Association of an Estrogen Receptor Variant with Increased Height in Women

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Summary

There is an association between a B region allele (here called the B' allele) of the estrogen receptor (ER) and a history of spontaneous abortion in women with ER positive breast cancer, but no such association for women with ER negative tumors or women without breast cancer. In this study we compared the heights of women carrying the B and B' alleles. The B' allele was identified by polymerase chain reaction to amplify genomic DNA around the polymorphic region of the ER gene, followed by allele specific oligonucleotide hybridization. This analysis used DNA obtained from blood lymphocytes. Women carrying the B' allele were significantly taller than those carrying the wild type allele (B allele). Multiple linear regression also demonstrated that this association remained (p = 0.017), controlling for the effects of age and race. Since the B' ER allele results from a silent mutation, a second mutation, segregating with it, no doubt plays a role in producing the high incidence of spontaneous abortion we reported previously and the height difference we report here. This second mutation might lie within the estrogen receptor itself or within one of the genes nearby.

Key words

Height - Estrogen Receptor - Polymorphism

Introduction

In 1988 we identified a variant allele of the estrogen receptor (ER) gene (Garcia, Lehrer, Bloomer and Schachter 1988). The variant differs from the wild type allele within the coding sequence for the B domain of the receptor (Kumar, Green, Stack, Berry, Jin and Chambon 1987) (Fig. 1), and is therefore referred to as the B' allele. About 12% of the general population carry the B' allele (Schmutzler, Sanchez, Lehrer, Chaparro, Phillips, Rabin and Schachter 1991).

Clinically, we noticed an association between the B' allele and a history of spontaneous abortion in women with estrogen receptor (ER) positive breast cancer (Lehrer, Sanchez, Song, Dalton, Levine, Savoretti, Thung, Schachter 1990). There seemed to be no such association for women with ER negative tumors. Nor was there any clear relationship between the carrier state for the allele and the risk of breast cancer in women without a history of spontaneous abortion (Lehrer, Schmutzler, Rabin and Schachter 1993).

The B' ER allele contains a guanine (G) to cytosine (C) transition at position 261, which causes a silent mutation in the alanine codon 87 (Macri, Khoriaty, Lehrer, Karurunaratne, Milne and Schachter 1992; Taylor, Li, You, Wilcox and Liu 1992). The mutation is called silent because the wild type triplet GCG and the variant triplet GCC both code for the amino acid alanine. Indeed, because there are only twenty amino acids and 64 possible codons, most amino acids are specified by more than one codon. Hence the genetic code is said to be degenerate, and 25% of all mutations are silent (Thompson, McInnes and Willard 1991).

We now report that women carrying the B' allele are significantly taller than those carrying the wild type allele (B allele).

Methods

We selected for study 456 normal women who had received care between 1989 and 1992 from a private physician affiliated with Mount Sinai Hospital in New York City or Long Island.

Fig. 1 Functional domains of the human estrogen receptor gene. Region A, function unknown; region B, transcription enhancement of ER regulated genes; region C, DNA binding domain; Region D, hinge region; region E, steroid hormone binding domain; region F, function unknown. The arrow indicates the position of the mutation described in this article.

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In addition to height, the other variables assessed by multiple regression were age and race (white-hispanic-other versus Black). All statistical analyses were performed with the SPSS system (Norusis 1992).

Results

Of the 456 women surveyed, the heights of the 402 women of genotype BB (i.e., homozygous for the B allele) ranged from 140 to 188 cm (mean = 162 cm), while the heights of the 53 women of genotype BB' (i.e., heterozygous for the B' allele), ranged from 150 cm to 178 cm (mean = 164 cm). One woman was a B'B' homozygote. She was white, 175 cm tall, and 25 years old.

The ages of women with genotype BB ranged from 15 to 85 (mean = 47.1), while those of genotype BB' were aged 24 to 75 (mean = 47.3). The racial-ethnic distribution was 13% Black, 6% Hispanic, 80% White, and 1% other (Asian, Indian, or Polynesian), with no significant difference in the racial/ethnic distribution between the two groups, BB and BB'.

The women of genotype BB' were significantly taller than the women of genotype BB (p = 0.028, Student's t-test, Fig. 2). Multiple linear regression (Table 1) showed that race/ethnicity was a significant confounder. Black women were significantly taller than the other women studied. But after controlling for age and race/ethnicity, BB' women remained significantly taller than BB women (p = 0.017). There was no significant difference in weight between the two groups (66.6 ± 0.73 kg, mean± SEM for BB women, 69.3 ± 1.8 kg for BB' women, p = 0.2). The one B'B' homozygote weighed 66 kg.

Discussion

Multiple ER variants have been identified (McGuire, Chamness and Fuqua 1992). One of these variants has been linked to the development of breast cancer in a family with late onset of disease (Zuppel, Hall, Lee, Ponglikitmongkol and King 1991). Since the B' ER variant results from a silent mutation, a second mutation, segregating with it, might play a role in producing the high incidence of spontaneous abortion we reported previously (Lehrer et al. 1990; Lehrer et al. 1993) and the height difference we report here. This second mutation might lie within the estrogen receptor itself or within one of the genes nearby. Alternatively, the silent mutation might affect RNA processing by changing splice site recognition (Newman and Norman 1991; Siddique, McPhaden, Lappin and Whaley 1991), leading to alterations in RNA levels and protein expression.

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growth and height, probably in fetal life, would be affected. In future studies, it would be worthwhile to correlate other growth parameters, such as upper to lower body ratios and arm spans, with the presence of the B' variant allele.

Sex hormones are also intimately involved in growth (Rosenfeld 1989). For example, estrogens can affect body size by causing epiphyseal closure (Jones and Wentz 1977); indeed, girls with early menarche are shorter than girls whose menarche is delayed (Frisch and Revelle 1971). Thus a defect in the ER could cause increased height by reducing estrogen sensitivity and possibly changing the timing of puberty, resulting in a different growth rate at that critical age. Further studies, perhaps of linkage disequilibrium (Weir and Cockerman 1979), may be helpful in localizing the second mutation. In addition, it would be interesting to know if the B' ER allele affected the timing of puberty.

References


