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The androgen receptor exon 1 trinucleotide repeat does not act as a modifier of the age of presentation in breast cancer

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Abstract

The CAG repeat in exon 1 of the *androgen receptor* (*AR*) genes has been postulated as both a susceptibility allele and phenotypic modifier in *BRCA1*-associated breast cancers. We have analysed this repeat in a set of 178 breast cancer cases who have been selected only for age of presentation at 65 years or less. No effect of repeat length on age of presentation was found and there was no association between repeat length and family history. In combination with the data from other workers, our findings suggest that the androgen receptor repeat does not act as a modifier gene or susceptibility locus outside the context of the hereditary breast/ovarian cancer syndrome.

Keywords: Breast cancer; Androgen receptor; Modifier genes

1. Introduction

The human *androgen receptor* (*AR*) gene contains a highly polymorphic, coding CAG-repeat in exon 1. Alleles of longer repeat lengths have been associated with decreased efficacy in inducing target gene transcription [1,2]. Giovannucci and colleagues [3] reported an effect of *AR* CAG repeat genotype on the development of late-stage prostate cancers. Fewer CAG repeats were associated with higher overall risk of prostate cancer. In particular, a shorter CAG repeat sequence was associated with cancers characterised by later stage or higher grade tumours. Eeles and colleagues [4] did not, however, find any such effects in prostate cancer. More recently, Rebbeck and coworkers [5] found that in a sample of 304 *BRCA1* mutation carriers, 165 of whom had developed breast cancer and 139 of whom had not, *AR* alleles containing 28 or more CAG repeats were over-represented in the cases. Women with at least one allele of 28, 29 or 30 repeats were diagnosed earlier by 0.8, 1.8, or 6.3 years, respectively, than women who did not carry at least one such allele. Thus, *AR* appeared to be a modifier gene for breast cancer risk in *BRCA1* mutation carriers.

Spurdle and colleagues [6] studied 368 unselected breast cancer cases presenting under 40 years of age and 284 age-matched controls. They found no association between CAG repeat number and either breast cancer risk or age at presentation. Thus, in these early-onset cases, *AR* did not contribute to breast cancer susceptibility, and an effect as a modifier of breast cancer phenotype appeared to be unlikely.

We have studied a set of 178 breast cancer cases diagnosed at 65 years or younger and determined each patient's alleles as regards the *AR* CAG repeat. Using these data, we have determined whether or not CAG repeat number acts as a modifier gene to influence age of presentation in this patient set. We have also determined whether or not *AR* alleles are associated with family history.

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2. Materials and methods

Female breast cancer cases presenting at 65 years or younger were recruited into the study from the records and clinics of the Department of Surgery, University College Hospital, Galway. Age of presentation was recorded, as was family history, a positive family history being defined for the purposes of this study as the presence of a first-degree relative with breast or ovarian cancer. No patient had bilateral breast cancer, although one had metachronous primary cancers of both the breast and ovary. Blood samples were obtained from a total of 178 women, of whom the great majority had been diagnosed less than 1 year previously. DNA was extracted from the blood samples using standard methods. Each patient was genotyped at the *AR* CAG repeat using oligonucleotides (5′-CAGAGCGTGCGCGA-AGTGAT-3′, 5′-GCTTGGGGAGAACCATCCTC-3′) designed specifically to amplify an approximately 225-bp fragment of exon 1 of the *AR* gene in the polymerase chain reaction (PCR) (exact size dependent on repeat length of allele). PCR was performed using standard conditions (1 cycle×95°C 1 min; 35 cycles ×95°C 1 min/60°C 1 min/72°C 1 min; 1 cycle×72°C 10 min). One oligonucleotide was dye-labelled to allow genotyping using the ABI377 semi-automated sequencer. *AR* alleles were scored using the Genotyper software. Associations of alleles with age of presentation were performed using linear regression analysis. Associations between high (28 or more) CAG repeat number and: (i) early age of presentation; and (ii) family history were determined using Fisher's exact test.

3. Results

A median *AR* CAG repeat number of 21 was found (range: 15–30). No association was detected between age of presentation (median: 54 years, range: 32–65)and repeat number. This was the case when associations were searched for using: (i) total repeat number summed over both alleles ($r^2 = 0.0020$, $P > 0.5$); (ii) longer allele repeat number only ($r^2 = 0.0036$, $P > 0.5$); and (iii) shorter allele repeat number only ($r^2 = 0.0045$, $P > 0.5$). There was no association between cases with one or both alleles with repeat numbers $\geqslant 28$ (9 patients) and earlier onset of disease. There was, moreover, no association between the presence of a family history of breast or ovarian cancer (58 patients positive) and the repeat number, using any of the above three measures (Fisher's exact test, $P > 0.5$ in all cases, data not shown).

4. Discussion

The *AR* CAG repeat appears not, therefore, to be a modifier of age of onset in unselected breast cancers. It remains possible, although unlikely, that analysis of a set of cancers derived from patients of a wider age spectrum would have detected such an effect, or that study of a larger sample would have detected a weak effect. With the proviso that disease modifiers and low-penetrance susceptibility alleles are not synonymous [7], our data are in general agreement with those of Spurdle and colleagues [6], who found no evidence that the *AR* genotype acts to increase the risk of early-onset breast cancer. The influence of *AR* on breast cancer detected by Rebbeck and colleagues [5] may: (i) be restricted to women with the hereditary breast/ovarian cancer syndrome (particularly those with *BRCA1* mutations); or (ii) result from linkage disequilibrium between *AR* repeat alleles and other variation nearby; or (iii) be a chance finding. *AR* CAG repeat genotype is probably of little clinical importance for the general population.

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