CASE REPORT

A Case of Complete Androgen Insensitivity Syndrome: Genetic Analysis of the Family

Kota Sunil K. · Kotni Gayatri · Pani Jaya P. ·
Modi Kirtikumar D.

Received: 9 August 2012 / Accepted: 27 March 2013 / Published online: 15 May 2013
© Federation of Obstetric & Gynecological Societies of India 2013

Introduction

Besides many other factors, androgens play a role in expression of male phenotype. Androgen activity is mediated by androgen receptor (AR). After binding to androgen, AR translocates to nucleus and adheres to the regulatory regions of specific chromosomal DNA sequences (androgen response elements/ARE), to activate androgen dependent genes.

The AR is encoded by the AR gene (Xq11–12). The gene is formed by 8 exons and 7 introns, spanning more than 90 kb. The functional domains are (a) exon 1 encoding the N-terminal domain (NTD) (1,586 bp); (b) exons 2 and 3 encode the DNA-binding domain (DBD) (152 and 117 bp); (c) the “hinge” region which binds the NTD and DBD consists of residues 628–669; (d) exons 4–8 encode the C-terminal ligand-binding domain (LBD),

(131–288 bp). The C-terminus of the LBD mediates the hormone-dependent transcription. Mutations in the LBD region of AR perturb the conformation of the helix. The mutant AR is unable to efficiently bind to dihydrotestosterone (DHT) and to transactivate AREs [1].

Mutations in the AR gene leading to disordered AR function results in different forms of X-linked male pseudohermaphroditism, known as androgen insensitivity syndrome (AIS). This affects XY female individuals with normal androgen production and metabolism. AIS is present in 1:20,000–64,000 male births. The presence of variable phenotypic expression allows for the classification of AIS into complete androgen insensitivity (CAIS), partial androgen insensitivity (PAIS), and mild androgen insensitivity (MAIS). Approximately, 90 % of molecular defects in AR gene are single base point mutations, mostly missense mutations [2]. Here, we describe a familial case of CAIS presenting with similar mutations described across three generations. To the best of our knowledge and belief, ours is first such report citing this mutation in an Indian family.

Case Report

A 10-year girl, born to parents of consanguineous marriage was referred for evaluation of palpable gonads in the inguinal region. She was delivered at term after an uneventful pregnancy by normal vaginal delivery with a

Kota S. K. (✉), DNB Resident · Modi K. D.,
Head of Department
Department of Endocrinology, Medwin Hospital, Chiragh Ali
Lane, Nampally, Hyderabad 500001, Andhra Pradesh, India
e-mail: hidocsunil@ibibo.com

Kotni G., Consultant
Department of Obstetrics and Gynecology, Riyadh Care
Hospital, Riyadh, Saudi Arabia

Pani J. P., Consultant
Department of Obstetrics and Gynecology, Apollo Hospitals,
Old Sainik School Road, Unit-15, Bhubaneswar, Orissa, India

Fig. 1 Female appearing external genitalia with bilateral inguinal gonads

birth weight of 2.6 kg and length of 48 cm. Bilateral inguinal gonads with short- and blind-ended vagina were detected at birth. She was followed up over a period of 8 months, after which assignment of female gender was decided. Corrective procedure for inguinal gonads had been planned, but was not done. On physical examination, she had typical female external genitalia. Palpable gonads were found bilaterally in the inguinal region (Fig. 1), pubertal stage was B4P5. Pelvic sonogram did not demonstrate any mullerian structures. Hormonal evaluation revealed FSH (5.4 mIU/mL; normal: 1.5–12.4), LH (21.2 mIU/mL; Normal: 1.7–8.6) and total testosterone (15 ng/mL; normal: 2.86–8.1). Karyotype was 46 XY. Testosterone (T) and dihydrotestosterone (DHT) synthesis defects were excluded by the normal rise of T and DHT after HCG stimulation (basal T: 15 ng/ml; basal DHT: 9.3 ng/ml; T/DHT ratio after HCG stimulation—7.9; and normal post-HCG stimulation, T/DHT ratio is <17). Gonadectomy was performed a few months later, and histologic analysis revealed bilateral testes with no evidence of malignancy. She subsequently underwent vaginoplasty and received therapy with estrogens. Three maternal aunts presented with primary amenorrhea with adequate breast and pubic hair development and palpable gonads in the age group between 15 and 20 years. They were treated with bilateral gonadectomy, vaginal reconstruction, and estrogen supplementation.

Peripheral blood samples were obtained from the girl and her maternal family members for molecular analysis. Genomic DNA was extracted with the use of PCR amplification of AR exonic fragments 1–8 followed by direct sequencing analysis of the PCR products. It revealed C 2754 to T transition in exon 6 (Fig. 2). The same mutation was confirmed in her mother and the three maternal aunts

Fig. 2 Chromosomal and DNA analysis of the three generations showing 46 XY karyotype with C 2754 to T transition of exon 6 *Red arrow* indicates the index case. *First row* fertile carrier grandmother, *Second row* fertile carrier mother with three affected aunts

and maternal grandmother. Her mother and maternal grandmother were fertile carriers with 46 XX karyotype.

Discussion

We report the familial occurrence of a mutation resulting from C to T transition. Six subjects in three generations carry the mutation. However, four were affected, and two were 46 XX fertile carriers. Missense mutations in AR protein may cause a spectrum of phenotypes. The phenotype variability reflects the degree to which ligand-binding and receptor functions are disrupted by different substitutions [2]. In addition, genetic background also influences the resulting phenotype since a same mutation may cause different forms of AIS within a family [2]. The most frequent are missense mutations that are found within two important areas of the receptor protein: DBD and LBD domains [2]. Out of 193 mutations, 103 causing CAIS are located in the LBD, 51 in the N-terminal, and 24 in the DNA-binding domain [2]. Mutations of a single amino acid in the LBD of the AR can induce functional abnormalities in androgen binding, stabilization of active conformation, or interaction with coactivators.

In our patient, the mutation (C 2754 to T transition in exon 6), alters a Gln codon to a termination codon (Q798X). This mutation has been described previously, and it leads to interruption of the amino acid sequence of LBD of AR between helices VII and VIII [3]. The truncated form of the receptor is devoid of 123 amino acids at the carboxyl end of LBD and the AT2 sequence responsible for activation of transcription. This renders the AR incapable of ligand binding and gene activation. The previously reported lady had sertoli cell adenoma in both gonads, which was lacking in our patient [3].

We conclude that the C2754T mutation described herein is responsible for the symptoms of CAIS in the investigated patient. The C 2754 T mutation is one of the 26 known mutations of the AR that cause the premature termination of translation [2, 3].

The characterization of mutations in the AR gene helps us in the diagnosis and molecular classification of AIS. Knowledge of the AR mutation and its functional consequences can provide useful information about the genotype–phenotype correlation, improving the management of

cases of male pseudohermaphroditism with regard to gender assignment, genital surgery, and gonadectomy.

Conflict of interest It is submitted with the full knowledge and approval of our institute and there is no conflict of interest to disclose from any of the authors with regards to publication of the manuscript or an institution or product that is mentioned in the manuscript. There are no competing interests to disclose, due to any reasons, with whom so ever concerned.

References

1. Adachi M, Takayanagi R, Tomura A, et al. Androgen-insensitivity syndrome as a possible coactivator disease. *N Engl J Med*. 2000; 343:856–62.
2. Gottlieb B, Beitel LK, Wu HJ, et al. The androgen receptor gene mutation database ARDB: 2004 update. *Hum Mutat*. 2004;23: 527–33.
3. Ignacak M, Turek-Plewa J, Limon J, et al. A novel c.C2754 > T transition in the androgen receptor gene introduces the premature termination codon Q798X and results in a truncated form of the receptor. *Gynecol Endocrinol*. 2004;19:178–81.