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# Androgen Receptor Polymorphism and Female Sexual Function and Desire

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## ABSTRACT

**Introduction:** The effect of testosterone depends on the exposure of and the sensitivity of the androgen receptor (AR). It has been shown that a cytosine–adenine–guanine (CAG) trinucleotide repeat polymorphism in the *AR* gene has an impact on AR functional capacity in men. However, large studies are lacking on the impact of this polymorphism on female sexual function.

**Aim:** To determine whether the CAG repeat length was associated with different aspects of women's sexual function and dysfunction, including desire, arousal, lubrication, orgasm, satisfaction, sexual pain, and sexually related personal distress.

**Methods:** This cross-sectional study included 529 healthy women, aged 19–65 years. Participants completed a questionnaire to provide demographic and sexual data. The CAG repeat length was analyzed in a blood sample. The correlations between CAG repeat lengths and different aspects of sexual function were calculated. Independent Student *t*-tests were performed to evaluate differences in the mean number of CAG repeats in the short and long allele and of the biallelic mean length determined by simple calculation and X-inactivation analysis, respectively, between women with sexual problems and women without sexual problems. *P* values $<.05$ were considered statistically significant.

**Main Outcome Measure:** We used the Female Sexual Function Index, with 6 subdomains, to distinguish between women without and women with impaired sexual function; low sexual desire; impaired arousal, lubrication, or orgasm; diminished satisfaction; or pain during sex. The Female Sexual Distress Scale was used to measure sexually related personal distress.

**Results:** Overall, we found that increasing numbers of CAG repeats were correlated to increased sexual function. We found that women with problems achieving orgasm had a significantly lower number of CAG repeats than women that reported no problems reaching orgasm. We found no associations between CAG repeat lengths and other aspects of female sexual dysfunction, including hypoactive sexual desire disorder.

**Clinical Implications:** The results could indicate an impact of the AR on women's sexual function, including the ability to reach orgasm.

**Strength & Limitations:** This is a large study using validated sexual questionnaires. A limitation is the cross-sectional design. Owing to the study design, this study is explorative and hypothesis generating.

**Conclusion:** In this large cross-sectional study, we demonstrated that CAG repeat length is positively correlated to sexual function and that women with a reduced ability to reach orgasm had smaller numbers of CAG repeats in the *AR* gene than women with no orgasmic problems. These findings indicated that androgens and ARs might play a role in women's sexual function. **Wåhlin-Jacobsen S, Flanagan JN, Pedersen AT, Kristensen E, Arver S, Giraldi A. Androgen Receptor Polymorphism and Female Sexual Function and Desire. J Sex Med 2018;15:1537–1546.**

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**Key Words:** Female Sexual Function; Female Sexual Dysfunction; Sexual Desire; Hypoactive Sexual Desire Disorder; Orgasm; Androgen; Androgen Receptor; CAG Repeat; Polymorphism; Testosterone

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## INTRODUCTION

Androgens, including testosterone and its precursors, are normally present in women. These hormones are secreted from the adrenal glands and the ovaries.[1] In contrast to other hormones, female testosterone is not regulated through any known feedback mechanism. The overall role of endogenous testosterone in women is not well understood but is proposed to be involved in sexual function including vaginal health, cardiovascular health, cognitive function, and musculoskeletal health in women, and testosterone therapy has been shown to have potentially positive cardiovascular effects and favorable effects on cognitive function.[2] Moreover, several studies have clearly demonstrated beneficial sexual effects of testosterone therapy in women with distressful low sexual desire.[3–5] Based on these results, the recent Endocrine Society Clinical Practice Guideline has recommended testosterone treatment for postmenopausal women with hypoactive sexual desire disorder (HSDD),[6] whereas the guideline recommend against making a diagnosis of androgen deficiency in women and against the generalized use of testosterone by women because the evidence is too sparse and because of the concerns of long-term safety.[7] Other guidelines recognize the off-label use of testosterone for HSDD in postmenopausal women.[8] Thus, we still need a better understanding of the clinical significance of testosterone in the sexual function of women.

Blood levels of androgens have been linked to sexual desire in both men and women. However, the relationship in women remains debated, owing to the lack of consistency in findings from previous epidemiologic studies that focused on circulating levels of androgens and androgen metabolites in relation to sexual desire and HSDD.[9,10] The 2 latest large studies in this field employed more accurate measurements of androgen levels in the female range. Those studies showed that androgen levels were significantly associated with sexual desire in women.[11–13]

An essential component of the androgen-signaling pathway is the androgen receptor (AR). The AR is a nuclear hormone receptor that is translocated from the cytoplasm to the nucleus, when it is activated by binding a ligand, such as testosterone or dihydrotestosterone.[14] The AR is expressed in most tissues, including the brain, muscle, bone, clitoris, and vagina.[15,16] In men, a cytosine–adenine–guanine (CAG) polymorphism in exon 1 of the gene encoding the transactivating domain of the AR has been linked to the functional capacity of the receptor, and the number of CAG repeats is used to estimate the receptor's sensitivity to testosterone.[17] Variations in the number of CAG repeats in the *AR* gene have been shown in vitro to modulate the transcriptional activity of the receptor.[18] It has been demonstrated that shorter CAG repeat polymorphisms were associated with higher receptor transcriptional activity,[19] expressed as a greater androgenic effect per unit of androgen.[17] Conversely, long CAG repeat polymorphisms in men were associated with hypoandrogenicity and male infertility.[20,21]

In women, few studies have investigated AR sensitivity as a function of CAG repeat length or its influence on female sexual function. 1 study that included 39 sexually active women taking combined hormonal contraception (CHC) showed that sexual desire was higher among women with either low or high numbers of CAG repeats in the *AR* gene.[22] Interestingly, the same ambiguous association has been found between sexual desire and the use of CHC, where the use of CHC was associated with reduced, improved, or unaffected sexual desire in different women.[23] Goldstein et al[24] showed that use of CHC was more likely to lead to vestibulodynia in women with a higher number of CAG repeats in the *AR* gene than in women with a lower number of CAG repeats. The latter result indicates that a high number of CAG repeats in the *AR* gene might lead to a less functional AR, resulting in low AR sensitivity to androgens in the genital tissue, causing sexual pain.

To summarize, the association between androgens and female sexual function or dysfunction remains inconclusive. The discrepancies among study results might be explained by a dependency of receptor function, which might be determined by the number of CAG repeats in the gene encoding the transactivating domain of the AR. Polymorphic variations in the *AR* gene are similar among men and women, but it remains unclear whether the clinical significance is similar in men and women. To our knowledge, this issue has not been investigated in a large cohort of women or in women who do not use CHC.

Based on previous research, we hypothesized that a higher number of CAG repeats might be negatively associated with the levels of desire and sexual function in women.

### Aims

We aimed to explore associations between CAG repeat lengths, as an indirect measure of AR sensitivity, and female sexual function. We also tested whether women with sexual dysfunction, including HSDD, exhibited differences in the *AR* gene measured as CAG repeat length compared with women without sexual dysfunctions.

## METHODS

### Study Design and Participants

This cross-sectional study included 529 healthy female volunteers, aged 19–65 years. The study was approved by the Regional Research Ethics Committee and the Danish Data Agency.[11] Women were recruited through advertisements at the hospital and via snowball sampling, as described in a previous publication.[11] Figure 1 shows a flowchart of participant selection. Women were excluded when they had a condition that could influence sex hormone levels or sexual function (eg, pregnancy, infant delivery within the past 6 months, breastfeeding, thyroid/pituitary diseases, polycystic ovary disorder, diabetes, a current or previous cancer disease, moderate to severe depressive symptoms, or use of antidepressant/antipsychotic medication within in the

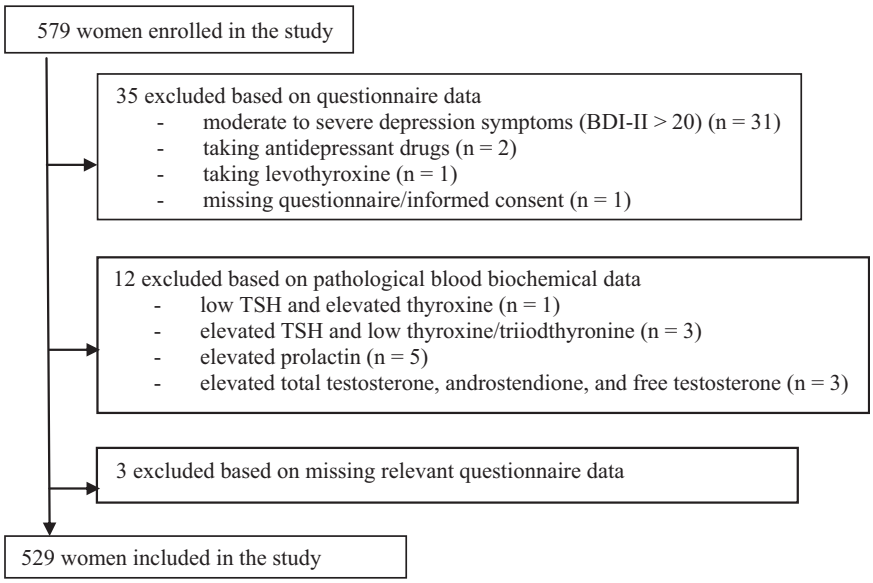


**Figure 1.** Flowchart of participant selection.

past 3 months). After receiving written and oral information, women provided informed consent before entering the study. Data and blood samples were collected from April 2009 to November 2011 at the University Hospital of Copenhagen, Denmark. In a single visit, all women provided a blood sample and completed a questionnaire, which included the Female Sexual Function Index (FSFI), the Female Sexual Distress Scale (FSDS), somatic health questions, and sociodemographic data. The cohort consisted of both premenopausal and postmenopausal women and included women who used CHC and menopausal hormone therapy.

## CAG Repeat Length Analysis

Considering that women have 2 copies of the X-chromosome where the gene encoding the AR is located, we chose to determine the number of CAG repeats in each woman by 4 different measures: 1) the number of CAG repeats in the allele containing the fewest CAG repeats (short allele), 2) the number of CAG repeats in the allele containing the most CAG repeats (long allele), 3) the mean number of CAG repeats of the long and short allele (calculated biallelic mean), and 4) the number of CAG repeats in the active X-chromosome based on X-inactivation analysis (X-weighted biallelic mean).

Genomic DNA was extracted from peripheral whole blood and analyzed at Karolinska University Hospital, Huddinge, Sweden. The CAG repeat region in the first exon of the *AR* gene on the X-chromosome was amplified from genomic DNA with polymerase chain reaction (PCR). The following published primers flanking the CAG repeats were used for amplification: 5'-FAM6-TCC AGA ATC TGT TCC AGA GCG TGC -3' and 5'- GCT GTG AAG GTT GCT GTT CCT CAT-3'.[25] Each PCR reaction contained a 40-ng genomic DNA template, 0.5 U HotStar Taq, 1X HotStar Taq buffer, 200-$\mu$M dNTP (with 50-$\mu$M dGTP and 150-$\mu$M 7-deaza dGTP), and 0.5 $\mu$M of each primer. The PCR protocol was performed on a GeneAmp 9700 thermocycler (Applied Biosystems, Waltham, MA, USA) as follows: 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 56.4°C for 30 seconds, and extension at 72°C for 30 seconds. Post-PCR FAM-labeled amplicons were mixed with GeneScan 500LIZ Size standards (Applied Biosystems). Then PCR-FAM amplicons were resolved with capillary electrophoresis and identified with an ABI 3730 Genetic Analyzer (Applied Biosystems). CAG repeat length of each allele was determined with GeneMapper Software (Applied Biosystems).

## X-inactivation Analysis

Methylation of a gene makes it inactive. Based on the methylation status of the 2 copies of the *AR* gene in each woman, it is possible to calculate a ratio, which is used to determine the mean number of CAG repeats of the active allele (X-weighted biallelic mean).

The X-inactivation assay and analyses were performed as described previously.[26] Within the CAG repeat region of the *AR* sequence lies a methylation-sensitive restriction site for HpaII endonuclease. When this site is methylated (inactive allele), it is insensitive to enzymatic cleavage, but an unmethylated (active allele) site is sensitive to enzymatic cleavage. Therefore, we digested the genomic DNA before performing PCR, and only intact CAG repeat segments (inactive alleles) were amplified in the PCR assay. For enzymatic digestion, 0.5 $\mu$g of genomic DNA was digested overnight at 37°C with 0.25 units of HpaII (NE Biolabs, Ipswich, MA, USA); mock digestion was performed for controls. We used 50 ng of digested or mock-digested genomic DNA as a template in each PCR reaction (described earlier). X-inactivation was quantified by calculating the

methylation status (ratio of the total peak areas of digested and undigested samples) for each allele; then, each allele length was multiplied by its total contribution to expression (1 minus the methylation status) and each adjusted weight allelic mean value were added together to obtain the overall X-weighted biallelic mean for each woman.[26]

## Main Outcome Measure

Sexual function was assessed with the FSFI, a validated, multidimensional, self-reporting instrument. The FSFI measures female sexual function in the prior 4 weeks, free of biases based on ethnicity, age, education, and economic status.[27] It is designed for heterosexual women with steady partners who have been sexually active during the prior 4 weeks. However, women without a partner or regular sexual activity can answer the 2 questions regarding sexual desire. The FSFI contains 19 items, subdivided into 6 sexual domains: sexual desire (FSFI-D), arousal (FSFI-A), lubrication (FSFI-L), orgasm (FSFI-O), satisfaction (FSFI-S), and pain during sex (FSFI-P). The FSFI was used in an XX translation that has previously been back-translated,[28] and the results showed that the translated FSFI questionnaire had a high degree of internal consistency (Cronbach $\alpha = 0.94$). Validated cut-off values were established to identify women with sexual problems in the prior 4 weeks. A total FSFI score (FSFI-total) <26.55 indicates female sexual dysfunction (FSD)[29], and an unweighted FSFI-D score <6 indicates HSDD (or a weighted score <3.6).[30] No validated cut-off values for the remaining domains have been established. Based on the distribution of the weighted domain scores, we selected the following cut-off values to discriminate between women without and women with specific sexual problems, including impaired arousal (FSFI-A <5.3), lubrication (FSFI-L <5.9), or orgasm (FSFI-O <5.9), diminished satisfaction (FSFI-S <5.9), or pain during sex (FSFI-P <5.9), in the prior 4 weeks.

HSDD was defined as a FSFI-D score <6 with concurrent sexual distress. Sexual distress was assessed with the FSDS, a validated self-reporting instrument. The FSDS provides data on sexual distress in the prior 30 days. It contains 12 items, and a total score ≥15 indicates sexual distress.[31] The FSDS was used in an Danish translation that had previously been back-translated,[28] and the results showed that the translated FSDS questionnaire had a high degree of internal consistency (Cronbach $\alpha = 0.94$). Women with HSDD were compared with a control group that comprised women with FSFI-D scores ≥6 and FSDS scores <15.

## Statistical Analysis

All analyses were performed with IBM SPSS Statistics 22.0 (SPSS Inc, Chicago, IL, USA). *P* values <.05 were considered statistically significant. The analyses of total scores from the FSFI and all sexual subdomains only included sexually active woman, but the analysis of the sexual desire subdomain also included sexually inactive women. The total scores from the FSFI and all of the sexual subdomains, except sexual desire, were skewed to the right. These scores could not be transformed into normal distributions; therefore, we chose to perform non-parametric correlations (Spearman) for analyses. Then, based on histograms of the distribution of the scores, we chose to dichotomize the sexual function endpoints. As mentioned earlier, the FSFI-total and FSFI-D scores could be dichotomized with previously validated cut-off values. For FSFI-arousal, the cut-off value we set for impaired arousal corresponded to either a "mild reduction in subjective arousal" marked for 3 of the 4 questions or "low subjective arousal" for at least 1 of the questions. The cut-off values for the remaining 5 subscales were placed to discriminate between women who reported no problems at all and women who reported any reduced function. The numbers of CAG repeats in the short and long alleles, the calculated biallelic mean, and the X-weighted biallelic mean were all normally distributed; therefore, comparisons were performed with the independent Student *t* test. All binary sexual endpoints, including comparisons between the HSDD and control group, were also evaluated with the independent Student *t* test.

**Table 1.** Descriptive data of the study cohort

| Characteristics | Values for the study population |
|---|---|
| No. of women | 529 |
| Age (y), mean (min, max) | 36.4 (19, 65) |
| BMI (kg/m$^2$), mean (min, max) | 23.4 (17.6, 38.5) |
| Steady relationship, N (%) | 401 (75.8) |
| Sexual activity with a partner in the past 4 wk, N (%) | 434 (82.0) |
| Premenopausal, N (%) | 428 (80.9) |
| Contraception, N (% of premenopausal women) | |
| CHC | 169 (39.5) |
| Progestin only | 45 (10.5) |
| Postmenopausal, N (%) | 101 (19.1) |
| Hormone therapy, N (% of postmenopausal women) | |
| Systemic | 8 (7.9) |
| Local estradiol | 13 (12.9) |

BMI = body mass index; CHC = combined hormonal contraception.

## RESULTS

Table 1 is a description of the total study population. The study population had a mean age of 36.4 years, 75.8% were in a steady relationship, and 82.0% had sexual activity with a partner in the prior 4 weeks. The proportions of premenopausal and postmenopausal women were 80.9% and 19.1%, respectively. Among premenopausal women, 39.5% used CHC. Among postmenopausal women, 7.9% used systemic menopausal hormone therapy.

For all women, the number of CAG repeats was within the range of 12-32 with no outliers. The mean numbers of CAG

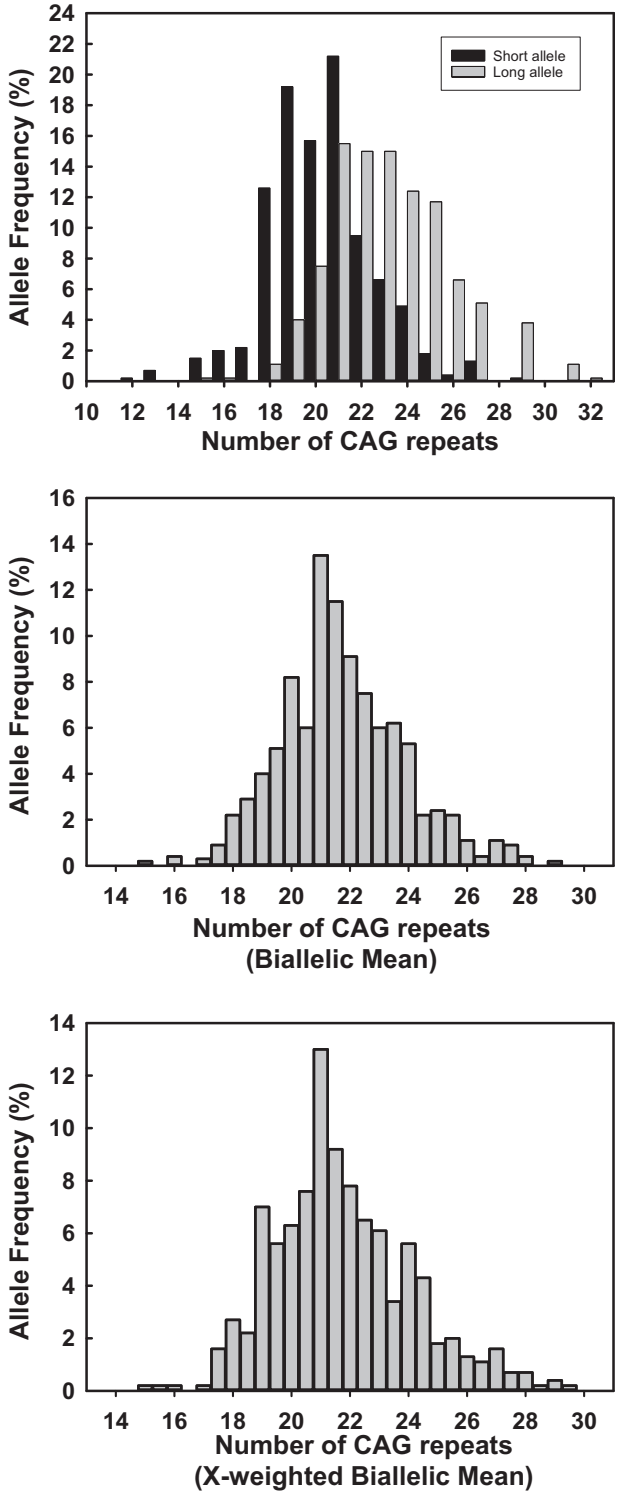


**Figure 2.** Frequency of *AR* alleles with different numbers of CAG repeats. Frequencies are shown separately for the numbers of CAG repeats (CAG lengths) in short and long alleles (A) and for CAG lengths as calculated biallelic means (B) or X-weighted biallelic means (C). CAG = cytosine–adenine–guanine.

repeats were 20.3 (range 12-29) for the short allele, 23.2 (range 15-32) for the long allele, 21.7 (range 15-29) for the calculated biallelic mean, and 21.7 (range 15-29.3) for the X-weighted biallelic mean. Figure 2 shows the frequency distributions of short and long alleles, the calculated biallelic means, and X-weighted biallelic means. The distributions were similar to those reported in previous studies on CAG repeats in women.[32,33]

Table 2 shows correlation coefficients between the 4 different measures of CAG repeat length and the different aspects of sexual function. Considering the short allele, we found significant positive correlations between the scores from the total FSFI ($P = .013$) and the FSFI-S ($P = .041$) and the number of CAG repeats. The scores from the total FSFI ($P = .043$) and FSFI-A ($P = .046$) were positively correlated to the X-weighted biallelic mean. The FSFI-O score was positively correlated to the number of CAG repeats in the long allele ($P = .004$), the X-weighted biallelic mean ($P = .029$), and the calculated biallelic mean ($P = .035$). Overall, increasing numbers of CAG repeats were associated with increased sexual function.

Tables 3 and 4 illustrate the differences in the mean number of CAG repeats of the 4 different measures of CAG repeat lengths between women with and without impairments in sexual function. Significantly fewer CAG repeats were observed in the long allele (22.9 vs 23.9, $P = .003$), and calculated biallelic mean (21.6 vs 22.3, $P = .017$) in women with impaired orgasmic function, compared with women who reported no significant problems achieving orgasm. No differences in the mean number of CAG repeats was demonstrated between the remaining sexual endpoints or in women with HSDD compared with controls.

## DISCUSSION

We hypothesized that longer CAG repeat lengths would be associated with sexual dysfunction in women primarily low sexual desire, because long CAG repeats were linked to reduced AR sensitivity in men.[17] Moreover, long CAG repeats were linked to sexual pain in women, in a small study of women that developed vestibulodynia with the use of CHC.[24] In contrast, the main findings of the present study showed that a tendency to longer repeat lengths were correlated to better sexual function in general, and no association was demonstrated between long CAG repeat lengths and sexual dysfunction including HSDD.

We previously demonstrated a positive correlation between the circulating levels of androgen and sexual desire in women.[11] In the present study, we found no association between low sexual desire and CAG repeat length, which indicated that the length of CAG repeats did not impact women's sexual desire. A potential explanation for this finding could be that because the present study was explorative, we assumed, like many other studies, that the CAG repeat length would be linearly related to AR functional capacity—for instance, AR sensitivity to androgens would decrease as the number of CAG repeats increased. However, the shape of the CAG repeat length vs AR function curve is unknown; it could be bell shaped, with 1 or more nadirs of low functional capacity at each pole, or it could be shaped like a staircase. Another explanation could be that in women, the number of CAG repeats does not significantly impact the AR sensitivity to testosterone as seen in men.

**Table 2.** Non-parametric (Spearman) correlation coefficients for associations between the CAG repeat length (evaluated separately for short alleles, long alleles, calculated biallelic means, and X-weighted biallelic means) and scores from the total FSFI, FSFI subdomains, and the FSDS, as continuous variables (N = 480)

| | Association with CAG repeat lengths | | | |
|---|---|---|---|---|
| Variables | Short allele | Long allele | Calculated biallelic mean | X-weighted biallelic mean |
| FSFI Total score | 0.143* | 0.079 | 0.112 | 0.118* |
| FSFI Desire | 0.086 | 0.013 | 0.058 | 0.045 |
| FSFI Arousal | 0.107 | 0.084 | 0.100 | 0.116* |
| FSFI Lubrication | 0.073 | 0.046 | 0.064 | 0.059 |
| FSFI Orgasm | 0.069 | 0.164** | 0.122* | 0.127* |
| FSFI Satisfaction | 0.118* | 0.020 | 0.079 | 0.081 |
| FSFI Pain | 0.093 | 0.011 | 0.036 | 0.036 |
| FSDS | −0.086 | 0.020 | -0.025 | 0.014 |

CAG = cytosine–adenine–guanine; FSFI = Female Sexual Function Index; FSDS = Female Sexual Distress Scale.
*$P < .05$.
**$P < .01$.

Thus, our results suggested that the clear association between CAG length and sexual function observed in men might be absent in women. In addition, conflicting results were reported in a small study that included women who used CHC; that study found that both women with rather short and long CAG repeat lengths had stronger sexual desire compared with women with CAG repeat lengths close to the mean length, indicating a bell-shaped association between CAG repeat length and sexual desire.[22] Instead of the inhibitory effect of the AR on testosterone production observed in men, a stimulatory effect has been proposed in women, because short CAG repeat lengths were found to be associated with higher levels of testosterone in 2 different studies of premenopausal women.[19,22] In a study that included 270 women, elevated levels of testosterone were not accompanied by elevated levels of luteinizing hormone; that finding suggested that AR expression in the adrenals and/or the ovaries had a direct effect on testosterone production rather than an indirect effect mediated via the hypothalamus. Another study failed to demonstrate an association between CAG repeat length and testosterone levels in women.[32] One explanation for the conflicting results of studies in women might be the bio-psychosocial nature of women's sexuality and sexual function, which makes it difficult to detect reliable associations in small samples or to detect the influence of any single factor on sexuality, as discussed previously.[13] An additional explanation could be that the physiology of androgens is, besides the dependency of the size of available amount of androgens and the functional capacity of the AR, also dependent on the expression of the AR.

Surprisingly, in the present study, we demonstrated a significant difference in mean CAG repeat lengths between women with and women without problems achieving orgasm. This result indicated that the AR might play a role in orgasmic function in women. It has been shown that the function of erectile tissue is regulated by androgens in men, and that an erection is important for a man's ability to achieve orgasm.[34] The woman's clitoris also contains erectile tissue,[35] and hyperandrogenic states have been linked to clitoromegaly. Despite the ongoing debate on the source of women's orgasms, there is a consensus that sufficient stimulation of the clitoris might be essential for the woman's ability to achieve orgasm.[36] Thus, the erectile function of the clitoris could very well be correlated to orgasmic function in women. Moreover, in women, genital arousal is characterized by increased blood flow to the genital tissue, and the engorgement of the clitoris is regulated by the tone of the vascular smooth muscle in the erectile tissue.[37] Different neurotransmitters and neuropeptides are involved in this regulation, and sex steroids are thought to regulate the synthesis, secretion, and reuptake of neurotransmitters.[37] In addition, estrogens and androgens, respectively, are important in the regulation of the size and function of different tissues and organs (eg, the genitals and mammae).[37] Accordingly, the decline in estrogen levels during the menopausal transition was associated with several changes in female genitals; those findings indicated that estrogen levels played a significant modulatory role in female sexual function. The role of androgens has been less well documented, apart from its role as the immediate precursor of estrogen synthesis. Nevertheless, in animal models, it has been demonstrated that androgens, independent of estrogens, were important in controlling the hemodynamics of female genitals, and in postmenopausal women it has been shown that vaginal atrophy is less in women with higher levels of androstenedione and testosterone,[16] and that vaginal sensation and congestion in response to sexual stimuli were better after administration of testosterone.[38] In the clitoris, animal studies have demonstrated that testosterone improved vascular smooth muscle relaxation.[39] Based on the findings of the present study, one could speculate that androgen levels and AR function might be important factors in the ability of women to reach orgasm, and previous studies

**Table 3.** CAG repeat lengths (mean number of trinucleotides [SD]) in women with and without impaired sexual function

| CAG measures | Mean number of CAG repeats in each type of sexual function/dysfunction | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FSFI Total | | FSFI Desire | | FSFI Arousal | | FSFI Lubrication | | FSFI Orgasm | | FSFI Satisfaction | | FSFI Pain | | | | | |
| | <26.55 | >26.55 | <6 | ≥6 | <5.3 | >5.3 | <5.9 | >5.9 | <5.9 | >5.9 | <5.9 | >5.9 | <5.9 | >5.9 | | | | |
| N (%) | 115 (32.1) | 243 (67.9) | 181 (34.2) | 348 (65.8) | 194 (55.0) | 159 (45.0) | 196 (55.5) | 157 (44.5) | 259 (73.4) | 94 (26.6) | 256 (72.5) | 97 (27.5) | 159 (45.0) | 194 (55.0) | | | | |
| Short allele | 20.22 (2.31) | 20.54 (2.34) | 20.01 (2.27) | 20.44 (2.33) | 20.23 (2.28) | 20.69 (2.40) | 20.35 (2.42) | 20.55 (2.26) | 20.35 (2.32) | 20.68 (2.40) | 20.45 (2.44) | 20.40 (2.08) | 20.29 (2.17) | 20.56 (2.48) | | | | |
| Long allele | 22.86 (2.67) | 23.24 (2.62) | 23.24 (2.61) | 23.15 (2.64) | 22.96 (2.59) | 23.34 (2.71) | 23.02 (2.60) | 23.27 (2.70) | 22.86** (2.52) | 23.89 (2.86) | 23.21 (2.69) | 22.91 (2.53) | 23.05 (2.57) | 23.20 (2.71) | | | | |
| Calculated biallelic mean | 21.54 (2.17) | 21.89 (2.14) | 21.62 (2.10) | 21.80 (2.16) | 21.59 (2.08) | 22.01 (2.26) | 21.69 (2.18) | 21.91 (2.17) | 21.61* (2.12) | 22.28 (2.26) | 21.83 (2.22) | 21.66 (2.03) | 21.67 (2.03) | 21.88 (2.28) | | | | |
| X-weighted biallelic mean | 21.47 (2.32) | 21.85 (2.28) | 21.63 (2.32) | 21.77 (2.39) | 21.51 (2.28) | 21.99 (2.30) | 21.63 (2.33) | 21.86 (2.27) | 21.58 (2.26) | 22.16 (2.38) | 21.78 (2.39) | 21.61 (2.07) | 21.61 (2.22) | 21.84 (2.37) | | | | |

Independent samples *t* test.
CAG = cytosine–adenine–guanine; FSFI = Female Sexual Function Index.
*$P < .05$.
**$P < .01$.

suggest the possibility that this effect might be mediated by androgen effects on erectile tissues in the genitals by increasing the sensitivity to circulating androgens. To our knowledge, no studies have investigated this possibility. However, a study on postmenopausal women who were not taking estrogens demonstrated that the group that received androgen therapy showed significantly higher FSFI-O scores compared with the group that received placebo.[40] Moreover, intravaginally administered dehydroepiandrosterone and testosterone were shown to improve arousal and orgasm compared with placebo in postmenopausal women.[41,42] The ability of women to reach orgasm is often seen as an exclusively acquired skill that depends on cultural and social conditioning; however, twin studies have demonstrated that orgasmic dysfunctions were heritable in approximately one-third of cases. This finding highlighted the role of biological factors in the female sexual response.[43,44]

## Strength and Limitations

Previous research in this area has focused on the effects of endogenous and exogenous testosterone on women's sexual function. This study contributed significant new knowledge on the genetic predisposition to androgenic effects in women. The large size of this study was a strength. However, a major challenge was the fact that each cell in a woman contains 2 X-chromosomes, each X-chromosome carries an allele that encodes the transactivating domain of AR, and 1 X-chromosome is randomly inactivated. However, owing to variations in which the X-chromosome is inactivated and the degree of X-inactivation in different tissues, X-inactivation can be skewed.[45] To address these challenges, we calculated both the biallelic mean and the X-weighted biallelic mean, determined by X-inactivation estimated from the methylation status observed in blood samples; nevertheless, methylation status can vary among blood, brain, and genital tissues.

A limitation of this study was that we did not measure AR receptor expression. Both the functional capacity and the expression levels of AR receptors are essential for evaluating the efficacy of androgens in different tissues. The study is a cross-sectional study and only gives a measure of the sexual function during the past 4 weeks. Moreover, the study does not consider other factors that are known to influence women's sexual function, including the impact of hormonal contraception and menopausal hormone therapy.

Sexual dysfunction has a multifactorial nature, and this study is limited because sexual function and dysfunction are not determined by a clinical interview but by quantitative data from validated questionnaires. Moreover, the clinical term *HSDD* has been used based on the conceptualization of HSDD at the time when the study was designed and the validated instruments used for the study. Since the initiation of the study, disorders of sexual desire and arousal have been merged into the diagnosis of sexual interest/arousal disorder in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, whereas desire and arousal

**Table 4.** CAG repeat lengths (mean number of trinucleotides [SD]) in women with HSDD and controls

| CAG measures | Women with HSDD | Control |
|---|---|---|
| N (%) | 94 (17.8) | 251 (47.4) |
| Short allele | 20.15 (2.40) | 20.48 (2.20) |
| Long allele | 23.30 (2.55) | 23.14 (2.57) |
| Calculated biallelic mean | 21.73 (2.12) | 21.81 (2.07) |
| X-weighted biallelic mean | 21.86 (2.42) | 21.77 (2.31) |

HSDD was defined as a score <6 on the desire subdomain of the FSFI and a score ≥15 on the FSDS. Controls have FSFI desire scores ≥6 and FSDS scores <15.
CAG = cytosine–adenine–guanine; FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index; HSDD = hypoactive sexual desire disorder.

disorders are kept separated in the *International Classification of Diseases, 11th Edition*, and other diagnostic proposals.[46–48]

The large number of sexual endpoints evaluated in this study allowed us to resolve effects on the different aspects of FSD, but it also increased the risk of type I errors. Therefore, our results should be considered explorative, not conclusive.

### Clinical Implications

This study questions whether CAG length measurement has a role in the treatment of sexual desire problems in women, because we do not find any relationship between sexual desire and number of CAG repeats. This does not neglect that testosterone has a role in sexual desire in women. However, a recent study showed that measurements of the number of CAG repeats in women could be used in sexual medicine to detect subgroups of women who are likely to benefit from androgen therapy. A preliminary study tested sublingual testosterone in combination with sildenafil and sublingual testosterone in combination with buspirone in women taking low-dose selective serotonin reuptake inhibitors (SSRIs) who developed SSRI-induced sexual dysfunction. They found that women with relatively long CAG repeat lengths showed significant improvements in sexual satisfaction with both treatments compared with women with short CAG repeat lengths.[49] CAG repeat measurements might also be useful for risk evaluation and counseling in women with a high risk of developing sexual side effects, owing to decreased androgen levels; in particular, women who use CHC and women with bilateral oophorectomies were shown to have possibly the greatest risk of developing sexual side effects.

## CONCLUSION

This large, cross-sectional, explorative study investigated the influence of *AR* polymorphisms (CAG repeats) as an indirect measure of AR sensitivity to androgens on female sexual function and dysfunction. Overall, higher numbers of CAG repeats were correlated with better sexual function in general. Shorter CAG repeat lengths were associated with a reduced ability to reach orgasm among women. This finding suggested that AR might play a role in women's sexual function, including women's ability to reach orgasm. The study demonstrated no associations between CAG repeat length and other aspects of FSD, including HSDD.

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