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 afffiliated with Mount Sinai Hospital in New York City or Long Island

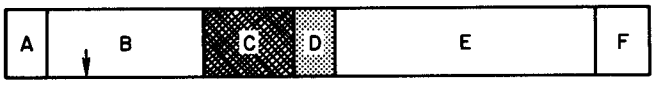

Fig. 1 Functional domains of the human estrogen receptor gene. Region A, function unknown; region B, transcription enhancement of ER regulated genes; region C, DNA binding domain; Region D, hinge region; region E, steroid hormone binding domain; region F, function unknown. The arrow indicates the position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

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Jewish Hospital. The women were seen for obstetrical care, routine gynecologic examinations, or minor outpatient surgery in Dermatology or Plastic Surgery. Height and weight, as well as ethnicity, age, reproductive status, and other historical details, were obtained by questionnaire.

The B′ allele of the estrogen receptor gene was identified by polymerase chain reaction to amplify genomic DNA around the polymorphic region of the ER gene, followed by allele specific oligonucleotide hybridization (PCR/ASO) (*Schmutzler* et al. 1991; *Lehrer* et al. 1993). This analysis used DNA obtained from blood lymphocytes of women, as we have described (*Schmutzler* et al. 1991).

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 (*Zuppan, 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.

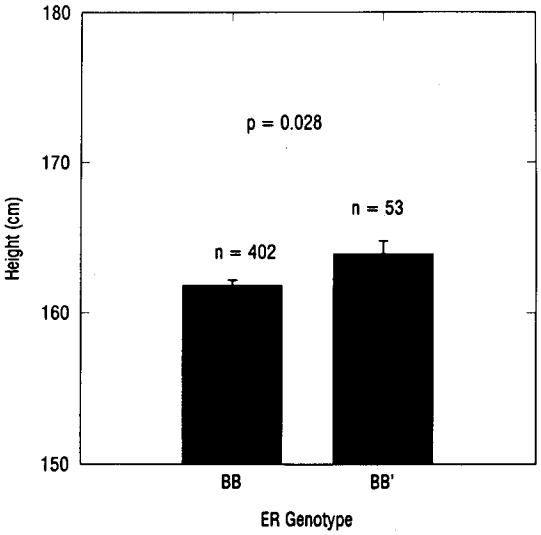

Fig. 2 Heights of women of genotype BB and genotype BB′ (mean ± SEM).

Table 1 Multiple linear regression analysis of the effect of ER genotype (that is, BB or BB′) on height, controlling for the effect of age and race (*white-hispanic-other versus Black).

Variable	Regression Coefficient	Standard Error	t-test	p-value
Genotype	2.19	0.919	2.39	0.017
Race*	3.50	0.88	3.95	0.0001
Age	− 0.03	0.019	− 1.67	0.09

The human ER gene is located on the long arm of chromosome 6 (6q24–27) (*Ziegler, Field* and *Sakaguchi* 1991). Other nearby genes on chromosome 6 are the liver arginase gene (6q23), the interferon gamma receptor 1 gene (6q23–24), the MASI oncogene (6q24–27), the vasoactive intestinal peptide gene (6q24–27), the insulin-like growth factor 2 receptor (type II IGF receptor which also functions as an M6P receptor) (*Dahms, Wick* and *Brzycki Wessel* 1994) gene (6q25–27), the apolipoprotein A gene (6q26–27), and the plasminogen gene (6q26–27) (*Ziegler, Field* and *Sakaguchi* 1991).

The IGF type II genes of the t-complex play a critical role in early development and growth. Mutated forms can be lethal to progeny under certain circumstances; or alternately lead to retarded or enhanced growth. In mice, the genes for type II IGF receptor, apolipoprotein A, and plasminogen are embedded in the t-complex region. Some of these genes control early fetal development and some are involved in ovarian and testicular development and spermatogenesis (*Lewis, Hynes, Zheng, Saibil* and *Willison* 1992; *Morita* et al. 1992). Laboratory animals with abnormalities in the IGF2R gene display abnormalities of body size (stunting or gigantism) (*Stöger, Kubicka, Liu, Kafri, Razin, Cedar* and *Barlow* 1993; *Sasaki, Jones, Chaillet, Ferguson Smith, Barton, Reik* and *Surani* 1992; *Goto, Figlewicz, Marineau, Khodr* and *Rouleau* 1992; *Hauptschein, Dalla-Favera* and *Gaidano* 1991; *Willison* 1991; *Jackson, Hodgkinson, Estivariz* and *Lowry* 1991). Therefore, if the functional mutation in question involved one of these genes,

growth and height, probably in fetal life, would be affected. In future studies, it would be worthwile 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 *Cockerham* 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.

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