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Mutation-in-Brief

A Novel Mutation of Androgen Receptor Gene in Complete Androgen Insensitivity Syndrome

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Androgen insensitivity syndrome (AIS) is an X-linked recessive disorder caused by mutation in the gene for the androgen receptor (AR) with 46,XY karyotype (OMIM 300068). The clinical phenotype of AIS is complete or partial. Complete AIS is characterized by a consistent phenotype: unambiguous female external genitalia, breast development at pubertal age, blind-ending vagina, absence of uterus, absent or scant pubic and axillary hair, and presence of normally differentiated testes in a girl or woman. However, the clinical features of partial AIS are variable: ambiguous external genitalia in a girl or woman, undervirilized external genitalia in a boy or man, or azospermia with unambiguous male external genitalia in a man (1–4). So far more than 300 mutations in all exons of the AR gene have been reported in complete AIS (5).

We report a novel mutation of the AR gene in a patient with complete AIS.

Patient Report

The patient, a Japanese girl, was born after a 39-wk uncomplicated pregnancy and delivery. Her birth weight was 2.90 kg, and length, 45.5 cm. Allegedly, a surgeon found her bilateral abdominal testes at the time of repair of bilateral inguinal hernia in infancy. At the age of 9 yr, the patient together with her mother visited our service to consult about the pathogenesis. The maternal uncle, reportedly, has "undervirilized external genitalia". The mother declined to tell further family history. On examination, the patient's height was 133.2 cm (≅25th percentile) and weight 44.7 kg (>97th percentile). She had normal female external genitalia. No tumor was palpable around the inguinal area. Breast as well as pubic hair were Tanner I. Operation scars were present on the abdominal wall. Endocrinological studies were as follows: serum LH, 0.3 mIU/mL (normal); FSH 3.7 mIU/mL (normal); testosterone 0.20 ng/ml (normal), which was increased to 1.82 ng/ml by hCG stimulation (3,000 IU/m^2/dose i.m. for three consecutive days, blood sampling on day 4). Her karyotype was 46,XY. Pelvic MRI revealed the right testis in the abdominal cavity and the left one in the inguinal canal. The patient was clinically diagnosed as having complete AIS.

Written informed consent for a genetic study of the AR gene for the patient, but not for the parents, was obtained from her parents. This study was approved by the ethical committee of our institution. Genomic DNA was extracted from the patient's peripheral lymphocytes. The AR coding region and flanking intronic sequences of all the exons were amplified by PCR, followed by direct sequencing as previously described (6). A hemizygous mutation (c.2125G>A, p.E709K)

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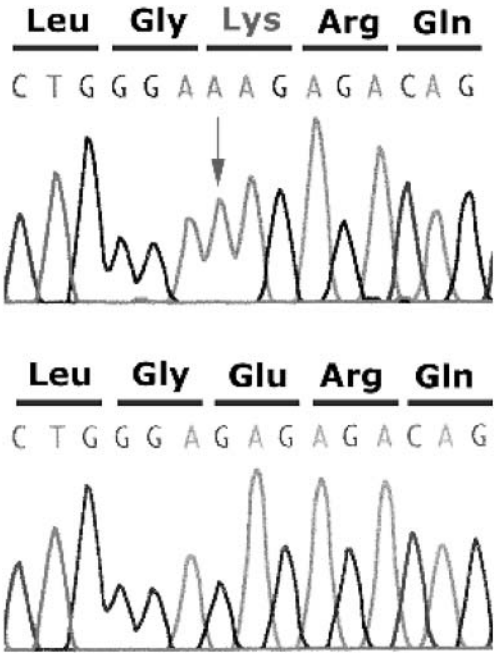

Fig. 1 Partial sequence of exon 4 of the AR gene. Upper panel: the patient has a hemizygous mutation (c.2125G>A, p.E709K) denoted by the arrow. Lower panel: the sequence of the wild type.

was identified in exon 4 of the AR gene of the patient (Fig. 1). The CAG repeat in exon 1 was 25, within the normal range. This mutation was not found in 50 healthy control male subjects.

Discussion

We identified a novel mutation (c.2125G>A, p.E709K) in exon 4 of the AR gene of the patient with complete AIS. Although we did not perform functional study, the AR function of this patient must be severely impaired by this mutation leading to complete AIS for the following reasons. First, the mutation changes the amino acid from acidic (glutamate) to basic (lysine). Second, the site of the mutation is in the amino-terminal portion of the ligand-binding domain, which is critical for AR function (1, 7). Third, the affected amino acids are conserved in the mouse, chicken, Japanese Takifugu fish and xenopus, indicating their functional importance (8, 9).

More than 300 mutations have been reported in patients with complete AIS. It has not been possible, however, to establish any clear genotype-phenotype (complete or partial) correlation to date, besides total deletion of the AR gene represented by complete AIS (1). Furthermore, an identical mutation could cause different phenotypes in different patients, or even within the same family, which might be the case with this family. Unfortunately, we could not analyze the patient's mother, who might be a carrier, and maternal uncle, who might be an affected patient, judging by the family history. Modulating factor(s), even genetically or environmentally, might exist causing different phenotypes with the same AR gene mutation.

In conclusion, we here identified a novel mutation of the AR gene in the patient with complete AIS.

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References

1. Quigley CA, De Bellis A, Marschke KB, el-Awady MK, Wilson EM, French FS. Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 1995;16:271–321.
2. McPhaul MJ. Androgen receptor mutations and androgen insensitivity. Mol Cell Endocrinol 2002;198:61–7.
3. McPhaul MJ. Molecular defects of the androgen receptor. Recent Prog Horm Res 2002;57:181–94.
4. Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. Adv Exp Med Biol 2002;511:121–31.
5. Lady Davis Institute for Medical Research, Sir

Mortimer B. Davis Jewish General Hospital. The Androgen Receptor Gene Mutations Database. Available online from: http://www.androgendb.mcgill.ca/
6. Ishii T, Sato S, Kosaki K, Sasaki G, Muroya K, Ogata T, Matsuo N. Micropenis and the AR gene: Mutation and CAG repeat-length analysis. J Clin Endocrinol Metab 2001;86:5372–78.
7. Lumbroso S, Lobaccaro JM, Georget V, Leger J, Poujol N, Terouanne B, Evain-Brion D, Czernichow P, Sultan C. A novel substitution (Leu707Arg) in exon 4 of androgen receptor gene causes complete androgen resistnace. J Clin Endocrinol Metab 1996;81:1984–8.
8. Available online from: http://www.ensembl.org
9. Available online from: http://www.ebi.ac.uk/clustalw/