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Short report

Identification of a novel mutation in the SRY gene in a 46, XY female patient

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Abstract

Background. - The SRY gene encodes for a testis-specific transcription factor (TDF, testis determining factor) that plays a key role in sexual differentiation and development in males. Several SRY mutations have been described in patients with gonadal dysgenesis, accounting for 10–15% of the sex reversal cases. The reported mutations are both point mutations and deletions, mostly involving the high mobility group (HMG) box domain of SRY, which is a conserved region through the evolution, suggesting that SRY function strictly depends on the HMG box.

Case presentation. - Here we describe the clinical, endocrinological and molecular data of a patient with complete 46, XY gonadal dysgenesis caused by SRY mutation located within the conserved HMG box. Using DNA direct sequencing of the SRY coding region, we identified a single nucleotide insertion at codon 89 with subsequent frameshift of the reading frame sequence, which results in a truncated protein as consequence of an introduction of a stop codon at the position 103.

Abbreviations: HMG, high mobility group; TDF, testis determining factor.

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Conclusion. - A novel SRY mutation has been described in a female with a gonadal dysgenesis associated with a 46, XY karyotype. The described case is of importance for genetic counseling.

Keywords: SRY gene; Swyer, TDF, testis determining factor

1. Introduction

Sex differentiation is a complex process involving several genes located on sex or autosomal chromosomes [2]. In humans, sex determination proceeds in female development unless genes involved in testis determination takes part. The SRY gene initiates testis development during embryogenesis [8]. This gene is located on the distal region of the Y chromosome short arm (Yp), and encodes for a testis–specific transcription factor (TDF, testis determining factor) that plays a crucial role in sexual differentiation and development in males. SRY gene mutations have been considered to account for 10–15% of the sex reversal cases, but mutations in other genes have been also reported [2,3]. Recently it has been also reported a three generation family in which 46, XY gonadal dysgenesis showed an autosomal dominant inheritance [5] suggesting that gonadal dysgenesis is a heterogeneous disorder. The majority of described SRY mutations are point mutations or deletions mainly involving the conserved DNA binding domain of SRY (HMG box), which represents the active site of SRY function. In this report we describe a sex reversal patient with a novel SRY mutation which is likely to critically affect DNA binding function.

2. Materials and methods

2.1. Clinical report

We report a 16-year-old female who presented with primary amenorrhea. The phenotype of the patient is feminine without any dysmorphic feature, with infantilism of secondary sexual characters (lost puberal development of mammary tissue). Height was 167 cm, weight was 55 kg. Outer genitals are clearly feminine, without sign of Wolf structure's derivatives, mullerian structures (uterus and fallopian tubes) are in normal status, as resulted from pelvic echography. Instrumental analysis (pelvic MR) show a uterus regularly connected to the vaginal cervical channel; the gonadal biopsy showed signs of fibrous tissue, typical stromal cells were observed without germ cells; there was neither evidence of gonadoblastoma nor of testicular tissue. A baseline blood sample was obtained for determination of serum concentration of FSH, LH, 17-beta-E2 and Dehydroepiandrosterone levels, resulted within the prepuberal range (laboratory results are reported in Table 1) and described a picture of primitive gonadal insufficiency, for what the patient was subjected to substitutive hormonal therapy. High gonadotropin levels and primary amenorrhea in 46, XY phenotype are homogenously present in Swyer syndrome cases, thus resulting in a higher gonadotropin levels than in normal subjects. The patient currently assumes hormonal therapy, but there is no evidence of follicle maturation in any successive pelvic echography.