46,XY complete gonadal dysgenesis in a familial case with a rare mutation in the desert hedgehog (DHH) gene

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Abstract

Purpose

Disorders of sex development (DSD) have been linked to gene defects that lead to gonadal dysgenesis. Herein, we aimed to identify the genetic cause of gonadal dysgenesis in a patient with primary amenorrhoea tracing it to a phenotypic female carrying a 46,XY karyotype of a consanguineous family.

Case presentation

We report the case of a 19-year-old phenotypic female patient of Iraqi background presenting with primary amenorrhoea and absent secondary sex characteristics. There was absence of axillary and pubic hair, and breast development was at Tanner stage I. There was no genital ambiguity.

The patient was previously investigated in Iraq at the age of 16 years, where she underwent a diagnostic laparoscopy following the results of her karyotype, which was 46, XY. Initial investigations revealed elevated LH (20.1 IU/L) and FSH levels (48.6 IU/L), with normal TSH (2.29 mIU/L) and PRL (250 mIU/L) levels. The results of the hCG stimulation test (hCG 2000 units for 3 days) are shown in Table 1 and are compatible with absence of testicular tissue. The CT of the abdomen/pelvis showed no functioning uterus or ovaries. A subsequent abdominal laparoscopy identified no uterus, and the remnants of gonadal tissue were removed. The irregularly shaped tissues were located close to the inguinal canals bilaterally.

Table 1. Hormonal levels before and after hCG stimulation

	Testosterone ng/ml	Androstenedione ng/ml	DHEAS µg/ml	17 OH progesterone ng/ml	DHT ng/ml	T/DHT
Before	0.19	0.7	1.35	1.09	0.012	15.8
After	0.19	0.9	1.45	1.85	0.023	8.2

Whole exome sequencing (WES) using the TruSeq Rapid Exome kit on an Illumina NextSeq500 system revealed the rare, only once reported in homozygosity, p.Arg164Pro missense mutation of the *DHH* gene [1]. Sanger sequencing confirmed p.Arg164Pro in homozygosity in our index patient [2]. Both consanguineous parents, who had no reproductive malformations, were identified as carrying the mutation in the heterozygous state (Figure 1).

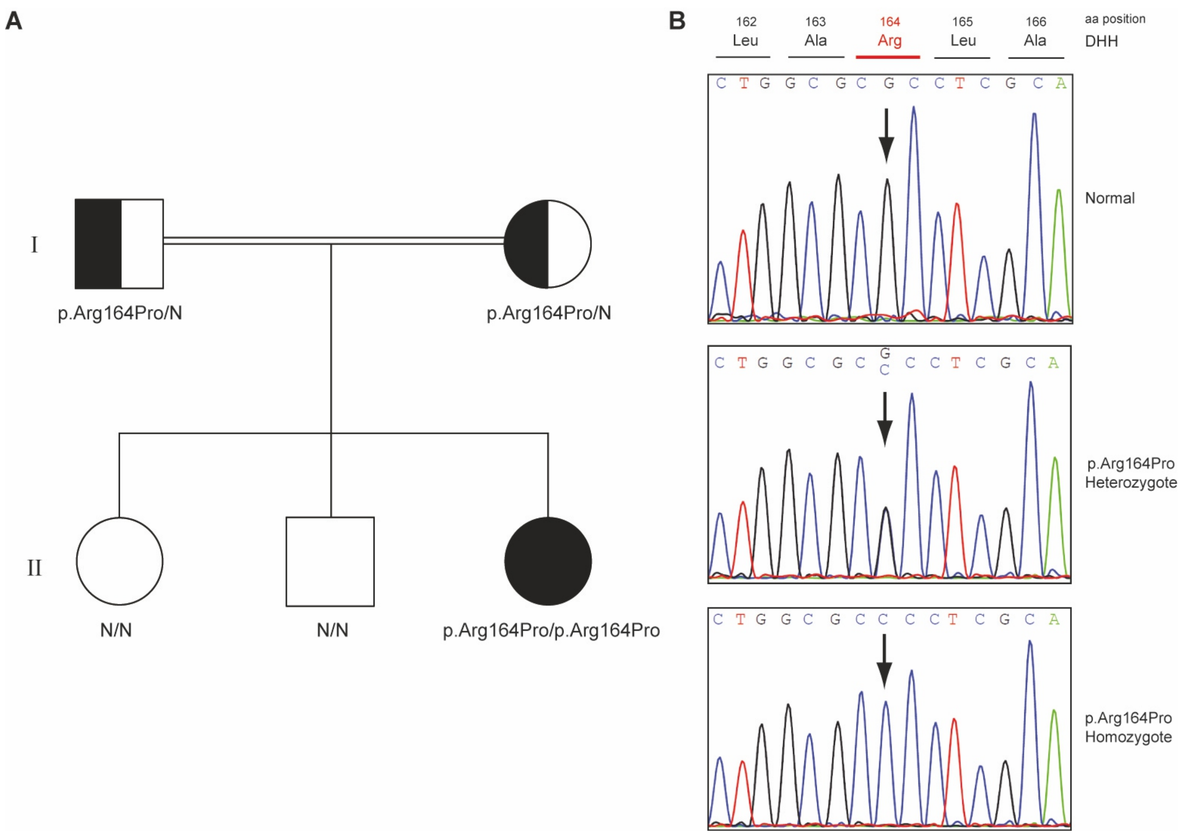

Figure 1. Genetic analysis of the patient with 46,XY DSD. A. Pedigree of the family. Squares and circles indicate males and females, respectively. Black shading indicates the presence of the DHH: p.Arg164Pro mutation. The consanguineous marriage is indicated by the double line. **B.** Sequence electropherograms of the novel DHH: p.Arg164Pro mutation in heterozygote and homozygote state.

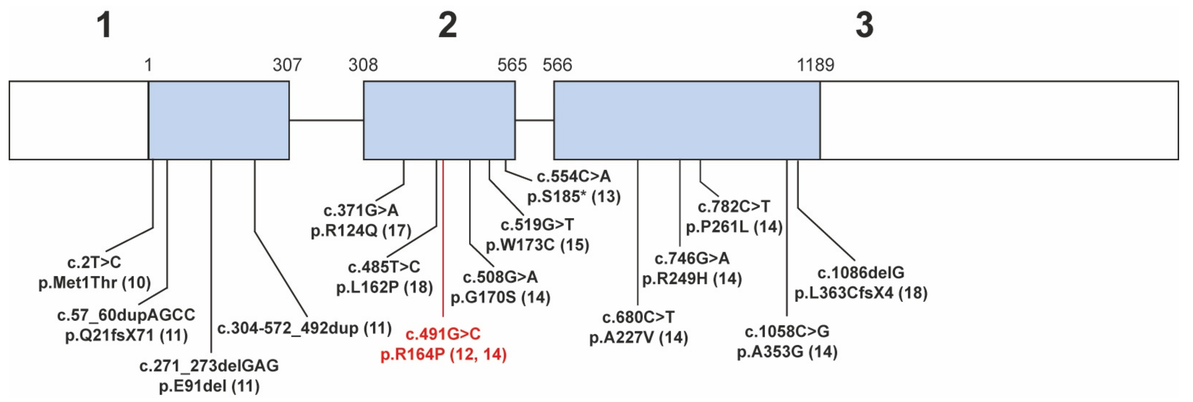

Figure 2. Schematic representation of the *DHH* exons 1-3 with all reported mutations to date. The DHH: p.Arg164Pro mutation identified in homozygosity is indicated in red.

Table 2. Genes involved in *46,XY* DSD - Disorders of testicular differentiation and *46,XY* DSD - Disorders of androgen synthesis and action.

46,XY DSD- Disorders of testicular differentiation (10-20%)		
	Gene	**Chromosomal locus**
Complete or partial gonadal dysgenesis	*ATRX*	Xq21.1
	CBX2	17q25.3
	DAX1 (*NR0B1*)	Xp.21
	DHH	12q13.12
	DMRT1	9p24.3
	EMX2	10q26.11
	ESR2	14q23.2–q23.3
	FGFR2	10q26.13
	GATA4	8p23.1
	HHAT	1q32.2
	MAP3K1 (*MEKK1*)	5q11.2
	NR5A1	9q33.3
	SOX9	17q24.3
	SRY	Yp11.2
	TSPYL1	6q22.1
	ZNRF3	22q12.1
	TSPYL1	6q22.1
	ZNRF3	22q12.1
Ovotesticular DSD	*WNT4*	1p36.12
	ZFPM2 (*FOG2*)	8q23.1
Persistent Mullerian duct syndrome	*AMH*	19p13.3
	AMHR2	12q13.13
***WT1* mutations (Denys-Drash syndrome, Frasier syndrome)**		
Vanishing testes – Congenital anorchia		
***46,XY* DSD - Disorders of androgen synthesis and action (undetermined frequency)**		
	Gene	**Chromosomal locus**
Abnormal LH	*LHB*	19q13.33
LH/CG insensitivity	*LHCGR*	2p16.3
7-Dehydro-cholesterol desmolase deficiency	*DHCR7*	11q13.4
STAR deficiency (lipoid CAH)	*STAR*	8p11.23
(1) Classical form		
(2) Non-classical form		
CAH with cholesterol desmolase deficiency	*CYP11A1*	15q24.1
CAH with 3β-hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2*	1p12
CAH with combined 17 hydroxylase/17,20-lyase deficiency	*CYP17A1*	10q24.32
Isolated 17,20-lyase deficiency		
P450-oxidoreductase deficiency	*POR*	7q11.23
Cytochrome b5 deficiency	*CYB5A*	18q22.3
17β-Hydroxysteroid-dehydrogenase type 3 (17-keto-reductase) deficiency	*HSD17B3*	9q22.32
5α-reductase type 2 deficiency	*SRD5A2*	2p23.1
Backdoor steroidogenesis deficiency	*AKR1C2*	10p15.1
	AKR1C4	10p15.1
Androgen insensitivity:	*AR*	Xq12
Complete (CAIS)		
Partial (PAIS)		
X-linked hypospadias	*MAMLD1 (CXOrf6)*	Xq28
Isolated hypospadias	*ATF3*	1q32.3
Cryptorchidism	*INSL3*	19p13.11

Conclusions

Defects in the *DHH* gene have been reported as a very rare cause of DSD, and this report increases the number of 46,XY gonadal dysgenesis cases. Additionally, the present study highlights the importance of genetic validation of patients with DSD, since this is likely to alleviate the considerable psychological distress experienced by both the patient and the parents.

References

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Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: Informed consent was obtained from the patient and the parents of the minors to be screened for mutations in the DHH gene. The project was approved by the Cyprus National Ethics Committee and all methods were performed in accordance with the relevant guidelines and regulations.

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