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A Challenging Diagnosis in Three 46, XY Females from Two Related Families.

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BACKGROUND

Mutations in the 17β-hydroxysteroid dehydrogenase (17betaHSD-3) result in 46, XY disorder of sex development (DSD). Biochemical hallmark of 17betaHSD-3 deficiency is a Testosterone/Androstenedione ratio (T/A ratio) less than 0.8. 17betaHSD-3 mutations have been associated with a wide spectrum of phenotypes, ranging from under-virilized male to a female appearance of genitalia at birth. Indeed, 17betaHSD-3 deficiency in prepubertal patients is often clinically indistinguishable from androgen insensitivity syndrome (AIS) and its diagnosis can be extremely challenging.

OBJECTIVE AND HYPOTHESIS

Three females from the same pedigree (two siblings and their first cousin) were suspected to be affected by 46, XY DSD because of clitoromegaly and inguinal masses.

METHODS

Basal and dynamic hormonal assessment as well as genetic tests have been performed in all subjects

RESULTS

The two sisters were admitted at the age of 2 and 6 years respectively, their cousin at the age of 10 years. Their karyotype was 46, XY. They were suspected to be affected by androgen insensitivity and thus they underwent gonadectomy. Molecular analysis of androgen receptor gene did not reveal any mutation. A low T/A ratio (<0.8) in one of the patient raised the suspicion of 17betaHSD-3 deficiency.
Molecular analysis of the HSD17B3 gene (which encodes for the 17betaHSD-3 enzyme) revealed a compound heterozygous mutation in all 3 girls.
The two sisters inherited a novel mutation IVS3+1 G<T from the mother and the rare mutation IVS3-1 G<C from their father. Their cousin inherited the RW80 mutation from the father and IVS3-1 G<C from the mother

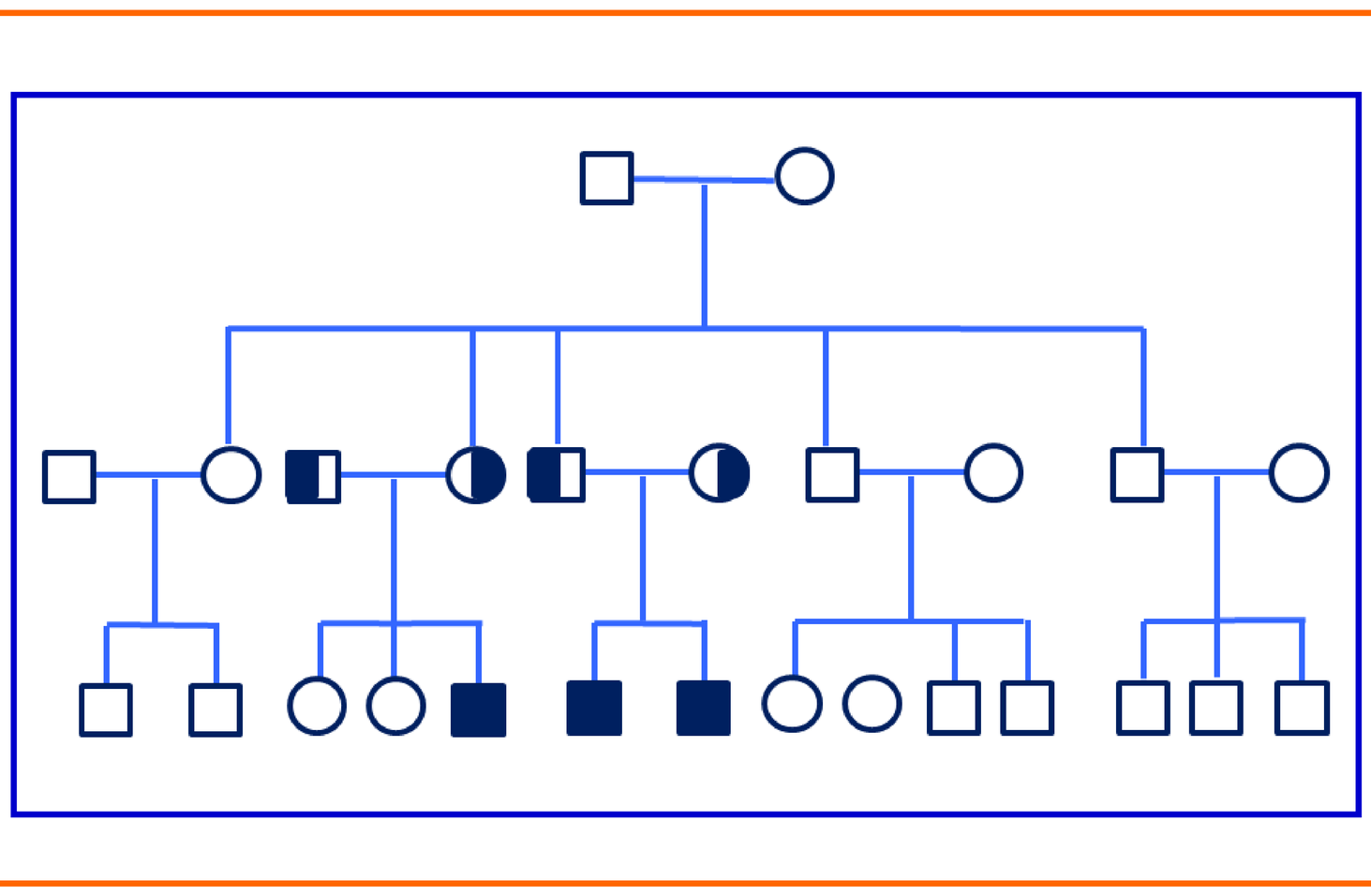

Fig.1 Pedigree

46,XY karyotype and female phenotype

CONCLUSIONS

Our cases suggest that 17βHSD 3 deficiency should be considered in 46,XY DSD cases with female appearance of external genitalia. Moreover, we reported a novel mutation of 17βHSD 3, causing 46,XY DSD in two out of three related subjects.