTS FROM A LARGE COHORT STUDY

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INTRODUCTION

Androgen insensitivity syndrome (AIS) is a 46,XY difference of sex development (DSD) classically caused by mutations in the X-chromosomal androgen receptor (*AR*) gene. Nevertheless, in over 50% of individuals with clinical AIS no *AR* coding gene mutation can be found. We previously established an assay (apolipoprotein D (APOD assay) that measures androgen dependent AR-activity in genital skin fibroblasts (GFs). Using this assay we identified a group of GFs with reduced AR function in the absence of an *AR* coding gene mutation, called AIS type II (1).

AIM

Investigation of the prevalence of AIS type II based on GFs derived from a large cohort of patients with DSD and clinically presumed AIS and further characterization of this group of *AR* mutation-negative AIS.

METHOD

Assessment of AR function in GFs from individuals with clinical AIS but no *AR* coding gene mutation (n=95). AR mRNA and protein expression measurement in GFs with reduced AR function and in male control GFs. DNA-methylation analysis of the *AR* promotor in GFs with reduced *AR* mRNA expression and in male control GFs. Exome-sequencing of AIS type II GFs.

RESULTS

31 out of 95 GFs (33%) from individuals with clinical AIS but no mutation in the *AR* gene fell in the group AIS type II. Three of them (9.6%) showed normal *AR* mRNA but reduced AR protein expression levels (2), nine (29%) showed reduced AR mRNA and protein expression levels and 19 (61%) showed normal AR mRNA and protein expression. Out of the nine GFs with reduced *AR* mRNA expression, four showed significantly higher *AR* promotor methylation levels explaining the reduced AR expression (3) (figure 1).

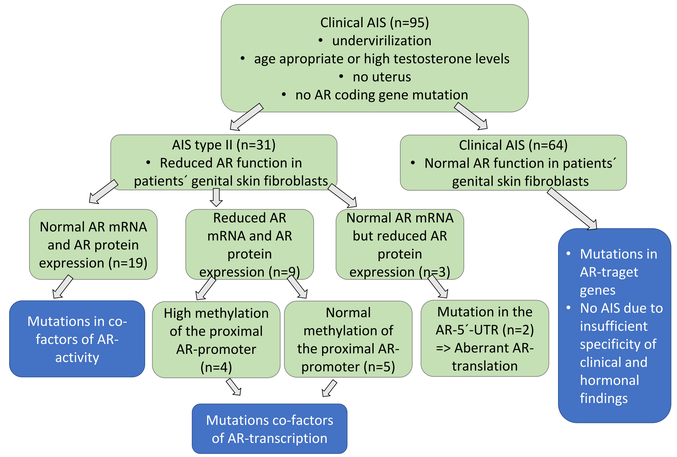

Figure 1. Functional characterization of AIS type II.

Exome-sequencing of 26 AIS type II GF revealed in 12 cases likely pathogenic variants in known DSD-genes other than the AR and in 10 cases likely pathogenic variants in genes so far unrelated to DSD. In four cases no candidate genes were identified (figure 2).

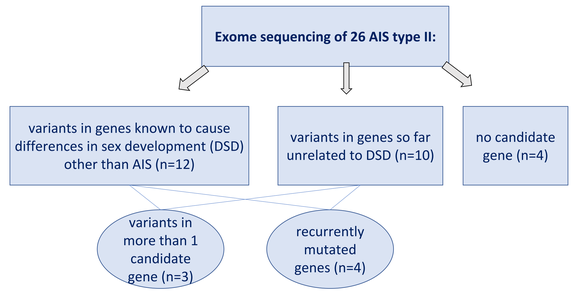

Figure 2: Exome sequencing on AIS type II

CONCLUSIONS

One third of individuals clinically diagnosed with AIS but without a mutation in the *AR* coding gene show a reduced expression and/or function of the AR (AIS type II). Exome sequencing of AIS type II GFs revealed both known and unknown candidate DSD-genes as potential cofactors of AR-activity. Two thirds of examined cases show a normal APOD induction. In these cases either transcriptional targets downstream of the AR could be affected or the underlying DSD diagnosis is not AIS due to insufficient specificity of the clinical and hormonal findings.

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