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Variants in *NWD1* gene leading to different degrees of gonadal dysgenesis

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Introduction

Mammalian sex development is directly dependent on gonadal determination. Whole exome sequencing in patients with differences of sex development (DSD) allows the discovery of new factors involved in human sex development. One of these factors is *NWD1* (NACHT and WD repeat domain containing 1) a cytosolic protein that seems to play a role in modulating androgen receptor signaling (*Figure 1*). We identified variants in the *NWD1* gene in six undervirilized XY patients and in two XX patients. The phenotype of one of the patients with XX karyotype is described here.

Case

A 15-year-old female adolescent with normal stature presented with delayed puberty (B1), primary amenorrhea, retarded bone maturation (bone age 11 years, Greulich & Pyle) and normal body proportions.

Lab work
LH 33.6 U/L (1.1-3.8 U/L); FSH 106 U/L (1.4-4.2 U/L); estradiol unmeasurable. Testosterone 1.2 nmol/L (0.2-0.6 nmol/L). Ovarian autoantibodies negative. AMH 0.1 pmol/l. Karyotype 46,XX.

The external genitalia were female, uterus was present and the ovaries were very small without follicles at ultrasound. Due to the elevated testosterone, diagnostic laparoscopy was performed, which revealed streak gonads on both sides. The repeated elevated testosterone values are therefore most likely derived from precursors of adrenal origin. Estrogen replacement therapy was leading to normal pubertal development and further growth. Under combined estrogen/progesterone therapy regular menses occurred.

Whole exome sequencing showed a novel mutation in *NWD1* gene:
The patient's variant (c.754delA (Het)) leads to a frameshift and premature stop codon (p.Asn252ThrfsTer11).

3D structure analysis shows that over 90% of the protein is lost leading most likely to either degradation or production of a shorter non-functional protein.

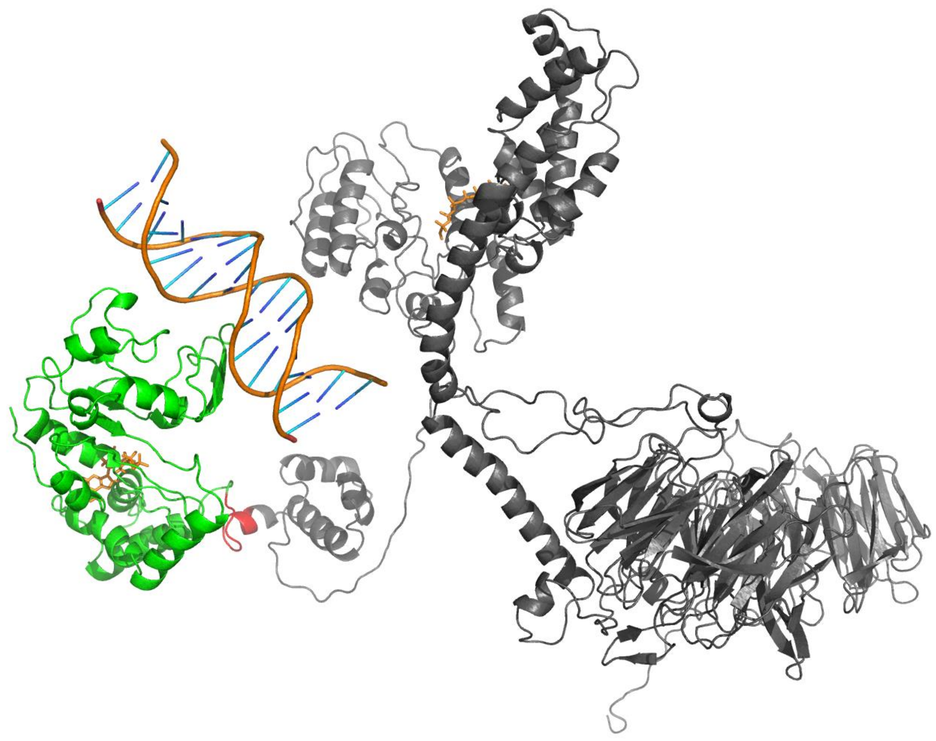

Fig. 1 3D model of patient NWD1 p.Asn252ThrfsTer11 variant.
The patient variant leads to a frameshift mutation and a premature stop codon. In green, the correctly expressed part compared to the WT. The red part are the 11 amino acids under frameshift and the greyed out part depicts the missing amino acids in the patient NWD1 variant.

Conclusion

The variant in *NWD1* gene is likely to be responsible for our patient's phenotype. Accordingly, 3D structure analysis showed that the mutation in this gene most likely leads to either **degradation** or **inactivation** of the protein.

Another seven patients with 46, XY and 46, XX DSD carry **pathogenic variants in *NWD1***, suggesting that this gene might be part of the **gonadal determination cascade in both sexes**, playing a role in modulating androgen receptor-signaling.

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