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).

INTRODUCTION

Androgen receptor function is essential for normal sexual differentiation in the human fetus. The classical form of the disease, called AIS, is caused by mutations in the AR gene. However, in over 50% of cases no AR coding gene mutations 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).

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 18 (61%) showed normal AR mRNA and protein expression. Out of the nine GFs with reduced AR mRNA expression, four showed significantly higher AR promoter methylation levels explaining the reduced AR expression (3) (figure 1).

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 GF 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.

REFERENCES

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CONTACT INFORMATION

Nadine.Homig@uksh.de