## ORIGINAL RESEARCH—DESIRE

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

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**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 $ESR_1$ and $ESR_2$ 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 $ESR_2$-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 $ESR_2$ 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 $ESR_1$ 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. Witting 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 *ESR$_1$*) is connected to sexual motivation and performance capability, as measured by, for example, lordosis behavior, rearing, kicking, and attempts to avoid mounts [19–21]. A more recent study [22] also suggests that the gene encoding for the β-variant of the estrogen receptor (commonly referred to as *ESR$_2$*), affects sexual behavior in female mice, with *ESR$_2$*-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 derivates) 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 studies in humans and 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 *ESR$_1$* and *ESR$_2$* 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).