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No associations between aromatase gene polymorphisms and breast cancer risk in Saudi patients

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Mohammed Alanazi[1]
Huda A Alabdulkarim[2]
Jilani P Shaik[1]
Abdulrahman Al Naeem[3]
Mohammad Elrobh[1]
Abdullah Al Amri[1]
Fatimah Basil al-Mukaynizi[1]
Abdelhabib Semlali[1]
Arjumand Warsy[1]
Narasimha Reddy Parine[1]

[1]Department of Biochemistry, College of Science, King Saud University, [2]Comprehensive Cancer Center at King Fahad Medical City, [3]Department of Women's Imaging, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

Background: Cytochrome P450 (CYP)19A1 encodes aromatase, the enzyme responsible for the conversion of androgens to estrogens, and may play a role in variation in outcomes among women with breast cancer. The aim of this study was to analyze the genetic association of rs4646 (A > C) and rs700518 (Val > Val) in the CYP19A1 gene with the risk of breast cancer.

Methods: These two single nucleotide polymorphisms (SNPs) were analyzed in a primary study group of breast cancer patients and healthy control subjects. Genotypes were determined by the TaqMan SNP analysis technique. The study data were analyzed using the chi-square or *t*-test and logistic regression analysis by Statistical Package for the Social Sciences version 16 software.

Results: rs4646 and rs700518 had no association with susceptibility to breast cancer. There was no significant association for either of these SNPs overall in breast cancer samples when compared with healthy control samples. Our data do not support a relationship between the CYP19A1 rs4646 and rs700518 SNPs and risk of breast cancer. It may be that there are ethnic differences with regard to this relationship.

Conclusion: This study demonstrated that CYP19A1 rs4646 and rs700518 SNPs may not be involved in the etiology of breast cancer in the Saudi population. Confirmation of our findings in larger populations of other ethnicities could provide evidence for the role of the CYP19A1 gene in breast carcinomas.

Keywords: CYP19A1, rs4646, rs700518, breast cancer, genetic polymorphisms

Introduction

Breast cancer is one of the most common types of malignancy and is a leading cause of death worldwide, accounting for nearly one million new cases diagnosed and half a million deaths annually.[1] Incidence rates vary widely according to region, being high in developed countries and lower in developing countries.[2] This type of cancer is obviously a significant public health problem in Saudi Arabia.

Cytochrome P450 (CYP)19A1 encodes the enzyme aromatase, which catalyzes the conversion of the C19 androgens, androstenedione and testosterone, to estrone and estradiol, respectively.[3,4] Specific single nucleotide polymorphisms (SNPs) in the intronic regions of CYP19A1 have been shown to play a role in altering regulation of transcription and/or splicing of CYP19A1, producing different enzyme products with variable enzymatic activity when compared with the normal gene product.[5,6] Studies have identified SNPs in CYP19A1 that are associated with an increased risk of cancer, primarily in European American, North Indian, and Chinese populations.[7,8] Several studies have been done on polymorphisms in the CYP19 gene in an attempt to identify

Correspondence: Narasimha Reddy Parine
Genome Research Chair, Department of Biochemistry, College of Science, PO Box 2455, King Saud University, Riyadh 11451, Kingdom of Saudi Arabia
Tel +966 11467 5802
Fax +966 11467 5802
Email reddyparine@gmail.com

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an association between genetic variations and breast cancer risk, but few studies have found such an association. One report suggested that a tetra-nucleotide repeat polymorphism in intron 4 (TTTA)n was strongly associated with the risk of breast cancer.[9] However, studies of other genetic variations have not shown a clear association with risk of breast cancer, thus generating a situation of inconsistent results.[10–13] Hence, in the present population-based, case–control study, we investigated the genotype distribution of rs4646 and rs700518 SNPs in patients with breast cancer.

Materials and methods

Study population

The study population comprised 148 females (median age 48 years) suffering from breast cancer and attending the outpatient clinics of the clinical co-investigators at King Fahad Medical City Hospital, Riyadh, Saudi Arabia, and 154 age-matched normal healthy controls also attending King Fahad Medical City Hospital for minor illnesses and recruited following physical examinations after exclusion of a breast cancer diagnosis and history of cancer or cancer-related diseases. The patients and controls were of Saudi Arabian ethnicity. Demographic data, age at diagnosis, tumor grade, and immunohistochemical determination of estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor status were recorded. The study was approved by the institutional review board of King Khalid University Hospital. Written informed consent was obtained from all participants.

Genotyping

Genomic DNA was extracted from blood samples taken from breast cancer cases and controls using a QIAmp DNA blood mini kit (Qiagen, Valencia, CA, USA) following the manufacturer's instructions. The rs1130409 SNP in the APE1 gene was genotyped using the TaqMan allelic discrimination assay as described previously.[14] Ten percent of the samples were subjected to repeated analysis for verification of the genotyping procedures.[15]

Statistical analysis

Genotype and allelic frequencies were compared using Fisher's Exact test (two-tailed) as described by Alanazi et al[15] to describe the χ^2 test and odds ratios, and 95% confidence intervals to know the variation between cancer cases and controls. The statistical analysis was performed using Statistical Package for the Social Sciences version 21.0 (SPSS Inc, Chicago, IL).[16]

Results

One hundred and forty-eight breast cancer cases and 154 healthy controls were included in this study. The clinical characteristics of the breast cancer cases and the healthy controls are given in Table 1. Of 148 confirmed cases of breast cancer, 67 were ER-positive, 78 were ER-negative, 89 were PR-positive, 59 were PR-negative, 57 were HER2-positive, and 89 were HER2-negative.

All the genotypic distributions were consistent with that expected in the Hardy–Weinberg model. The homozygous wild-type allele was used as a reference to calculate the odds of acquiring breast cancer in comparison with the other two genotypes. The genotype frequencies of the analyzed SNPs along with the resulting odds ratio and significance levels are shown in Table 1. We did not find any significant association between the two SNPs and risk of breast cancer.

In the present study, we found no association with CYP19A1 rs4646 and rs700518 genotypes between breast cancer cases and matched healthy controls. The frequencies of rs4646 (A > C) genotypes in breast cancer cases were 8 (0.05), 46 (0.31), and 94 (0.64), respectively, whereas in

Table 1 Genotype frequencies of *Aromatase* gene polymorphism in breast cancer cases and controls

SNP	Variant	Cases	Controls	OR	CI	χ^2 value	*P*-value
rs4646	AA	8 (0.05)	8 (0.05)	Ref			
	AC	46 (0.31)	47 (0.31)	0.979	0.339–2.828	0.002	0.96831
	CC	94 (0.64)	99 (0.64)	0.949	0.350–2.625	0.01	0.93490
	AC + CC	140 (0.95)	146 (0.95)	0.959	0.350–2.625	0.01	0.93490
	A	62 (0.20)	63 (0.20)	Ref			
	C	234 (0.80)	245 (0.80)	0.971	0.655–1.439	0.02	0.88154
rs700518	AA	60 (0.41)	55 (0.36)	Ref			
Val > Val	AG	66 (0.45)	71 (0.46)	0.852	0.519–1.400	0.40	0.52715
	GG	22 (0.15)	28 (0.18)	0.720	0.369–1.404	0.93	0.33451
	AG + GG	88 (0.59)	99 (0.64)	0.815	0.512–1.297	0.75	0.38789
	A	186 (0.63)	181 (0.59)	Ref			
	G	110 (0.37)	127 (0.41)	0.843	0.608–1.169	1.05	0.30561

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; SNP, single nuclear polymorphism.

healthy controls the frequencies were 8 (0.05), 47 (0.30), and 99 (0.65), respectively. Breast cancer patients did not show any risk when compared with healthy individuals (Table 1). As shown in Table 1, the frequency of the rs700518, (A > G) A/A, A/G, and G/G genotypes were 60 (0.41), 66 (0.45), and 22 (0.15), respectively, in breast cancer patients and 55 (0. 36), 71 (0.46), and 28 (0.18), respectively, in controls. Breast cancer patients did not show any risk when compared with healthy individuals (Table 1).

The correlation between CYP19A1 rs4646 and rs700518 SNP status and clinicopathological characteristics was also analyzed, but interestingly none of these parameters showed an association with breast cancer in this Saudi population. Breast cancer patients did not show any association between age and ER-positive, ER-negative, PR-positive, HER2-positive, and HER2-negative status (Tables 2–5).

We also generated a regional linkage disequilibrium (LD) plot using SNAP (SNP Annotation and Proxy Search, http://www.broadinstitute.org/mpg/snap/ldplot.php) for CYP19A1 rs4646 and rs700518. The LD plot indicated that there are multiple loci near rs4646 and rs700518 with high LD (r^2>0.8), which suggests that fine mapping is necessary to evaluate the genetic effect of CYP19A1 on cancer as well as functional studies (Figures 1 and 2).

Discussion

Numerous genetic variations of CYP19A1 have been reported, even though the possible functional significance of most of these polymorphisms is still undefined. Various studies conducted in specific breast cancer populations have analyzed a few common CYP19A1 polymorphisms and generated inconsistent results with regard to their possible association with cancer risk, sex hormone levels, HER2 status, and survival.[9,17–20] In the present study, our data do not support any appreciable association between CYP19A1 rs4646 and rs700518 genotypes and breast cancer risk in the Saudi population (Table 1). We analyzed the association of both these SNPs with various clinical parameters and found no evidence of heterogeneity for either rs4646 or rs700518 in Saudi breast cancer patients, and found no association except with rs4646 in PR-negative patients (Tables 2–5).

Table 2 Genotype frequencies of *Aromatase* gene polymorphism in breast cancer cases (above 48 years old versus below 48 years old)

SNP	Variant	Cases	Controls	OR	CI	χ^2 value	*P*-value
rs4646		**Above 48**					
	AA	4 (0.06)	1 (0.01)	Ref			
	AC	21 (0.30)	20 (0.29)	0.263	0.027–2.554	1.49	0.22256
	CC	45 (0.64)	47 (0.69)	0.239	0.026–2.224	1.83	0.17573
	AC + CC	66 (0.94)	67 (0.99)	0.246	0.027–2.262	1.78	0.18228
	AA	29 (0.21)	22 (0.16)	Ref			
	CC	111 (0.79)	114 (0.84)	0.739	0.400–1.363	0.94	0.33150
rs4646		**Below 48**					
	AA	4 (0.49)	7 (0.08)	Ref			
	AC	25 (0.44)	27 (0.31)	1.620	0.423–6.210	0.50	0.47887
	CC	49 (0.07)	52 (0.60)	1.649	0.454–5.984	0.59	0.44337
	AC + CC	74 (0.51)	79 (0.92)	1.639	0.461–5.830	0.58	0.44136
	AA	33 (0.71)	41 (0.24)	Ref			
	CC	123 (0.29)	131 (0.76)	1.167	0.693–1.963	0.34	0.56148
rs700518		**Above 48**					
Val > Val	AA	34 (0.33)	24 (0.35)	Ref			
	AG	31 (0.45)	36 (0.53)	0.608	0.299–1.236	1.90	0.16804
	GG	5 (0.22)	8 (0.12)	0.441	0.129–1.515	1.74	0.18673
	AG + GG	36 (0.67)	44 (0.65)	0.578	0.292–1.144	2.50	0.11416
	AA	99 (0.56)	84 (0.62)	Ref			
	GG	41 (0.44)	52 (0.38)	0.669	0.405–1.105	2.47	0.11581
rs700518		**Below 48**					
Val > Val	AA	26 (0.0)	31 (0.36)	Ref			
	AG	35 (0.0)	39 (0.45)	1.070	0.535–2.139	0.04	0.84815
	GG	17 (0.0)	16 (0.19)	1.267	0.537–2.990	0.29	0.58913
	AG + GG	52 (0.0)	55 (0.64)	1.127	0.592–2.148	0.13	0.71557
	AA	87 (0.0)	101 (0.59)	Ref			
	GG	69 (0.0)	71 (0.41)	1.128	0.728–1.749	0.29	0.58937

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; SNP, single nuclear polymorphism.

Table 3 Genotype frequencies of *Aromatase* gene polymorphism in breast cancer cases (ER-positive versus ER-negative)

SNP	Variant	Cases	Controls	OR	CI	χ^2 value	*P*-value
rs4646		**ER-positive**					
	AA	2 (0.03)	8 (0.05)	Ref			
	AC	18 (0.27)	47 (0.31)	1.532	0.297–7.913	0.26	0.60859
	CC	47 (0.70)	99 (0.64)	1.899	0.388–9.293	0.65	0.42165
	AC + CC	65 (0.97)	146 (0.95)	1.781	0.368–8.618	0.53	0.46758
	AA	22 (0.16)	63 (0.20)	Ref			
	CC	112 (0.84)	245 (0.80)	1.309	0.767–2.234	0.98	0.32231
rs4646		**ER-negative**					
	AA	6 (0.08)	8 (0.05)	Ref			
	AC	26 (0.33)	47 (0.31)	0.738	0.231–2.357	0.26	0.60680
	CC	46 (0.59)	99 (0.64)	0.620	0.203–1.889	0.72	0.39647
	AC + CC	72 (0.92)	146 (0.95)	0.658	0.220–1.966	0.57	0.45044
	AA	38 (0.24)	63 (0.20)	Ref			
	CC	118 (0.76)	245 (0.80)	0.798	0.505–1.263	0.93	0.33564
rs700518		**ER-positive**					
Val > Val	AA	30 (0.45)	55 (0.36)	Ref			
	AG	32 (0.48)	71 (0.46)	0.775	0.418–1.435	0.66	0.41646
	GG	5 (0.07)	28 (0.18)	0.458	0.179–1.173	2.72	0.09915
	AG + GG	37 (0.55)	99 (0.64)	0.685	0.382–1.228	1.62	0.20312
	AA	92 (0.69)	181 (0.59)	Ref			
	GG	42 (0.31)	127 (0.41)	0.697	0.455–1.067	2.78	0.09567
rs700518		**ER-negative**					
Val > Val	AA	28 (0.36)	55 (0.36)	Ref			
	AG	33 (0.42)	71 (0.46)	0.913	0.494–1.688	0.08	0.77148
	GG	17 (0.22)	28 (0.18)	1.193	0.560–2.538	0.21	0.64739
	AG + GG	50 (0.64)	99 (0.64)	0.992	0.562–1.751	0.001	0.97807
	AA	89 (0.57)	181 (0.59)	Ref			
	GG	67 (0.43)	127 (0.41)	1.073	0.727–1.584	0.13	0.72348

Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio; Ref, reference; SNP, single nuclear polymorphism.

Table 4 Genotype frequencies of *Aromatase* gene polymorphism in breast cancer cases (PR-positive versus PR-negative)

SNP	Variant	Cases	Controls	OR	CI	χ^2 value	*P*-value
rs4646		**PR-positive**					
	AA	5 (0.06)	8 (0.05)	Ref			
	AC	28 (0.31)	47 (0.31)	0.953	0.284–3.201	0.01	0.93817
	CC	56 (0.63)	99 (0.64)	0.905	0.282–2.900	0.03	0.86660
	AC + CC	84 (0.94)	146 (0.95)	0.921	0.292–2.905	0.02	0.88768
	AA	38 (0.21)	63 (0.20)	Ref			
	CC	140 (0.79)	245 (0.80)	0.947	0.602–1.490	0.05	0.81502
rs4646		**PR-negative**					
	AA	3 (0.05)	8 (0.05)	Ref			
	AC	18 (0.31)	47 (0.31)	1.021	0.243–4.284	0.0001	0.97704
	CC	38 (0.64)	99 (0.64)	1.024	0.258–4.063	0.0012	0.97358
	AC + CC	56 (0.95)	146 (0.95)	1.023	0.262–3.994	0.001	0.97409
	AA	24 (0.20)	63 (0.20)	Ref			
	CC	94 (0.80)	245 (0.80)	1.007	0.595–1.706	0.001	0.97888
rs700518		**PR-positive**					
Val > Val	AA	39 (0.44)	55 (0.36)	Ref			
	AG	38 (0.43)	71 (0.46)	0.755	0.427–1.333	0.94	0.33189
	GG	12 (0.13)	28 (0.18)	0.604	0.274–1.333	1.57	0.21003
	AG + GG	50 (0.66)	99 (0.64)	0.712	0.418–1.214	1.56	0.21131
	AA	116 (0.65)	181 (0.59)	Ref			
	GG	62 (0.35)	127 (0.41)	0.762	0.519–1.117	1.95	0.16306
rs700518		**PR-negative**					
Val > Val	AA	21 (0.36)	55 (0.36)	Ref			
	AG	28 (0.47)	71 (0.46)	1.033	0.530–2.011	0.01	0.92423
	GG	10 (0.17)	28 (0.18)	0.935	0.388–2.255	0.02	0.88168
	AG + GG	38 (0.64)	99 (0.64)	1.005	0.537–1.881	0.0012	0.98683
	AA	70 (0.59)	181 (0.59)	Ref			
	GG	48 (0.41)	127 (0.41)	0.977	0.635–1.505	0.01	0.91689

Abbreviations: CI, confidence interval; PR, progesterone receptor; OR, odds ratio; Ref, reference; SNP, single nuclear polymorphism.

Table 5 Genotype frequencies of *Aromatase* gene polymorphism in breast cancer cases (HER2-positive versus HER2-negative)

SNP	Variant	Case	Control	OR	CI	χ^2 value	*P*-value
rs4646		**HER2-positive**					
	AA	3 (0.05)	8 (0.05)	Ref			
	AC	21 (0.37)	47 (0.31)	1.191	0.287–4.945	0.06	0.80916
	CC	33 (0.58)	99 (0.64)	0.889	0.223–3.548	0.03	0.86748
	AC + CC	54 (0.95)	146 (0.95)	0.986	0.252–3.855	0.0001	0.98418
	AA	27 (0.24)	63 (0.20)	Ref			
	CC	87 (0.76)	245 (0.80)	0.829	0.496–1.384	0.52	0.47202
rs4646		**HER2-negative**					
	AA	4 (0.04)	8 (0.05)	Ref			
	AC	25 (0.28)	47 (0.31)	1.064	0.292–3.882	0.01	0.92536
	CC	60 (0.67)	99 (0.64)	1.212	0.350–4.198	0.09	0.76122
	AC + CC	85 (0.96)	146 (0.95)	1.164	0.340–3.982	0.06	0.80817
	AA	33 (0.19)	63 (0.20)	Ref			
	CC	145 (0.81)	245 (0.80)	1.130	0.707–1.805	0.26	0.60941
rs700518		**HER2-positive**					
Val > Val	AA	24 (0.42)	55 (0.36)	Ref			
	AG	25 (0.44)	71 (0.46)	0.807	0.416–1.564	0.40	0.52475
	GG	8 (0.14)	28 (0.18)	0.655	0.261–1.644	0.82	0.36534
	AG + GG	33 (0.58)	99 (0.64)	0.764	0.411–1.421	0.73	0.39436
	AA	73 (0.64)	181 (0.59)	Ref			
	GG	41 (0.36)	127 (0.41)	0.800	0.513–1.249	0.96	0.32619
rs700518		**HER2-negative**					
Val > Val	AA	35 (0.39)	55 (0.36)	Ref			
	AG	41 (0.46)	71 (0.46)	0.907	0.512–1.608	0.11	0.73934
	GG	13 (0.15)	28 (0.18)	0.730	0.334–1.596	0.63	0.42891
	AG + GG	54 (0.61)	99 (0.64)	0.857	0.500–1.468	0.32	0.57434
	AA	111 (0.62)	181 (0.59)	Ref			
	GG	67 (0.38)	127 (0.41)	0.860	0.589–1.256	0.61	0.43580

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; SNP, single nuclear polymorphism.

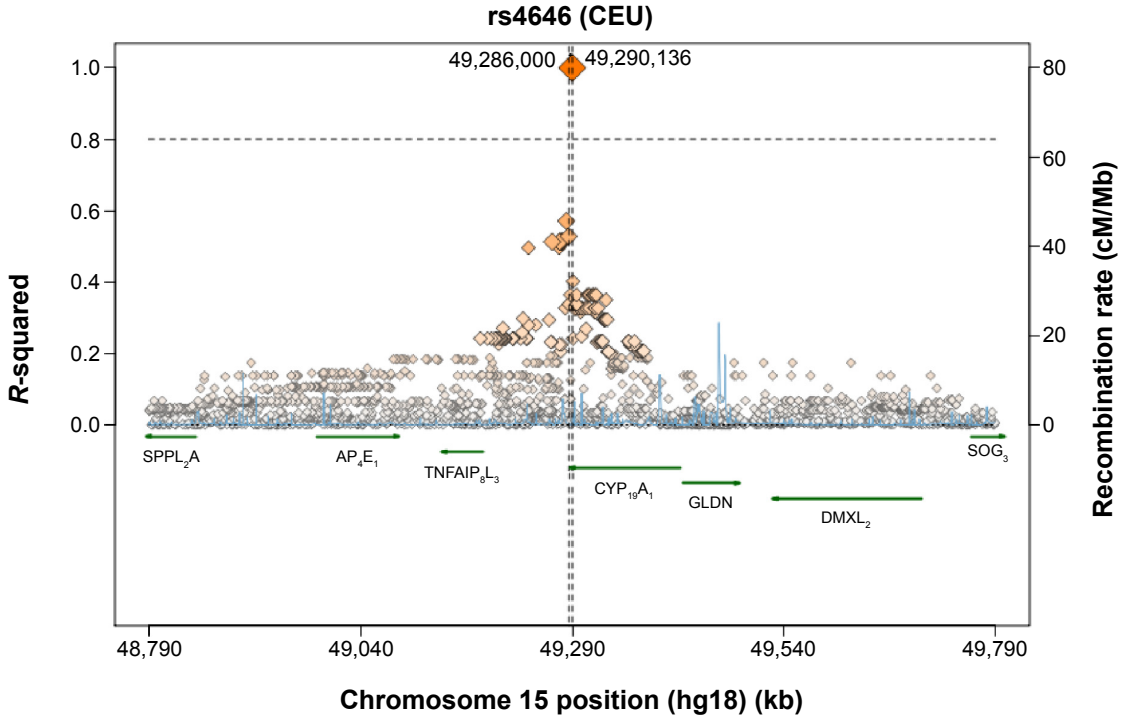

Figure 1 Regional linkage disequilibrium plot for the single nuclear polymorphism rs4646.

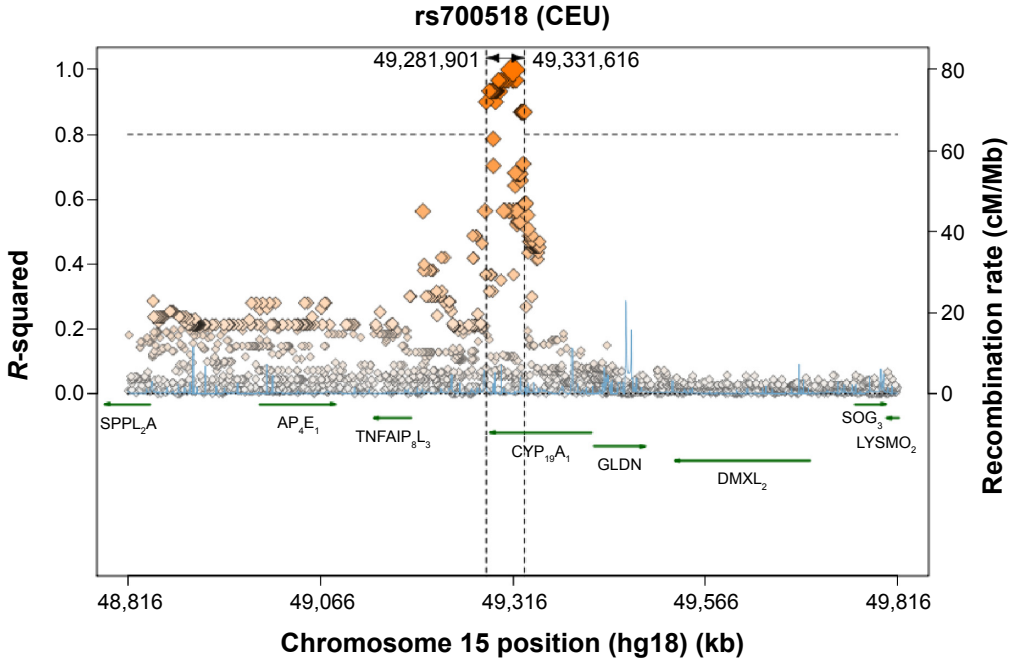

Figure 2 Regional linkage disequilibrium plot for the rs700518 single nuclear polymorphism.

Some strengths and limitations of our study should be noted. Its strengths include the population-based and prospective study design in the central region of Saudi Arabia, thereby minimizing selection bias, and the detailed review of the cancer diagnosis, thereby minimizing disease misclassification. However, our nested case–control sample was relatively small in size, which hampered our ability to evaluate specific gene-disease association. Confirmation of our findings in larger populations of women of different ethnicities could provide evidence for the role of the CYP19A1 gene in breast carcinoma.

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Disclosure

The authors declare that they have no competing interests in this work.

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