

MEN'S SEXUAL HEALTH

Androgen Receptor CAG Repeat Length as a Risk Factor of Late-Onset Hypogonadism in a Korean Male Population



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ABSTRACT

Background: Testosterone action is mediated through the androgen receptor (AR), whose sensitivity is influenced by the AR CAG repeat polymorphism. However, the relation between late-onset hypogonadism (LOH) and AR CAG repeat length is unclear and studies of Asian populations are limited.

Aim: To investigate the relation between AR CAG repeat length and LOH in Korean men.

Methods: 263 Korean men (mean age = 63.43 ± 10.9 years) were enrolled from 2014 to 2015. LOH diagnosis was based on a serum testosterone level lower than 3.5 ng/mL and positive androgen deficiency according to the Aging Males' Symptom Scale (AMS). Total testosterone levels and answers to the LOH-related questionnaire were analyzed.

Outcomes: The relation between AR CAG repeat length and LOH was determined.

Results: Mean CAG repeat length was 22.1 ± 4.6 and mean serum testosterone levels were 2.6 ± 0.7 and 6.0 ± 2.0 ng/mL in men with and without LOH, respectively. Men with LOH showed significantly longer AR CAG repeat lengths than men without LOH (26.1 vs 21.6, $P < .001$). Longer CAG repeat lengths were correlated with higher AMS total scores ($r = 0.454$, $P = .001$) and AMS psychotic, somatic, and sexual subscores ($r = 0.276$, 0.246, and 0.571, $P = .006$, .007, .001, respectively) and significantly lower 5-item International Index of Erectile Function scores ($r = -0.261$, $P = .001$). Multivariate analysis showed that patient age and CAG repeat length were independently associated with LOH (odds ratio = 1.05 and 1.29, $P = .041$ and $<.001$, respectively).

Clinical Implications: A longer CAG repeat length is associated with LOH symptoms and LOH.

Strengths and Limitations: Associations between CAG repeats and LOH were verified in Korean patients. Moreover, a longer CAG repeat length was shown to be an independent risk factor for LOH. Limitations included the small number of LOH patients studied and that other sex hormone-associated factors were not measured.

Conclusions: AR CAG repeat length was associated with LOH prevalence and clinical symptoms in this Korean male population. Thus, it is important to measure CAG repeat length for patients with LOH symptoms with normal testosterone levels. **Kim JW, Bae YD, Ahn ST, et al. Androgen Receptor CAG Repeat Length as a Risk Factor of Late-Onset Hypogonadism in a Korean Male Population. Sex Med 2018;6:203–209.**

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Key Words: Androgen Receptor; CAG Repeat; Late-Onset Hypogonadism; Testosterone

Received November 23, 2017. Accepted April 1, 2018.

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<https://doi.org/10.1016/j.esxm.2018.04.002>

INTRODUCTION

Late-onset hypogonadism (LOH) or testosterone deficiency syndrome, a clinical and biochemical syndrome characterized by typical symptoms and a deficiency in serum testosterone, can adversely affect multiple organ functions and quality of life.^{1–3} LOH is diagnosed by testosterone measurement and symptom questionnaires; however, these methods have limitations.

Table 1. Comparison of demographic characteristics and laboratory data between men with LOH and those without LOH

	All (N = 262)	LOH(-) (n = 229)	LOH(+) (n = 33)	P value
Age (y)	63.5 ± 7.4	63.0 ± 7.4	66.1 ± 7.7	.024*
CAG repeat length	22.1 ± 4.6	21.5 ± 4.4	26.1 ± 4.0	<.001*
Total testosterone (ng/mL)	5.6 ± 2.2	6.0 ± 2.0	2.6 ± 0.7	<.001*
IPSS total score	14.0 ± 7.8	13.9 ± 7.7	14.0 ± 8.2	.949
IPSS voiding score	8.2 ± 5.2	8.1 ± 5.2	8.2 ± 5.2	.915
IPSS storage score	5.6 ± 3.5	5.6 ± 3.4	5.6 ± 3.8	.956
IPSS QOL score	3.5 ± 1.2	3.5 ± 1.2	3.7 ± 1.3	.266
AMS total score	34.5 ± 11.4	34.0 ± 11.5	38.4 ± 10.2	.038*
AMS psychological score	8.1 ± 3.2	8.0 ± 3.3	8.6 ± 2.3	.294
AMS somato-vegetative score	13.9 ± 4.8	14.0 ± 4.9	13.8 ± 4.2	.826
AMS sexual factor score	12.5 ± 5.5	12.0 ± 5.3	16.0 ± 5.6	<.001*
IIEF-5 total score	11.6 ± 7.3	11.9 ± 7.3	9.7 ± 7.0	.102
PHQ total score	3.1 ± 3.9	3.17 ± 4.1	2.9 ± 2.9	.690

AMS = Aging Males' Symptom Scale; IIEF-5 = 5-item International Index of Erectile Function; IPSS = International Prostate Symptom Score; LOH = late-onset hypogonadism; PHQ = Patient Health Questionnaire-9; QOL = quality of life.

* $P < .05$.

Although symptom questionnaires such as the Androgen Deficiency in Aging Males (ADAM) questionnaire,⁴ the Aging Males' Symptom Scale (AMS),⁵ the Massachusetts Male Aging Study questionnaire (MMAS), the New England Research Institute Hypogonadism Screener, and the ANDROTEST are universally applied, they exhibit low specificity.⁶ Morley et al⁷ reported sensitivities of 97% for the ADAM questionnaire, 83% for the AMS, and 60% for the MMAS questionnaire. Specificities were only 30% for the ADAM questionnaire, 39% for the AMS, and 59% for the MMAS questionnaire.

Moreover, some investigators reported that total, free, and bioavailable testosterone levels do not correlate with the clinical symptoms of LOH.^{8,9} In addition, testosterone is characterized by diurnal and yearly variations, resulting in differentiations in its measurements for the same person depending on the time of measurement. Because of their inaccuracies in testosterone measurements and questionnaire answers, LOH is not easily diagnosed, limiting effective treatment.

The effect of testosterone is mediated through the androgen receptor (AR), the gene for which is located on Xq11-12 and contains 8 exons.¹⁰ The AR gene contains a repeated nucleotide sequence region, [CAG]_nCAA (known as the CAG repeat polymorphism and denoted as [CAG]_n), which codes for a polyglutamine tract in the N-terminal transactivation domain of exon 1.¹¹

The repeat length of CAG is negatively correlated with the transcriptional activity of target genes and can modulate AR activity.¹² The length of the CAG repeat sequence spans 9 to 36 repeats, with an average length of 21 repeats in Caucasian populations.¹³ However, there are significant ethnic variations in the allelic distribution of the AR CAG repeat.^{13,14} Although [CAG]_n appears to be associated with LOH or testosterone deficiency, the number of studies of [CAG]_n in Asian male populations is very limited.

We explored the relation between AR [CAG]_n and serum testosterone levels and LOH in a Korean male population.

METHODS

Subjects

The study protocol was reviewed and approved by the institutional review board of Korea University Guro Hospital (Seoul, Korea).

A cross-sectional study was carried out at the university hospital from June 2014 to May 2015. The inclusion criterion was men older than 40 years who were recruited from an LOH

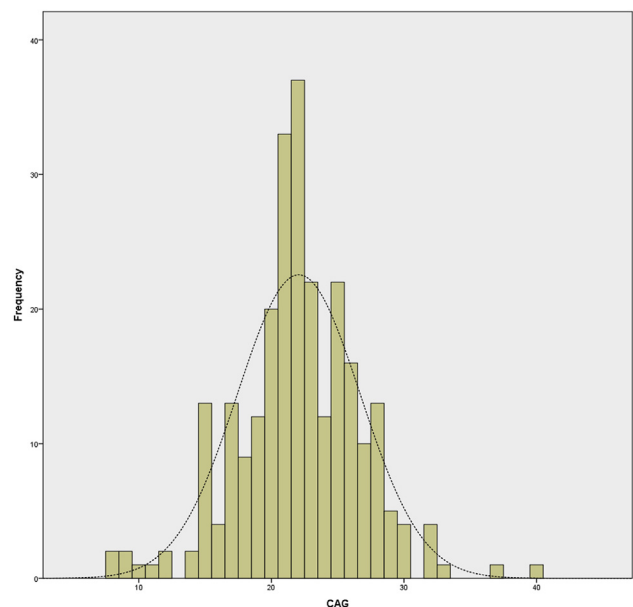


Figure 1. Distribution of the number of androgen receptor CAG repeats in the study population. AMS = Aging Males' Symptom Scale.

Table 2. Multivariate analysis associated with late-onset hypogonadism

Variables	B	SE	P Value	Exp(B)	95% CI for Exp(B)
Age (year)	0.050	0.025	.041*	1.05	1.00–1.10
CAG repeat length	0.252	0.053	<.001*	1.29	1.16–1.43
AMS total score	–0.036	0.031	.252	0.97	0.91–1.03
AMS sexual factor score	0.035	0.066	.593	1.036	0.91–1.18

AMS = Aging Males' Symptom Scale; B = regression coefficient; Exp(B) = odds ratio; SE = standard error.

* $P < .05$.

screening program. Exclusion criteria were the presence of Klinefelter syndrome, Kallmann syndrome, primary hypogonadism, hypogonadotropic hypogonadism, and previous medical use of testosterone or androgen products.

At the time of recruitment, informed consent was obtained and details of each participant's characteristics, medical history, and drug history were recorded. Clinical and biochemical assessments of the participants were made using questionnaires and laboratory tests. To minimize the alteration of circadian variations in testosterone levels, blood samples were collected from 8:00 to 11:00 AM from all men. Concentrations of total testosterone (TT) were measured using radioimmunoassay kits (Testo-RIA-CT, DIAsource ImmunoAssays, Nivelles, Belgium).

The participants completed several questionnaires related to LOH: the AMS, the 5-item International Index of Erectile Function (IIEF-5), the Patient Health Questionnaire–9 (PHQ), and the International Prostate Symptom Score.

LOH was diagnosed based on a serum testosterone level lower than 3.5 ng/mL and a positive score on the ADAM questionnaire,¹⁵ which was defined as a "yes" answer to questions 1 or 7 or any 3 other questions.^{1,4}

Genotyping

The AR CAG repeat length of each participant was determined by microsatellite fragment sizing, as described by Stanworth et al.^{16,17} Genomic DNA was extracted from peripheral blood treated with ethylenediaminetetra-acetic acid and subjected to polymerase chain reaction to amplify exon 1 of the AR gene. DNA samples were stored at -80°C until analysis. DNA amplification was performed using an automated thermal cycler with PCR Master Mix (ABGene, Epsom, UK). After magnetic separation of the polymerase chain reaction products, each sample was analyzed using a capillary-based AB3730 automated sequencer (Applied Biosystems, Foster City, CA, USA), which produces electropherograms from which the DNA sequence can be derived.

Statistical Analysis

Data are presented as mean \pm SD for continuous variables or as proportions for categorical variables. Baseline

characteristics of the men in the 2 groups (ie, with and without LOH) were compared using a t-test for continuous variables. Associations between CAG repeat length and questionnaire replies were analyzed using correlation analysis and are expressed as a Pearson correlation coefficient (r) with the associated P value. To assess the hazard ratio for LOH, a multivariate logistic regression analysis was performed. All statistical analyses were performed using SPSS 20.0 (SPSS, Inc, Chicago, IL, USA) and a P value less than .05 was considered statistically significant.

RESULTS

262 Korean men were enrolled in the study; the mean age of the participants was 63.4 ± 10.9 years (range = 51–93). The mean AR CAG repeat length was 22.1 ± 4.6 and the mean serum TT level was 5.6 ± 2.2 ng/mL (Table 1 and Figure 1).

Overall, 225 participants (85.9%) had a positive ADAM score and 65 (18.3%) had low serum TT levels (<3.5 ng/mL). Based on the LOH diagnostic criteria used, 33 men (12.6%) were determined to have the condition. Mean serum testosterone levels were 2.6 ± 0.7 and 6.0 ± 2.0 ng/mL in men with and without LOH, respectively. Men with a positive ADAM score showed significantly longer AR CAG repeat lengths than did men with a negative ADAM score (22.3 vs 20.4, $P = .018$).

Men with LOH showed significantly longer AR CAG repeat lengths compared with men without LOH (26.1 vs 21.5, $P < .001$). A comparison of data between these 2 groups of men showed significant differences in age ($P = .024$), CAG repeat length ($P < .001$), and TT level ($P < .001$). For the questionnaires, there were significant differences between the 2 groups in the AMS total score ($P = .04$) and the AMS sexual factor sub-score ($P = .002$). Although the mean scores for the IIEF-5 and PHQ questionnaires were lower in men with LOH, the differences were not significant (Table 2).

In the correlation analysis between [CAG]n and testosterone level, there was no association between CAG repeat length and TT (data not shown). In the correlation analysis between [CAG]n and the questionnaire results, there were increases in the AMS total score ($r = 0.454$, $P = .001$) and the AMS

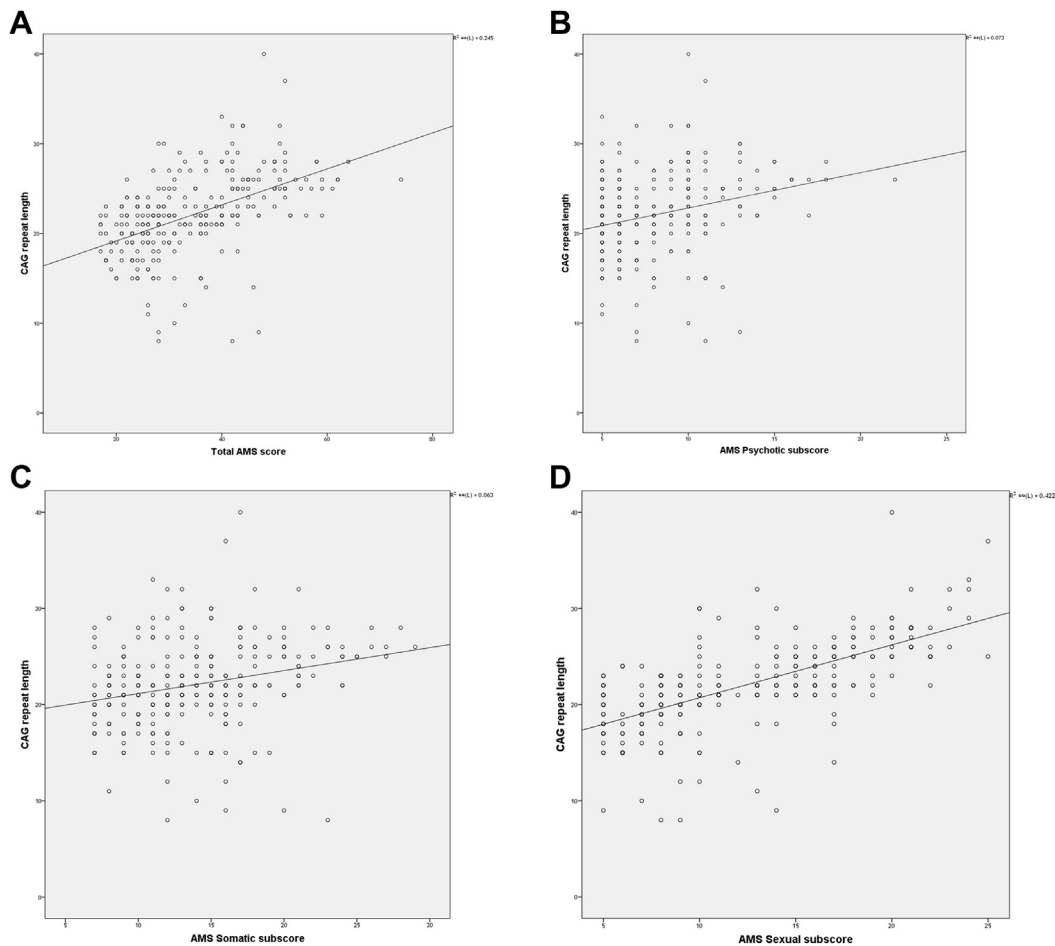


Figure 2. Correlation analysis between androgen receptor CAG repeat length and AMS scores. Panels A through D show the correlation between longer CAG repeat lengths and increased AMS total scores ($r = 0.454$, $P = .001$), AMS psychotic sub-score ($r = 0.276$, $P = .001$), AMS somatic sub-score ($r = 0.246$, $P = .001$), and AMS sexual sub-score ($r = 0.571$, $P = .001$), respectively. AMS = Aging Males' Symptom Scale.

psychotic ($r = 0.276$, $P = .006$), somatic ($r = 0.246$, $P = .007$), and sexual ($r = 0.571$, $P = .001$) sub-scores (Figure 2A–D) and significant decreases in IIEF-5 scores ($r = -0.261$, $P = .001$; Figure 3) with increasing CAG repeat length. In a subgroup analysis of the normal testosterone group, there were significant correlations of [CAG] n with the AMS total score ($r = 0.301$, $P < .001$) and the AMS psychotic ($r = 0.224$, $P = .001$), somatic ($r = 0.239$, $P < .001$), and sexual ($r = 0.328$, $P < .001$) sub-scores and IIEF-5 scores ($r = -0.223$, $P = .001$).

In the receiver-operator characteristics curve analysis to identify the potential criteria for the CAG repeat length predictive of the presence of LOH, the CAG repeat length showed an area under the curve of 0.800 (95% CI = 0.72–0.88, $P < .001$; Figure 4). The optimal cutoff value to maximize the Youden index was 24 for the CAG repeat length (Youden index = 0.496). Using this cutoff value of 24 for the CAG repeat length, the sensitivity and specificity were 72.7% and 76.9%, respectively.

Multivariate analysis showed an independent association of patient age (odds ratio = 1.05, $P = .041$) and CAG repeat length (odds ratio = 1.29, $P < .001$) with LOH (Table 2).

DISCUSSION

Several studies have reported an ethnic variation in the distribution of AR CAG repeats.^{13,14} Previous studies have shown that the number of AR CAG repeats is shortest in African Americans, intermediate in whites, and longest in Asians, which corresponds well with the variable phenotypes of disease such as prostate cancer.^{18,19} This ethnic variation in AR CAG repeats could help explain part of the large racial difference of disease.²⁰ However, the number of studies of AR CAG and LOH in Asian male populations is very limited.

In our study of the relation between AR [CAG] n and testosterone deficiency, we found a negative association between the CAG repeat length and LOH. In the multivariate analysis, a longer CAG repeat length was an independent risk factor for

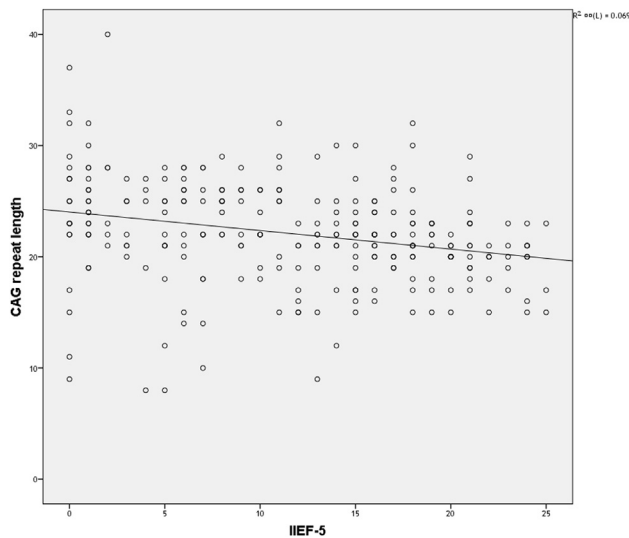


Figure 3. Correlation analysis between androgen receptor CAG repeat length and IIEF-5 score. With longer CAG repeat lengths, the IIEF-5 score decreased significantly ($r = -0.261$, $P = .001$). IIEF-5 = 5-item International Index of Erectile Function.

LOH. However, our data showed no correlation between CAG and hormonal levels.

Several researchers have examined the relation between [CAG]n and testosterone levels or LOH.

Huhtaniemi et al²¹ conducted a multinational prospective study and investigated the relation between various reproductive hormones and AR CAG repeat length in the European Male Ageing study. Men with longer AR CAG repeats had higher testosterone levels, which could adequately compensate for the lower AR activity.

Stanworth et al¹⁷ evaluated the relations among AR CAG repeat length, sex hormones, and clinical variables in 244 men with type 2 diabetes and found the testosterone level to be negatively correlated with leptin level and obesity, whereas AR [CAG]n showed a positive correlation with these 2 parameters. AR [CAG]n was not associated with symptoms of hypogonadism or with SHBG, estradiol, and hemoglobin A_{1c} levels.

Crabbe et al²² studied serum hormone levels and AR CAG repeat lengths by cross-sectional analysis of healthy men in 2 independent studies (2,322 men in the Belstress study and 358 in the SIBLOS study). Their results showed that the CAG repeat length was positively correlated with TT and free testosterone (FT) levels. The variability in serum FT levels in healthy men was related in part to differences in androgen sensitivity and feedback set points associated with AR polymorphism.

Krithivas et al²³ compared the CAG repeat length with TT, FT, albumin-binding testosterone, dihydrotestosterone, SHBG, and luteinizing hormone (LH) levels in 882 men in the MMAS. The CAG repeat length was significantly associated with TT, FT, and albumin-bound testosterone levels. Androgen levels could be regulated by the genotype of the AR gene.

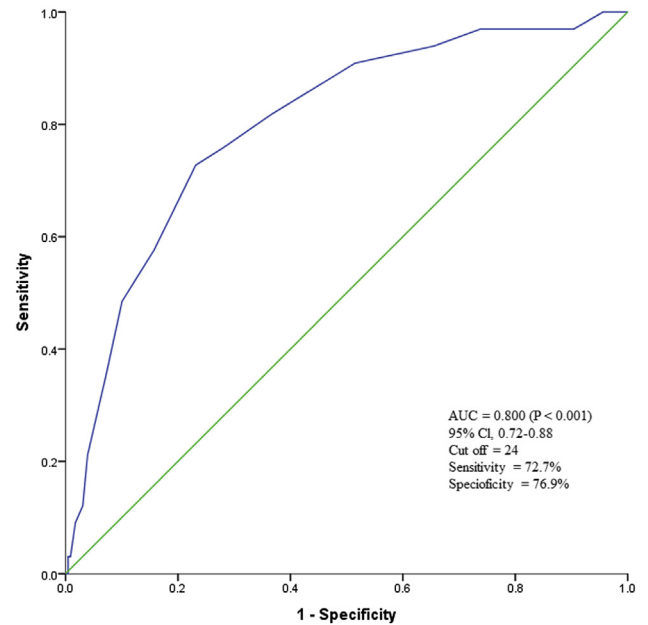


Figure 4. In the receiver-operator characteristics curve analysis to identify the potential criteria for the CAG repeat length predictive of the presence of late-onset hypogonadism, the CAG repeat length showed an AUC of 0.800 (95% CI = 0.72–0.88, $P < .001$). AUC = area under the curve.

Travison et al²⁴ studied the association of [CAG]n with TT and FT levels and frailty in 624 elderly men in the MMAS. CAG repeat length was positively correlated with TT and FT levels. Multivariate regression analysis showed no effect of [CAG]n on hormone levels and the prevalence of frailty. Their study did not support the hypothesis that a lack of association between circulating androgens and the frailty phenotype could be explained by interpersonal differences in the CAG repeat.

In contrast, some studies showed that [CAG]n and testosterone levels or LOH are not related. Harkonen et al²⁵ found no significant correlation between testosterone level and AR CAG repeat lengths. They explained the results were due to the wide fluctuation of testosterone levels and the cross-sectional nature of their study. However, they found a positive correlation between LH and the severity of erectile dysfunction and a relation between CAG and various age-related conditions and symptoms.

Goutou et al²⁶ examined the association between AR gene polymorphism and serum hormone and lipid profiles in 170 healthy men. They found no significant correlation between AR [CAG]n and gonadal steroid levels (TT, FT, and total and free estradiol) and lipid profiles (triglyceride and total, high-density lipoprotein, and low-density lipoprotein cholesterol). They concluded that AR [CAG]n might not predict sex hormone levels in healthy men, and the effects of the CAG repeat length on lipid levels remained unclear.

Van Pottelbergh et al²⁷ evaluated the individual variability of serum testosterone levels and potential contribution of AR [CAG]n to bone metabolism in 273 elderly men. They found no

significant correlation between AR CAG repeat length and TT, FT, and LH levels. There also was no correlation between AR CAG repeat length and bone mineral density in the hips and forearms. Moreover, AR [CAG]_n was not associated with biochemical markers of bone turnover rate. This study did not support the hypothesis that AR [CAG]_n affects interpersonal differences in serum testosterone, bone turnover rate, and bone mineral density.

In the present study, we found no relation between [CAG]_n and TT, perhaps because of the influence of various environmental factors. (i) The fluctuation of TT levels should be considered. (ii) According to Skjaerpe et al,²⁸ the lower AR sensitivity in men with higher CAG repeat numbers can be compensated, at least in part, by higher testosterone levels. However, the extent of compensation is not known and can vary from person to person. In addition, this was a cross-sectional study. In the MMAS, which was a longitudinal study of 882 men 40 to 70 years old, a difference in TT alteration according to CAG length was found. Therefore, to obtain a definite conclusion, additional studies are needed.

However, regarding the questionnaires, our results showed that the AR CAG repeat length was associated with the clinical symptoms of LOH. In correlation analysis, [CAG]_n was associated with the AMS total score and AMS sexual sub-score. The importance of these results is unclear because of the difficulty in controlling environmental variables associated with each participant. In multivariate analysis for LOH, the questionnaire had less influence than the AR CAG repeat length. However, when an ideal method for testosterone measurement is not available, CAG measurement for patients with LOH symptoms is meaningful. In particular, CAG should be measured in men with normal testosterone levels and in those with LOH symptoms.

Our study had several limitations. This study evaluated a small number of participants in a single institution. Because of the small sample, the number of patients with LOH was very small. In addition, other sex hormone-associated factors such as SHBG, follicle-stimulating hormone, and LH were not measured. This cross-sectional study examined only a single measurement of the CAG repeat length.

Despite these limitations, our study showed an association between [CAG]_n and LOH in Korean men, which is the 1st such finding in an Asian male population. Moreover, from the multivariate analysis, a longer CAG repeat length was found to be an independent risk factor for LOH. Thus, measurement of CAG repeat length can play a role in the diagnosis and evaluation of LOH in patients with LOH symptoms (even if they show normal testosterone levels). Further prospective studies of a larger population and in collaboration with other centers, while controlling environmental variables, are needed to verify our conclusions.

CONCLUSIONS

AR CAG repeat length was found to be associated with the prevalence and clinical symptoms of LOH in a Korean male population. It is important to measure CAG in patients with LOH symptoms even if their testosterone level is not low.

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Conflicts of Interest: The authors declare no conflicts of interest.

Funding: The Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (R1304182).

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