

Complete Androgen Insensitivity in Three Generations of a Family

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ABSTRACT Four individuals of a family, spanning across three generations, showed primary amenorrhea. Karyotyping of the proband and her two aunts revealed a normal 46, XY cell line in all cells. Hormonal profile of all three individuals showed normal serum FSH, slightly elevated serum LH and testosterone levels in the normal male range. Their clinical features, karyotypes and hormonal profiles indicate complete androgen insensitivity syndrome. A case study hence is presented in a family.

INTRODUCTION

The genetic control of sex determination is mediated by a number of genes, one of the most important being the Sex determining Region on Y chromosome (SRY). It initiates a cascade of events that ultimately leads to testes formation followed by male differentiation. Anti-Mullerian Hormone (AMH) causes regression of the Mullerian derivatives, while testosterone (T) leads to differentiation of the Wolffian ducts. T is also metabolized to dihydrotestosterone (DHT), a more potent androgen, responsible for the differentiation of the prostate and development of the urogenital system and external genitalia.

The action of both T and DHT is mediated by a single nuclear androgen receptor, the gene for which is localized at Xp11-12 (Lubahn et al. 1988). Different types of mutations in the AR gene cause resistance of the target organs to androgen action (Gottlieb 2004), leading to absent or deficient virilization of the genitalia in the 46,XY individuals, making them phenotypic females. This type of end organ insensitivity to androgens is designated as androgen insensitivity syndrome (AIS). Mutations that severely affect the AR protein structure which is of a current research cause complete androgen insensitivity syndrome (CAIS). These individuals usually present for investigation with inguinal hernia at

a young age or with primary amenorrhea later. More subtle changes in the receptor function lead to partial androgen insensitivity syndrome (PAIS) which manifests as male undermasculinization. Here, we present a case of familial CAIS where the affected individuals are spread across three generations.

CASE REPORT

Figure 1 shows the pedigree of the proband, a 19 year old female (IV 6), referred for karyotyping with a complaint of primary amenorrhea. She was 5'5" tall, weighed 54 kgs and had an absence of secondary sex characteristics. Her external genitalia were normal. Ultrasonography of the proband showed a blind vagina with absence of ovaries and Mullerian structures like uterus and fallopian tubes. Her family history revealed three other females, on the maternal side, with similar complaints. She had a normal brother. The proband's mother (III 12) had a delayed menarche at the age of 19 years while two of her sisters, aged 50 (III 6) and 46 years (III 10), had primary amenorrhea, normal breast development, normal female external genitalia but absence of axillary and pubic hair. They had never been investigated and were leading a normal married life. The proband's mother had a maternal aunt (II 3), aged 86 years with similar complaints, who was not available for study.

As shown in Table 1 the proband and her two affected maternal aunts had highly elevated serum testosterone levels which were in the normal range for males. Serum FSH was normal while

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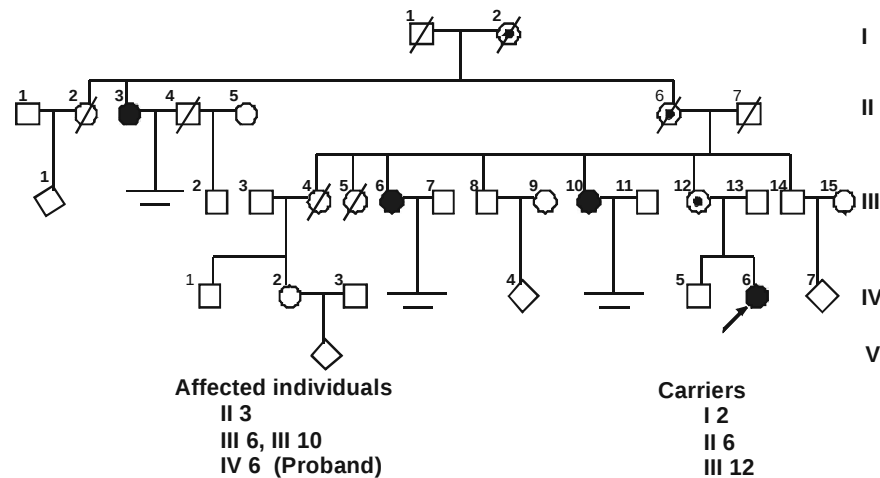


Fig. 1. Pedigree of the proband, showing five generations, affected individuals and carriers.

serum LH was elevated compared to normal male levels. Serum T levels indicated presence of testes which were not detected sonographically in the proband.

Table 1: Hormone levels in the proband and her two affected maternal aunts.

Hormones	Proband (IV 6)	Maternal Aunt (III 6)	Maternal Aunt (III 10)
s.T (ng/ml) (2.8 – 8.0)	8.76	4.00	5.45
s.FSH (mIU/ml) (1.4 – 15.4)	4.15	8.86	16.12
s.LH (mIU/ml) (1.2 – 7.8)	18.29	15.55	22.73

Figures in parentheses indicate normal male range.

Cytogenetic study from the peripheral blood lymphocytes revealed a 46,XY karyotype in the three affected individuals analyzed. Presence of Y chromosome was confirmed by C-banding and PCR analysis detected the presence of SRY.

DISCUSSION

Detailed information on genotype/phenotype relationship in AIS is important for sex assignment, treatment of AIS patients, genetic counseling of their families and insights into the functional domains of the AR. The development of Wolffian ducts is commonly accepted to be dependant on fetal androgens. Hence, the present family was studied using the phenotype,

genotype and hormonal profile for correct diagnosis and counseling.

In the present family all affected individuals had a 46,XY karyotype, which is known to be the case with CAIS patients previously reported (Brinkmann 2001). The pedigree indicates that the defective gene has been transmitted through the generations via carrier females. No phenotypic variation was observed between the affected members of this family as also noted by Boehmer and colleagues (2001) for families with CAIS. Although mutation analysis has not been done in our case, most cases of CAIS are due to mutations in the AR gene (Gottlieb 2004). A few cases however, that failed to show any mutation in the coding region of the AR gene, have been explained by defects in the coregulator proteins (Adachi et al. 2000).

All the affected individuals had a near normal female phenotype with a normal female habitus. Even in absence of ovaries, breast development is induced by aromatization of androgens to estrogens and an unopposed inhibitory action of androgens (Hughes 2000), as seen in the present study. Mullerian duct regression starts at 8 weeks of gestation in males through the action of AMH secreted by Sertoli cells (Allard et al. 2000). The missing Mullerian duct derivatives in the proband indicate presence of functional Sertoli cells. The normal male serum T levels in the affected individuals suggest presence of functional Leydig cells. Malfunction of AR

leads to regression of Wolffian ducts, as seen by the absence of Wolffian structures despite normal levels of T. Even though the testes were not sonographically detected in the proband, the hormonal profile and phenotypic characteristics confirm presence of the same. Brinkmann (2001) too has reported that the main phenotypic characteristics of individuals with CAIS are female external genitalia, a short, blind ending vagina, absence of Wolffian duct derived structures, absence of prostate and development of gynecomastia. It is further mentioned that usually T levels are elevated at time of puberty and also elevated LH levels are found.

Gonadectomy is advisable in affected individuals as the undescended testes can undergo neoplastic changes in almost 30% cases. Post pubertal gonadectomy, after complete feminization, should be preferred. Prepubertal gonadectomy, if undertaken, should be followed by estrogen replacement therapy to initiate puberty, maintain feminization and avoid osteoporosis (Gottlieb et al. 2005). Accordingly, our case was counseled regarding the long term health implications and appropriate treatment options available.

Thus, the clinical, chromosomal, hormonal features of CAIS provide a human model for understanding the role of androgen and its receptor in the induction and maintenance of male sex differentiation and function.

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