Absence of puberty and estrogen resistance by estrogen alpha receptor inactivation in two sisters: a mutation for variable phenotypic severity

Delcour C1, Khawaja N2, Mammeri H3, Drira L3, Chevenne D4, Ajlouni K2, de Roux N1,4


Introduction

Estrogens play an essential role in reproduction and their peripheral action is mediated via nuclear alpha (ERα) and beta (ERβ) receptors as well as membrane receptors. To date, only 3 females and 2 males from 3 families with a loss of function of ERα have been reported [2,3]. The phenotype in these families was strongly suggestive of an estrogen resistance with an absence of a complete puberty, a delay in epiphyseal maturation with high estradiol levels and elevated gonadotropin levels.

Materials and methods

A 36-year-old woman with a primary amenorrhea and no breast development (S1), had elevated 17β-estradiol (1497 pg/ml), high FSH (57 IU/L) and LH (21 IU/L) plasma levels (Table 1), and enlarged multifollicular ovaries (11 and 17 ml) (Figure 1). Her 18-year-old sister also had a primary amenorrhea with no breast development and had moderate increases in 17β-estradiol (204 pg/ml) with high FSH (29 IU/L) and LH (22 IU/L) plasma levels. Pelvic MRI shows ovaries of normal size and the uterus was not seen (Table 1). The parents are first cousins.

Results

In both cases, genetic analysis identified a homozygous variant of ESR1 (c.1154A>T) leading to the substitution of the highly conserved glutamic acid at position 385 by a valine (p.E385V) (Figure 2A). Both parents as well as an unaffected sister were heterozygous for the variant (Figure 2B). The E385 is located in the ligand binding domain (Figure 2B) and the in-silico analysis predicted a deleterious effect on the protein function (Figure 2C). Modeling study of the ERα-E385 variant showed a slight displacement of the H4 to H12 helix, suggesting that the E385V replacement might preclude the activation of the receptor (Figure 2D). A functional analysis was performed by transient expression of WT-ERα or E385V-ERα in HEK293A cells. E385V-ERα transfected cells showed a strong decrease in transcriptional activation by 17β-estradiol of a reporter gene controlled by a standard estradiol-responsive-element (Figure 3) as well as a loss of inhibition of the KISS1 promoter (Figure 4) when compared to WT-ERα. Immunofluorescence analysis showed lower nuclear translocation of E385V-ERα in the presence of 17β-estradiol as compared to WT-ERα (Figure 5 and Table 2).

Conclusion

These two new cases are remarkable as they are sisters and they display a different level of severity of the ovarian and hormonal phenotypes. This phenotypic discrepancy could be attributable to a mechanism that could partially compensate the ERα inactivation.

Bibliography