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Literature Review

Polymorphic CAG and GGN repeats in Cryptorchidism patient risk: A meta-analytical study

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ABSTRACT

Genetic mutations in the androgen receptor (AR) gene have been identified as the cause of androgen insensitivity syndrome. These mutations are linked to inconsistent development of the Wolffian duct and may result in conditions such as micropenis, hypospadias, and cryptorchidism. The androgen receptor has two polymorphic sites located in exon 1, which consists of varying amounts of CAG and GGN repeats. These repetitions lead to the formation of polyglutamine and polyglycine stretches of varied lengths. Increased CAG repeats lead to a decrease in androgen receptor transcriptional activity, but the impact of GGN triplets is less well understood. This research examined the CAG and GGN repeat lengths in males who had a past medical record of cryptorchidism. Prospective and retrospective observational studies from PubMed, Science Direct, and Embase were systematically searched up to 15th November 2020. Primary outcomes were analyzed using a fixed or random effect model regarding its heterogeneity and continued with multilevel modeling of each polymorphism and ethnicity. CAG and GGN repeat polymorphism was found to be significantly different compared to control in contributing to cryptorchidism (CAG: 0.55 [CI 95%=0.19-0.91]; p-value=0.003 and GGN 0.90 [CI95%=0.65-1.15]; p value<0.000). In conclusion, CAG and GGN repeat polymorphism have an essential role in the incidence of cryptorchidism.

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INTRODUCTION

Cryptorchidism, also known as undescended testes (UDT), is the condition when one or both testes fail to descend to their usual position in the scrotum. This disorder is a common congenital anomaly, with a prevalence rate of roughly 2-9% among full-term male neonates (Skakkebaek *et al*., 2016). Cryptorchidism is linked to many reproductive problems, such as a reduction in germ cells at an early stage, abnormalities in the epididymis, and a higher likelihood of developing testicular germ cell malignancies (Kollin & Ritzen, 2014). The process of testicular descent takes place in two hormonally controlled stages during fetal development: the first stage happens between 8 and 15 weeks of gestation, while the second stage occurs between 25 and 35 weeks (Hutson *et al*., 2013). Any disturbances during these stages may lead to the development of persistent cryptorchidism (Gurney *et al*., 2017). The precise cause of cryptorchidism is still uncertain, however, it is thought to arise from a mix of genetic and environmental influences (Rodprasert *et al*., 2020). In recent decades, researchers have found genetic defects that have a major impact on hormone production and receptor function. The study conducted by Koster *et al*. in 2014 has identified gene polymorphisms that may have a role in testicular descent.

The process of testicular descent is intricate, requiring the interaction of anatomical and hormonal variables (Hutson *et al*., 2013). Hormones, namely testosterone, play a vital role in the process of testicular descent (Wilhelm *et al*., 2013). The androgen receptor (AR) is essential for the proper development of basic male sexual characteristics during prenatal development and secondary male sexual features throughout puberty. The androgen receptor (AR) operates via testosterone or its powerful derivative, 5α-dihydrotestosterone (Eisermann *et al*., 2013). The AR gene is situated on chromosome Xq11-12 and consists of eight exons and seven introns (Katagiri *et al*., 2006). The N-terminal domain in exon 1 is the area with the most variability, including many highly repetitive DNA sequences, such as CAG and GGN repeats. The range of CAG repeats usually falls between 10 and 35, which encodes polyglutamine tracts in the AR transactivation region (Zitzmann and Nieschlag *et al*., 2003). The number of CAG repeats has an inverse correlation with the transcriptional activity of AR, which in turn affects the physiologic consequences of testosterone (Mosaad *et al*., 2012). Exon 1 has a highly repeated sequence known as the GGN repeat. This repeat consists of 10 to 35 repetitions, with an average of 23 repeats in the general male population (Grigorova *et al*., 2017). The GGN repeat, situated inside the transactivation domain of the AR, is expected to have an impact on the functioning of the receptor.

Several studies have examined the correlation between the lengths of CAG/GGN repeats in the AR gene and the likelihood of developing cryptorchidism. Nevertheless, the results have proved inconclusive. While several meta-analyses have investigated the correlation between AR CAG/GGN repeats and male infertility or hypospadias (Huang *et al*., 2015), only a limited number of research have explicitly addressed the relationship between these genetic variations and the likelihood of cryptorchidism. Prior meta-analyses were constrained by the limited number of research and small sample sizes, which might weaken the validity of their findings. To overcome these restrictions and provide more reliable information, this research does an extensive meta-analysis using a bigger dataset to elucidate the relationship between CAG/GGN repeat lengths and the likelihood of developing cryptorchidism.

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METHODS

Study Strategy

A meta-analysis was conducted and documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Two reviewers, NCL and AFP, did thorough searches of the PubMed, Science Direct, and Embase databases starting from the earliest known date, November 15th, 2020. The searches were completed separately. The search phrases used were "androgen receptor," "polyglutamine," "CAG," "GGC," "GGN," "AR," "cryptorchidism," "infertility," "testicular diseases," "genetic polymorphism," and "polymorphism." In addition, we conducted manual searches of reference lists from pertinent reviews and extracted papers. Initially, 625 papers were identified. After screening titles and abstracts, 542 papers were excluded due to irrelevance. A detailed review of the remaining studies resulted in the inclusion of 8 studies for the meta-analysis.

Inclusion and Exclusion Criteria

Included in this analysis were observational studies, both retrospective and prospective, that examined the relationship between CAG and GGN repeat polymorphisms in the androgen receptor (AR) gene and cryptorchidism. These studies provided enough data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Only studies conducted in English and including original research were evaluated for inclusion.

Studies were excluded if they had irrelevant titles or abstracts, meaning they did not focus on the research question. Family-based studies were also excluded as they involved genetics within families rather than broader population-based samples. Review articles or commentaries, which are non-original research articles summarizing existing knowledge or providing opinions, were not included. Studies with incomplete or non-generalizable data were excluded, as were duplicate studies using the same data as another included study. Finally, studies were excluded if they deviated from Hardy-Weinberg equilibrium, indicated by a chi-square (X^2) value greater than 3.84. The meta-analysis intended to create a comprehensive dataset that correctly represents the link between AR gene polymorphisms and the risk of cryptorchidism by following certain criteria for inclusion and exclusion.

Data Extraction

The extracted data included the author's name, publication year, geographic location, ethnicity, research type (retrospective, prospective, cross-sectional), sample sizes, and the mean and standard deviation (SD) of CAG and GGN repeat lengths. The quality of the studies was evaluated using the Hardy-Weinberg equilibrium (HWE) for validation. In case of any discrepancies, they were addressed by conversation or by consulting a third researcher, if necessary.

Data Analysis

The meta-analysis was conducted using the Revman 5.4 software. The P-values were calculated using a two-sided test. To determine the variations in repetition length between patients and controls, we estimated the overall weighted mean difference (WMD) and 95% confidence intervals (CIs). Analyzed subgroups were categorized according to ethnicity, geographic region, and research methodology. The heterogeneity across studies was evaluated using Cochran's Q statistic and Higgins' I^2 statistic. The classification for Higgins' I^2 statistic is as follows: I^2 = 0–25%, indicating negligible heterogeneity; I^2 = 25–50%, indicating moderate heterogeneity; I^2 = 50–75%, indicating high heterogeneity; and I^2 = 75–100%, indicating severe heterogeneity.

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In instances where there was considerable heterogeneity, a random-effects model (specifically, the DerSimonian and Laird method) was used. Conversely, where there was no significant heterogeneity, a fixed-effects model (specifically, the Mantel and Haenszel method) was employed. Publication bias was evaluated by using Begg's funnel plots and Egger's test, where a significance level of $P < 0.05$ was deemed statistically significant.

RESULTS

Characteristics of the Study

Figure 1 depicts the procedure of doing a literature search and selecting relevant materials. A total of 625 studies were initially discovered from PubMed, Science Direct, and Embase. After eliminating duplicate entries, a total of 81 distinct studies were left for further evaluation. After examining the abstracts, 73 articles were eliminated because they were not relevant, leaving 8 research that satisfied the initial inclusion criterion. The eligibility of these 8 papers for inclusion in the meta-analysis was established by comprehensive assessments of their full texts.

The characteristics of the chosen studies are outlined in Table 1. Of these studies, six focused on Caucasian populations, specifically individuals from Iran, Sweden, Portugal, Hispanic regions, and Chile. The remaining two studies were conducted on Asian populations from China and Japan. The control groups in these studies consisted of healthy boys or male adults with no history of cryptorchidism.

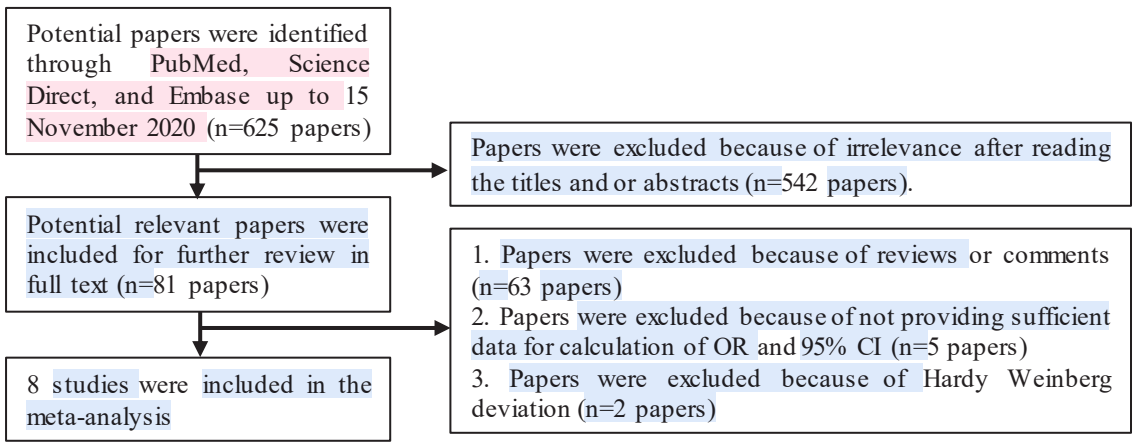

Figure 1. Workflow diagram of the search and screening process

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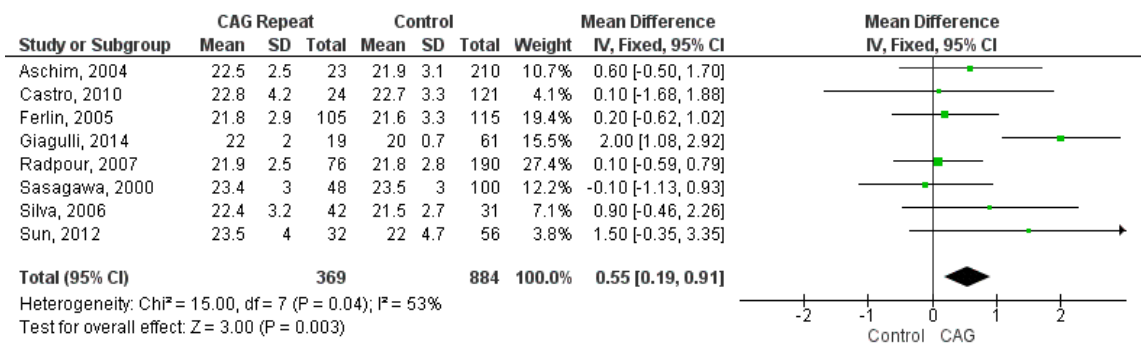
Cryptorchidism CAG vs. Control

The meta-analysis examining the correlation between CAG repeat lengths in the AR gene and cryptorchidism found a significant disparity between individuals with cryptorchidism and those without the condition. The level of variation across the studies examined was moderate, as shown by a Chi^2 value of 15.00 with 7 degrees of freedom (P = 0.04) and an I^2 value of 53%. This indicates that around 50% of the variation seen in different research may be attributed to heterogeneity rather than random chance. The test for the overall impact yielded a Z value of 3.00 (P = 0.003), showing a statistically significant disparity in CAG repeat lengths between the two groups. The weighted mean difference (WMD) was 0.55, with a 95% confidence interval (CI) ranging from 0.19 to 0.91. This study's findings reveal that individuals with cryptorchidism had a lower mean CAG repeat length compared to those without the condition. This suggests that a shorter CAG repeat length may be linked to a higher risk of developing cryptorchidism. The forest plot and funnel plot in Figure 2 below display the results.

Table 1. Key characteristics of the research included

Author & year	Geographic Location	Ethnicity	Study Design	CAG repeat length						GGN repeat length						X2 HWE (control)
				Cryptorchidism			Control			Cryptorchidism			Control			
				N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Aschim, 2004	Sweden	Caucasian	PCC	23	22.5	2.5	210	21.9	3.1	23	23.6	0.5	210	22.6	2.4	0.8093
Castro, 2010	South America	Caucasian	HCC	24	22.8	4.2	121	22.7	3.3	24	22.7	2.7	121	23.1	1.1	0.838
Ferlin, 2005	Italy	Caucasian	PCC	105	21.8	2.9	115	21.6	3.3	105	17.4	1.4	115	17.0	1.7	0.0603
Giagulli, 2014	Italy	Caucasian	HCC	19	22.0	2.0	61	20.0	0.7	-	-	-	-	-	-	1.775
Radpour, 2007	Iran	Caucasian	PCC	76	21.9	2.5	190	21.8	2.8	76	24.5	2.4	190	22.3	2.1	1.6
Sasagawa, 2000	Japan	Asian	HCC	48	23.4	3	100	23.5	3	-	-	-	-	-	-	1.699
Silva, 2006	Portugal	Caucasian	HCC	42	22.4	3.2	31	21.5	2.7	-	-	-	-	-	-	1.6743
Sun, 2012	China	Asian	HCC	32	23.5	4.0	56	22.0	4.7	-	-	-	-	-	-	0.1794



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Polymorphic CAG and GGN repeats in Cryptorchidism patient risk: A meta-analytical study

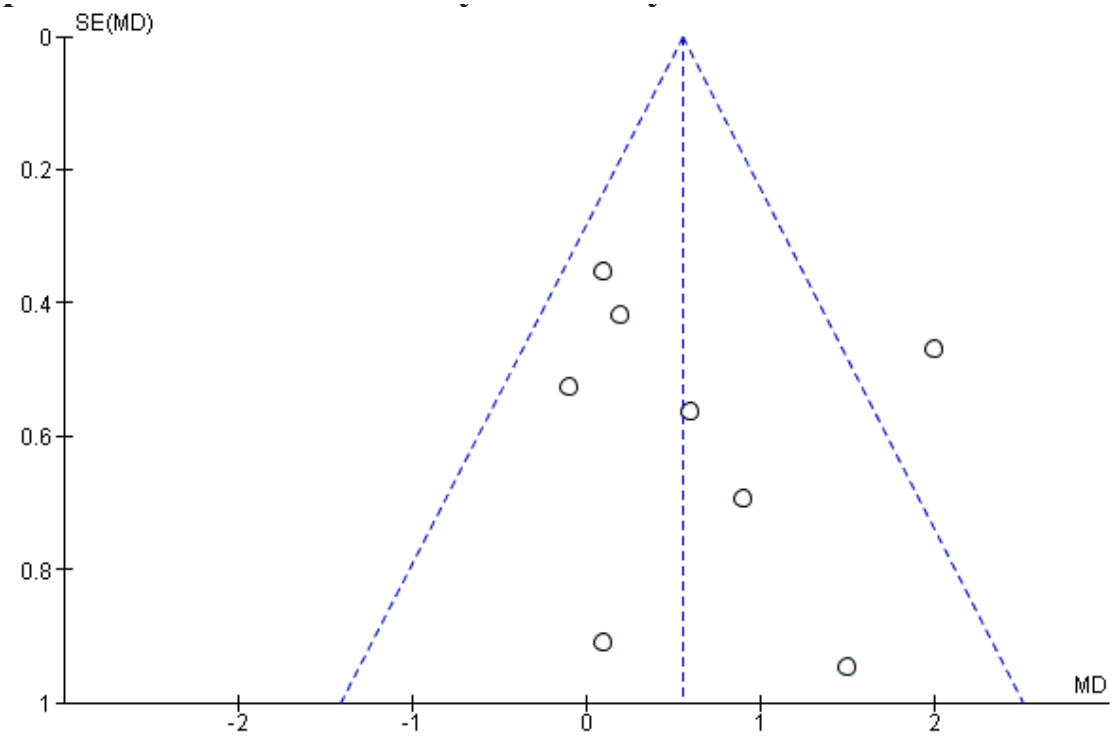

Figure 2. Forest plot and funnel plot for CAG repeats against control

Cryptorchidism GGN vs Control

The meta-analysis also found a significant variation in the GGN repeat lengths in the AR gene between patients with cryptorchidism and healthy controls. The studies exhibited a significant level of heterogeneity, as shown by a Chi² value of 28.43 and 3 degrees of freedom ($P < 0.00001$), and an I^2 value of 89%. The high I^2 score implies significant heterogeneity across the research, indicating that the variations in study findings cannot be solely attributed to random chance.

The test for the overall impact resulted in a Z value of 7.12 ($P < 0.00001$), indicating a very significant disparity in GGN repeat lengths across the groups. The weighted mean difference (WMD) was 0.90, with a 95% confidence interval (CI) ranging from 0.65 to 1.15. This study demonstrates that the average GGN repeat length is considerably distinct in patients with cryptorchidism compared to the control group. This finding provides more evidence to support the idea that differences in GGN repeat lengths can contribute to the development of cryptorchidism. The forest plot and funnel plot in Figure 3 below show the results.

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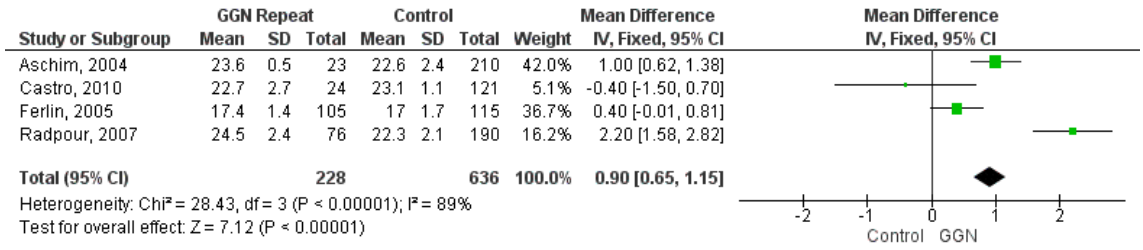

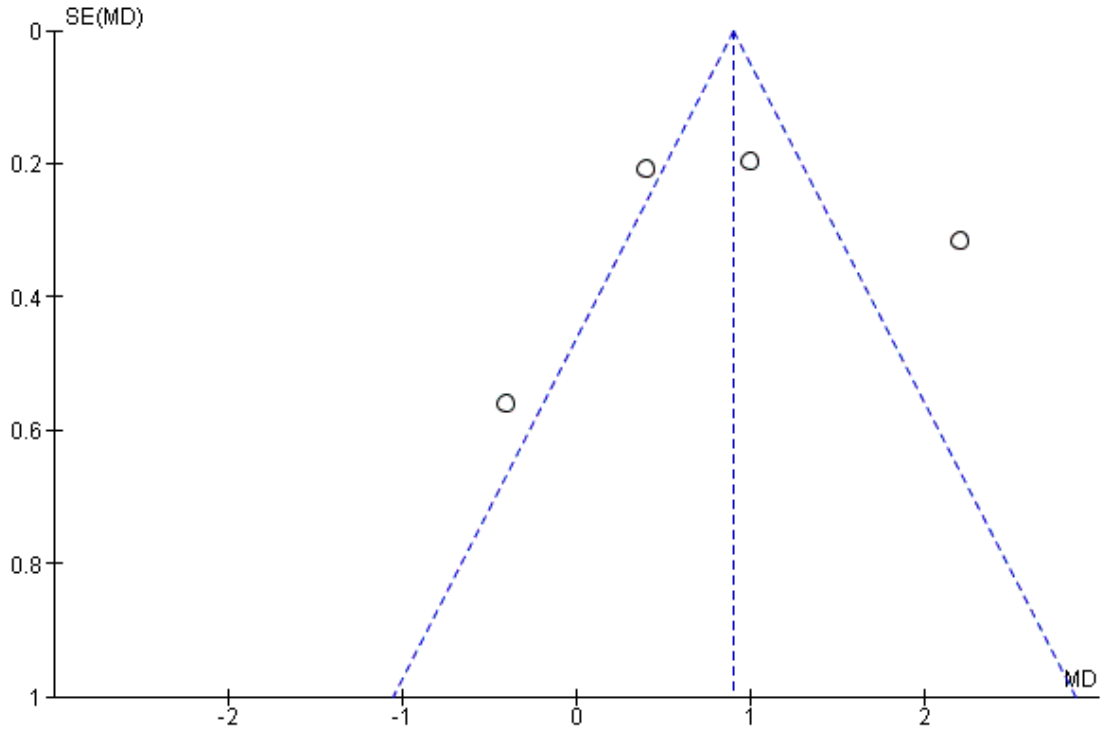

Figure 3. Fores plot and funnel plot for GGN repeats against control

DISCUSSION

The process of testicular descent is thought to happen in two stages that are governed by hormones. However, the exact factors that contribute to the development of cryptorchidism are still unknown (Gurney *et al*., 2017). The inability of a testis to descend permanently is most likely caused by disturbances in one or both of these stages. However, the particular causes and processes of these disturbances are still not completely understood. Studies have shown that hormone levels are notably reduced in individuals with bilateral cryptorchidism (Hamdi *et al*., 2017). Increased CAG and GGN repeats in the androgen receptor (AR) gene result in decreased AR transcriptional activity and lower impact of testosterone, which is necessary for proper testicular descent. This may elucidate the reason why bilateral cryptorchidism is often correlated with longer CAG and GGN repeats.

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Prior research investigating the correlation between the length of CAG and GGN repeats and the likelihood of cryptorchidism has shown inconclusive findings. Despite Wang *et al.*'s (2018) effort to address these inconsistencies using a meta-analysis, the findings reached were constrained by the limited number of studies and small sample sizes. In order to overcome these constraints, the present meta-analysis used a higher quantity of papers and a bigger sample size. The investigation revealed that the CAG and GGN repeats in the AR gene were of greater length in patients with cryptorchidism as compared to the control group. Both longer CAG and GGN repetitions were strongly linked to a higher likelihood of cryptorchidism.

This meta-analysis aims to examine the correlation between CAG and GGN repeat polymorphisms in the androgen receptor (AR) gene with the likelihood of developing cryptorchidism. The results demonstrate substantial variations in the lengths of these repetitive sequences among individuals with cryptorchidism compared to those without the ailment, indicating a possible genetic origin for the disorder.

The investigation demonstrated that a decrease in the number of CAG repeats in the AR gene is linked to a higher likelihood of developing cryptorchidism. The weighted mean difference (WMD) of 0.55 [95% CI: 0.19-0.91; P = 0.003] suggests that patients with cryptorchidism often had shorter CAG repeats than the control group. This finding aligns with other research indicating that shorter CAG repeats might intensify androgen receptor function, possibly interfering with the appropriate descent of the testes during fetal development (Lanciotti *et al.*, 2019; delli Muti *et al.*, 2014, Tirabassi *et al.*, 2014).

Reduced CAG repeat lengths are recognized to enhance the transcriptional activity of the androgen receptor, perhaps causing disruptions in the hormonal control of testicular descent. This disturbance may lead to the inability of the testes to descend correctly, thereby raising the likelihood of developing cryptorchidism. The results of this study are consistent with prior research that suggests that differences in the length of the CAG repeat may have a major effect on the functioning of the androgen receptor and, as a result, the development of male reproductive organs (Nenonen *et al.*, 2009).

Similarly, the meta-analysis showed a strong connection between GGN repeat lengths and cryptorchidism, with a weighted mean difference (WMD) of 0.90 [95% confidence interval (CI): 0.65-1.15; P < 0.00001]. The analysis revealed a high level of heterogeneity (I^2 = 89%), indicating significant variation across the research included. This variation may be due to variations in the populations and methodology used in the investigations.

The function of GGN repeats in the AR gene is not as well known as that of CAG repeats. Prior research has shown that differences in the lengths of GGN repeats may impact the functioning of the androgen receptor and have a role in sexual development abnormalities, such as cryptorchidism (Bogaert *et al.*, 2009; Rodriguez *et al.*, 2024). The strong correlation shown in this meta-analysis provides evidence to support the theory that GGN repeat polymorphisms contribute to the development of cryptorchidism.

The results of this meta-analysis highlight the significance of genetic variables in the development of cryptorchidism. Gaining insight into the function of AR gene polymorphisms in the progression of this disorder might have substantial consequences for both the

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identification and management of the disease. Performing genetic screening to determine the lengths of CAG and GGN repeats in the AR gene may aid in the identification of people with an increased susceptibility to cryptorchidism. This can enable early intervention and treatment of the condition.

Future research should prioritize investigating the specific mechanisms via which these genetic variations impact the functioning of the androgen receptor and the descent of the testicles. Further research is required to validate these results and investigate the possible interplay between genetic and environmental elements in the onset of cryptorchidism. This necessitates conducting longitudinal studies and larger-scale trials involving many centers.

There are many constraints associated with this meta-analysis. The significant heterogeneity revealed in the analysis of GGN repeats suggests that there is variation across the research included, which may impact the reliability of the findings. In addition, the sample sizes of several studies included in the analysis were quite small, which might possibly restrict the applicability of the results. Notwithstanding these constraints, the overall findings provide useful understanding of the genetic foundations of cryptorchidism.

CONCLUSION

To summarize, our meta-analysis establishes a clear link between CAG and GGN repeat polymorphisms in the AR gene and the likelihood of developing cryptorchidism. The findings highlight the potential genetic basis of cryptorchidism and underscore the need for further research to fully understand the mechanisms involved. Early identification and intervention for individuals with these genetic risk factors could improve outcomes for those affected by this common congenital anomaly.

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