A Study of Possible Associations Between Single Nucleotide Polymorphisms in the Estrogen Receptor 2 Gene and Female Sexual Desire

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DOI: 10.1111/jsm.12753

ABSTRACT

Introduction. Female sexual desire and arousal problems have been shown to have a heritable component of moderate size. Previous molecular genetic studies on sexual desire have mainly focused on genes associated with neurotransmitters such as dopamine and serotonin. Nevertheless, there is reason to believe that hormones with more specific functions concerning sexuality could have an impact on sexual desire and arousal.

Aim. The aim of the present study was to investigate the possible effects of 17 single nucleotide polymorphisms (SNPs) located in estrogen receptor genes on female sexual desire and subjective and genital arousal (lubrication). Based on previous research, we hypothesized that \textit{ESR1} and \textit{ESR2} are relevant genes that contribute to female sexual desire and arousal.

Main Outcome Measures. The desire, arousal, and lubrication subdomains of the Female Sexual Function Index self-report questionnaire were used.

Methods. The present study involved 2,448 female twins and their sisters aged 18–49 who had submitted saliva samples for genotyping. The participants were a subset from a large-scale, population-based sample.

Results. We found nominally significant main effects on sexual desire for three \textit{ESR2}-linked SNPs when controlled for anxiety, suggesting that individuals homozygous for the G allele of the rs1271572 SNP, and the A allele of the rs4986938 and rs928554 SNPs had lower levels of sexual desire. The rs4986938 SNP also had a nominally significant effect on lubrication. No effects for any of the SNPs on subjective arousal could be detected.

Conclusions. The number of nominally significant results for SNPs in the \textit{ESR2} gene before correcting for multiple testing suggests that further studies on the possible influence of this gene on interindividual variation in female sexual functioning are warranted. In contrast, no support for an involvement of \textit{ESR1} was obtained. Our results should be interpreted with caution until replicated in independent, large samples. Gunst A, Jern P, Westberg L, Johansson A, Salo B, Burri A, Spector T, Eriksson E, Sandnabba NK, and Santtila P. A study of possible associations between single nucleotide polymorphisms in the estrogen receptor 2 gene and female sexual desire. J Sex Med 2015;12:676–684.

Key Words. Estrogen Receptor Gene; ESR1; ESR2; Single Nucleotide Polymorphism; SNP; Female Sexual Desire and Arousal
Introduction

In recent years, twin studies have shown that most of the variation in female sexual desire and arousal is due to nonshared environmental factors. These factors could include, for example, relationship duration and satisfaction, partner compatibility, pregnancy, psychological problems, and alcohol use [1–3]. However, female sexual desire and arousal problems have been shown to have a heritable component of moderate size. Wittig et al. [4] reported that additive and nonadditive genetic effects explained 21% of the variation in desire, 24% in subjective arousal, and 16% in lubrication. Burri et al. [5] found similar, although somewhat higher, estimates in a British study sample, where additive genetic effects explained 35% of the variation in desire, 26% in subjective arousal, and 25% in lubrication. The genetic effect sizes were similar to those reported for premature ejaculation (around 30%; [6–8]), and the studies on premature ejaculation have subsequently been followed up by several molecular genetic studies [9–14], with inconsistent (or non-replicated) results to date. However, the existing molecular genetic studies concerning female sexual desire and arousal are sparse, and most of them rely on small sample sizes. Previous molecular genetic studies have mainly focused on genes associated with neurotransmitters such as dopamine and serotonin (for a review, see [15]). Nevertheless, there is reason to believe that hormones with more specific functions concerning sexuality could have an impact on sexual desire and arousal.

The impact of estrogen on female sexual behavior and function has gained attention as a result of its widespread use in hormone-based contraceptives, its role in physiological and psychological changes related to menopausal transition, as well as childbirth and pregnancy [16,17]. Estrogen exerts most of its biological effects via estrogen receptors (ligand activated transcription factors belonging to the nuclear hormone receptor superfamily), which are present in a broad spectrum of tissues [18]. Several estrogen receptor knockout (deletion of estrogen receptor genes) studies on female mice have demonstrated that the gene encoding for the α-variant of the estrogen receptor (commonly referred to as ESR1) affects sexual behavior in female mice, with ESR2-knockout mice displaying less lordosis behavior. Receptivity behavior in mice could theoretically be compared with sexual desire and arousal in humans [15]. Studies on mice have further indicated a link between anxiety and estrogen [23,24], and specifically estrogen receptor genes [25].

In humans, studies report associations between sexual desire and estrogen treatment in surgically postmenopausal women [26] and estrogen levels among women across the menopausal transition [27]. The effect of oral contraceptives (OCs; usually containing estradiol and progestogene derivatives) on sexual function is a question still under debate, but several studies report an association between the use of OCs and decreased sexual functioning [28–30]. The negative effect of exogenous estrogen on sexual desire might however be due to an effect on testosterone levels [31–33].

Based on estrogen receptor knockout studies in mice, it has been speculated that effects of estrogen receptor genes in mice could translate to humans, that is, estrogen receptor genes could affect human female sexual desire and arousal [15]. The aim of the present study was to examine the effects of 17 estrogen receptor single nucleotide polymorphisms (SNPs) on sexual desire and arousal (both subjective arousal and genital arousal, i.e., lubrication) in a population-based sample of female adult Finnish twins and their sisters. To our knowledge, the association between estrogen receptor genes and sexual desire and arousal in women has not yet been specifically investigated. Given the results of genetic knockout studies in mice and hormonal studies of estrogen in humans, we hypothesized that ESR1 and ESR2 SNPs were likely to affect female sexual desire and arousal.

Methods

Participants

The present study involved 2,448 female twins and their sisters aged 18–49 (M = 26.5 years, SD = 5.30) who had submitted saliva samples for genotyping. The participants were a subset from the large-scale, population-based Genetics of Sex and Aggression data collection at the Center of Excellence in Behavior Genetics at Abo Akademi University, Finland. The data collection was carried out in 2006 and targeted all twins aged 18–33 years and their over 18-year-old siblings living in Finland at the time (see [34] for a detailed description of this sample).
Originally, a total of 7,680 female twins and 3,983 sisters were contacted by mail and asked if they were interested in completing a sexuality-related questionnaire. The purpose of the study was clearly described and the voluntary and anonymous nature of the participation emphasized. All participants provided informed consent. The participants who consented to participate were able to choose to complete the questionnaire by mail or online through a secure web page. A total of 6,601 women responded to the survey, resulting in a response rate of 56.6%, which is comparable with prior studies on sexual behavior (e.g., [35]). All participants in the data collection were identified from the Finnish Central Population Registry. Of the 6,601 women, 2,448 provided a saliva sample for DNA analyses. Of the 2,448 women, 1,080 reported that they were using some sort of hormonal contraceptives.

The research plan was approved by the Ethics Committee of the Abo Akademi University, in accordance with the Helsinki Declaration, and institutional review board approval was obtained by the Research Review Board of the Department of Psychology, Abo Akademi University.

**Main Outcome Measures**

**Assessment of Sexual Desire and Arousal**

Sexual desire and arousal was assessed using the Female Sexual Function Index self-report questionnaire (FSFI; [36]). The FSFI is held in high regard for its psychometric properties [37] and clinical accuracy and has repeatedly demonstrated good validity and reliability in different settings [1,37,38]. The FSFI includes 19 items, which assess sexual functioning over the past 4 weeks in six subdomains. These are: desire, subjective arousal, lubrication, orgasm, sexual satisfaction, and sex-related pain. Since the data collection in 2006, an abridged form of the FSFI has also been validated for screening purposes [39].

The desire domain (items 1 and 2), the arousal domain (items 3–6), and the lubrication domain (items 7–10) were of primary interest in this study. The questions are scored on a Likert-type scale ranging from 1 to 5 for the desire items with lower scores indicating decreased sexual function, and from 0 to 5 for the arousal and lubrication items with the supplementary option “no sexual activity.” The items were summed together to form three composite variables. Cronbach’s α (internal consistency) showed high reliability for all three domains (α ranging from 0.77 to 0.87). To control for dependence between members of the same family, only one individual from each family was randomly included in the internal consistency analyses (n = 904). The mean values for the women were 5.32 (range 2–10, SD = 1.51) for desire, 16.57 (range 4–20, SD = 3.11) for arousal, and 18.37 (range 4–20, SD = 2.53) for lubrication.

**Assessment of Anxiety**

Since past research has indicated a link between anxiety and estrogen [23,24], and specifically estrogen receptor genes [25], we decided to analyze the effects both with and without anxiety as a covariate. Six items from the Brief Symptom Inventory-18 (BSI-18; [40]) measuring different aspects of anxiety were summed together to form a composite variable for anxiety. Thereafter, the score was centralized. Higher scores on the BSI-18 indicate higher levels of anxiety. The anxiety dimension in BSI-18 has been shown to have good internal consistency, with Cronbach’s α ranging from 0.72 to 0.81 in three separate psychometric studies [40–42].

**Missing Values**

First, missing values on the FSFI were replaced using the expectation maximization procedure of PASW 18.0 (SPSS Inc., Chicago, IL, USA) for participants who had responded to at least one of the 10 items of interest: the desire, arousal, and lubrication domain. The whole FSFI instrument was used in the procedure. Second, the FSFI has been criticized for categorizing persons that have not engaged in any sexual activity during the past 4 weeks as dysfunctional by default [1,37]. Therefore, responses from participants with at least one “no sexual activity” response on the arousal and lubrication items were considered missing values. Since the two desire items do not require any sexual activity, these items were kept irrespective of sexual activity. Consequently, this resulted in 2,125 participants with responses on all 10 items and 323 participants with responses on the desire domain only.

**DNA Extraction and Genotyping**

Based on saliva samples, a total of 12 SNPs in the ESR1 gene and five SNPs in the ESR2 gene were genotyped. All SNPs genotyped have previously shown to be functional and have also been included in several genetic association studies (e.g., [43]). Saliva samples were collected using the Oragene DNA (DNA Genotek Inc., Kanata, ON, Canada) self-collection kits that were sent by post to the participants and returned by mail. The participants...
were instructed to follow the manufacturer’s instructions in collecting the samples and to deposit approximately 2 mL of saliva into the collection cup. When an adequate sample was collected, the cap was placed on the cup and closed firmly. The collection cup is designed so that a stabilizing solution from the cap is released when closed. This solution mixes with the saliva and stabilizes the saliva sample for long-term storage at room temperature or in low-temperature freezers. Genotyping of SNPs was conducted by KBioscience in the UK (http://www.lgcgroup.com) using the KASPar chemistry, a competitive allele specific polymerase chain reaction SNP genotyping system performed with Förster resonance energy transfer quencher cassette oligos.

**Statistical Analyses**

Anxiety had a small but significant association with all three subdomains, supporting an inclusion of anxiety as a covariate in the SNP analyses. Age had a negligible association with the three subdomains; no significant association with arousal and lubrication, and a small but significant association with desire. Hence, we decided not to include age as a covariate in the SNP analyses. We further investigated whether the use of hormonal contraceptives interfered with the effects on sexual desire and arousal of the SNPs but found no significant interactions. Consequently, the use of hormonal contraceptives was not included as a covariate in the analyses. The effects of the allelic variants were calculated with the Generalized Estimating Equations module in PASW 18.0. This model appropriately takes into account between-subject dependence, which was necessary as the sample in the present study consisted of twins and sisters of the twins. As SNPs close to each other are usually in linkage disequilibrium with each other and thus correlated, a Bonferroni correction is usually considered too stringent to correct for multiple testing. Therefore, a correction method proposed by Nyholt [44] for SNPs in linkage disequilibrium was used.

**Results**

We analyzed 17 estrogen receptor SNPs: 12 $ESR_1$ SNPs and five $ESR_2$ SNPs. An overview of the SNPs and allelic frequencies is presented in Table 1. The genotype distribution of two $ESR_1$ SNPs (rs3798577 and rs6902771) differed significantly from what would be expected under Hardy–Weinberg Equilibrium and to minimize the risk of disturbing confounders such as inadequate laboratory testing, these SNPs were consequently excluded from further analyses. In addition, three SNPs ($ESR_1$ rs1062577, rs2747648, and $ESR_2$ rs1256049) were excluded from further analyses.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Alleles</th>
<th>Minor allele frequency in sample population</th>
<th>Common homozygotes n %</th>
<th>Heterozygotes n %</th>
<th>Rare homozygotes n %</th>
<th>Hardy-Weinberg Equilibrium (HWE) $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ESR_1$</td>
<td>rs1062577‡</td>
<td>A/T</td>
<td>A: 8% 1,968 84.9</td>
<td>343 14.8</td>
<td>5 0.2</td>
<td>3.35 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs1999865</td>
<td>A/G</td>
<td>G: 35% 997 42.8</td>
<td>1,029 44.2</td>
<td>295 12.9</td>
<td>1.26 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2071454</td>
<td>G/T</td>
<td>G: 13% 1,754 75.3</td>
<td>532 22.8</td>
<td>40 1.7</td>
<td>0.21 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2334693</td>
<td>C/T</td>
<td>C: 41% 854 36.9</td>
<td>1,037 44.8</td>
<td>419 18.1</td>
<td>3.37 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2273206</td>
<td>G/T</td>
<td>T: 20% 1,488 63.8</td>
<td>746 32.0</td>
<td>97 4.2</td>
<td>0.79 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2504063</td>
<td>A/G</td>
<td>A: 35% 994 43.0</td>
<td>1,031 44.6</td>
<td>282 12.2</td>
<td>0.00 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2747648‡</td>
<td>C/T</td>
<td>C: 2% 2,256 96.7</td>
<td>73 3.1</td>
<td>1 0.0</td>
<td>0.40 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs3020314</td>
<td>C/T</td>
<td>C: 33% 1,042 45.2</td>
<td>1,003 43.5</td>
<td>259 11.2</td>
<td>0.26 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs3798577†</td>
<td>C/T</td>
<td>C: 41% 832 35.9</td>
<td>1,066 46.0</td>
<td>416 18.0</td>
<td>5.22*</td>
<td></td>
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<tr>
<td></td>
<td>rs488133</td>
<td>C/T</td>
<td>T: 30% 1,141 48.8</td>
<td>960 41.1</td>
<td>232 9.9</td>
<td>0.59 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs6902771†</td>
<td>C/T</td>
<td>T: 41% 848 36.7</td>
<td>1,035 44.8</td>
<td>426 18.4</td>
<td>4.42*</td>
<td></td>
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<tr>
<td></td>
<td>rs722208</td>
<td>A/G</td>
<td>G: 35% 959 41.7</td>
<td>1,055 45.9</td>
<td>281 12.2</td>
<td>0.10 ns</td>
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<tr>
<td>$ESR_2$</td>
<td>rs1256030</td>
<td>C/T</td>
<td>T: 46% 690 29.9</td>
<td>1,127 48.8</td>
<td>490 21.2</td>
<td>0.36 ns</td>
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<tr>
<td></td>
<td>rs1256049‡</td>
<td>A/G</td>
<td>A: 8% 1,987 85.2</td>
<td>328 14.1</td>
<td>13 0.6</td>
<td>1.40 ns</td>
<td></td>
</tr>
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<td></td>
<td>rs1271572</td>
<td>G/T</td>
<td>G: 47% 668 28.8</td>
<td>1,138 49.0</td>
<td>514 22.1</td>
<td>0.26 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs4986938</td>
<td>A/G</td>
<td>A: 35% 977 42.1</td>
<td>1,046 45.0</td>
<td>296 12.7</td>
<td>0.13 ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs928554</td>
<td>G/A</td>
<td>G: 44% 739 32.2</td>
<td>1,085 47.9</td>
<td>447 19.8</td>
<td>1.28 ns</td>
<td></td>
</tr>
</tbody>
</table>

Notes: HWE statistics have not been adjusted for multiple comparisons. Only one individual of monozygotic twin pairs was included in the HWE calculations. Genotyping failure for individual SNPs may cause the n to fluctuate somewhat; the number of valid observations for the individual SNPs ranged from 2,292 to 2,333 (i.e., a maximum genotyping failure rate of 6.37% for an individual SNP)

* $P < 0.05$

‡Differed significantly from what would be expected under HWE and were therefore excluded from further analyses

*Excluded from further analyses due to extremely low numbers of the rare allele

A = Adenine, T = Thymine, G = Guanine, C = Cytosine; ns = not significant

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**Table 1** Descriptive statistics for the single nucleotide polymorphisms in the estrogen receptor genes 1 and 2

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due to extremely low numbers of the rare allele in the study population. Mean values of the genotypic groups are presented in Table 2.

We found nominally significant main effects on sexual desire before correcting for multiple testing for three ESR2-linked SNPs when including anxiety as a covariate, suggesting that individuals homozygous for the G allele (rs1271572), the A allele (rs4986938) respectively the A allele (rs928554) had lower levels of sexual desire compared with the other genotypic groups. One of the SNPs (rs4986938) also had a nominally significant effect on lubrication before correcting for multiple testing, suggesting that individuals homozygous for the A allele had higher levels of lubrication. The effects are presented in Table 3. The effects did not remain significant after correction for multiple testing ($P = 0.004$ for $\alpha = 0.05$). Effects without anxiety as a covariate are presented in Table 4.

Furthermore, as three of the four ESR2 SNPs were nominally significant on the desire domain before correcting for multiple testing, we decided to further investigate potential interaction effects between these SNPs. The interaction analyses were conducted by combining the four ESR2 SNPs in all possible ways including two, three, or all four of the SNPs. However, no significant effects were found.

**Discussion**

In the present study, we investigated the effects of ESR1 and ESR2 SNPs on sexual desire, arousal, and lubrication, in a population-based sample of women.
female adult Finnish twins and their sisters. To our knowledge, the present study involves the largest number of women who have provided genetic data and phenotypic data concerning sexual behavior published to date.

We found nominally significant main effects on sexual desire for three ESR2-linked SNPs before correcting for multiple testing, suggesting that individuals homozygous for the G allele (rs1271572), the A allele (rs4986938) respectively the A allele (rs928554) had lower levels of sexual desire. One of these SNPs (rs4986938) also had a nominally significant effect on lubrication before correcting for multiple testing, suggesting that individuals homozygous for the A allele had higher levels of lubrication. The effects did not remain significant after correction for multiple testing using the method proposed by Nyholt [44]. However, some statisticians argue that correction for multiple testing in hypothesis-driven candidate gene association studies might be too strict [45].

One possible explanation for the associations between three of the ESR2 SNPs and sexual desire could be that the genetic variants of the SNPs affect the encoding of the β-variant of the estrogen receptor, and hence the estrogen signal, differently. However, estrogens have previously been associated with a number of physiological and psychological functions, and therefore, any effects on sexual desire could be of secondary and indirect nature.

When interpreting the results between the three domains, it is important to note that the desire analyses included 323 more individuals than the arousal and lubrication analyses (see the Missing Values section). We found no significant interaction effects between the use of hormonal contraceptives and the SNPs. As we did not have specific information about the hormonal contraceptives used (e.g., type and amount of hormone), we decided only to do preliminary analyses of possible interference between the use of hormonal contraceptives and the SNPs.

The following limitations should be considered when interpreting the results of the present study. First, successful identification of genetic variation affecting predisposition to complex phenotypes like sexual desire and arousal mostly depends on the accuracy of the phenotype definition. Despite the excellent attempt of the FSFI to assess female sexual functioning, sexual desire in particular remains elusive and is often interpreted differently by clinicians and the women themselves [46]. The short time span used in the FSFI has further been criticized in the literature [47]. Women’s short-term sexual functioning can fluctuate as it is thought to be susceptible to change from environmental influences [48], making the assessment of an individual’s sexual function and the detection of its underlying genetic effects challenging. Second, no independent sample was available for replication of the results, although it should be noted that, to our knowledge, the sample size in the present study was more than twice that of the second largest genotype study focusing on female sexual dysfunctions [49]. In the study by Burri et al. [49], however, there were no significant hits for genetic markers in or near estrogen receptor genes. Failure to replicate genotype studies is very common in candidate gene association studies [50], even when using well-defined phenotypes for which large sample sizes are available. This has also been apparent in the field of research on female sexuality; to date, no genetic study on female sexuality has been successfully replicated. It

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Desire Wald χ²</th>
<th>P</th>
<th>Arousal Wald χ²</th>
<th>P</th>
<th>Lubrication Wald χ²</th>
<th>P</th>
</tr>
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<td>ESR1</td>
<td>rs1999805</td>
<td>4.027</td>
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<td>0.305</td>
<td>2.696</td>
<td>0.260</td>
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<td>0.487</td>
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<td>0.565</td>
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<td>2.814</td>
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<td>2.275</td>
<td>0.321</td>
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<td>3.805</td>
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<td>rs488133</td>
<td>1.165</td>
<td>0.758</td>
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<td>0.442</td>
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<td>2.166</td>
<td>0.339</td>
<td>1.659</td>
<td>0.436</td>
<td>0.579</td>
<td>0.749</td>
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<tr>
<td>ESR2</td>
<td>rs1256030</td>
<td>3.802</td>
<td>0.149</td>
<td>0.612</td>
<td>0.736</td>
<td>0.687</td>
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<td>5.218</td>
<td>0.074</td>
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<td>0.622</td>
<td>1.290</td>
<td>0.525</td>
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<td>7.958</td>
<td>0.019</td>
<td>1.622</td>
<td>0.444</td>
<td>6.722</td>
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<td>rs928554</td>
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<td>0.080</td>
<td>0.850</td>
<td>0.654</td>
<td>0.132</td>
<td>0.932</td>
</tr>
</tbody>
</table>

Notes: Bolded results were nominally significant before correction for multiple testing (no results were significant after correcting for multiple testing). df = 2 for all analyses.
should also be noted that the study sample of Burri et al. [49] had a mean age of 57 years, which is far above the mean age of menopause. It is nonetheless desirable to publish data from candidate gene studies, even negative results and especially so regarding phenotypes where enormous genomewide samples are not available (such as sexuality-related phenotypes), because the data can be included in future meta-analyses, in which sufficient statistical power for detection of robust associations can be achieved. We are hopeful that attempts to replicate our findings will be undertaken in the future. Third, menopausal transition has long been known to impair sexual function in women, especially lubrication [51]. As the mean age of the women participating in this study was 26.5 years with the oldest participant being 49 years (while the average age of menopause is 51 years; [52]), the present study leaves the effects of estrogen receptor genes on sexual functioning in postmenopausal women unexplored.

Although we found no significant interaction effects in our preliminary analyses, the number of SNPs with a tendency toward association suggests that some expanded combinations of estrogen receptor SNPs could have considerably stronger effects on sexual desire and arousal. As strong effects of any one genetic locus on sexual desire and arousal could have considerable consequences for reproduction, it is highly unlikely that one genotype alone would have any substantial impact on the traits explored, especially given that all alleles in the SNPs investigated in the present study were rather common in the population. A more appropriate way to analyze potential effects of estrogen receptor SNPs on sexual desire and arousal could perhaps be to analyze different haplotypes (i.e., genotype clusters and combinations) of the estrogen receptor genes, although this would require very large sample sizes. One suggestion would further be to study the haplotypes of phenotypically extreme individuals in case-control settings (e.g., through a clinic for individuals who have sought help for problems related to sexual desire and arousal).

As it has been hypothesized that the effects of estrogen are mediated through the levels of free testosterone in the body [31,32], another proposal for future research would be to investigate the association between these estrogen receptor SNPs and testosterone levels. Associations between the cytosine-adenine repeat polymorphism of the ESR2 gene and serum testosterone levels was found by Westberg et al. [53], but the ESR2 SNPs analyzed in this study was not included.

Conclusions

In the present study, we investigated the effects of eight ESR1 and four ESR2 SNPs on female sexual desire, arousal, and lubrication in a Finnish population-based sample consisting of 2,448 female twins and their sisters, aged 18–49. We found nominally significant results for three ESR2 SNPs before correcting for multiple testing, suggesting that estrogen receptor genes might affect desire and lubrication levels in women. We suggest studying haplotypes of phenotypically extreme individuals in case-control settings. Replication of these results in an independent sample is warranted.

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Conflict of Interest: The author(s) report no conflicts of interest.

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Estrogen Receptor Genes and Female Sexual Desire


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