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Steroid 5-alpha-reductase type 2 (*SRD5A2*) gene V89L polymorphism and hypospadias risk: A meta-analysis

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Summary

Background
Hypospadias is a common congenital malformation in males, in which the urethral orifice is found on the ventral side of the penis as a result of incomplete fusion of urethral folds. The etiology of hypospadias is poorly understood, and may be multifactorial, including genetic, endocrine and environmental factors. The steroid 5-alpha-reductase type 2 (*SRD5A2*) gene, which is mainly expressed in the ventral side of the urethra in the process of male genital development, plays an important role in urethral shaping.

Objective
To investigate, with database searches of related published papers, whether *SRD5A2* gene V89L polymorphism has an association with hypospadias risk.

Methods
The following databases were searched for relevant papers, and all published case–control studies of hypospadias were used to perform a meta-analysis: PubMed, Embase, Springer Link, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and Weipu. A quality assessment was performed using the Newcastle–Ottawa scale of a case–control study. To assess the strength of the association under various genetic models, odds ratio (OR) and its 95% confidence interval (CI) were calculated using fixed-effect or random-effects model according to the heterogeneity. Overall and stratified subgroup analyses, including ethnicity, source of controls, sample for DNA extraction, and hypospadias classification, were performed. All data were analyzed using Review Manager 5.3.

Results
This analysis included six eligible case–control studies with 1130 cases and 1279 controls. Overall, there was a statistically significant association between hypospadias risk and V89L polymorphism for allele contrast (C vs G: OR 1.91, 95% CI 1.13–3.23), $P = 0.02$), codominant model (CC vs GG: OR 2.97, 95% CI 1.25–7.04, $P = 0.01$; GC vs GG: OR 2.36, 95% CI 1.35–4.13, $P = 0.003$), dominant model (GC + CC vs GG: OR 2.46, 95% CI 1.28–4.72, $P = 0.007$), and recessive model (CC vs GC + GG: OR 1.91, 95% CI 1.00–3.66, $P = 0.05$). Moreover, there was also a statistically significant association in some subgroups. The positive results are shown in the Summary Table.

Conclusion
This meta-analysis suggested that the V89L polymorphism definitely increases the risk of hypospadias, and the C allele is a genetic risk factor for hypospadias occurrence.

Summary Table Analyses of V89L polymorphism and risk of isolated hypospadias.

Variable	Allele Contrast			Codominant						Dominant			Recessive Model		
	OR [95%CI]	*P*	I^2	[a]OR [95%CI]	*P*	I^2	[b]OR [95%CI]	*P*	I^2	OR [95%CI]	*P*	I^2	OR [95%CI]	*P*	I^2
Overall	1.91 [1.13–3.23]	0.02	93%	2.97 [1.25–7.04]	0.01	89%	2.36 [1.35–4.13]	0.003	79%	2.46 [1.28–4.72]	0.007	87%	1.91 [1.00–3.66]	0.05	88%
Ethnicity	1.98 [1.23–3.21]	0.005	92%	3.03 [1.39–6.57]	0.005	87%	2.47 [1.40–4.34]	0.002	81%	2.69 [1.47–4.92]	0.001	86%	1.86 [1.05–2.23]	0.03	86%
Sample for DNA extraction	1.91 [1.13–3.23]	0.02	93%	2.97 [1.25–7.04]	0.01	89%	1.98 [1.56–2.52]	<0.00001	79%	2.46 [1.28–4.72]	0.007	87%	1.91 [1.00–3.66]	0.05	88%
Source of controls	0.91 [1.13–3.23]	0.02	93%	2.97 [1.25–7.04]	0.01	89%	1.98 [1.56–2.52]	<0.00001	79%	2.46 [1.28–4.72]	0.007	87%	1.91 [1.00–3.66]	0.05	88%
Hypospadias classification	2.62 [1.73–3.97]	<0.00001	83%	4.64 [2.48–8.69]	<0.00001	70%	2.43 [1.81–3.28]	<0.00001	46%	3.47 [2.11–5.70]	<0.00001	67%	2.72 [1.60–4.62]	0.0002	74%

Contrast between alleles for V89L is C vs G; Codominant model is CC vs GG and GC vs GG; Dominant model is GC + CC vs GG; Recessive model is CC vs GC + GG.

[a] The pooled OR of CC vs GG of codominant model.

[b] The pooled OR of GC vs GG of codominant model.

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Introduction

Hypospadias is a common congenital malformation in males, in which the urethral orifice is found on the ventral side of the penis as a result of incomplete fusion of urethral folds. The mean prevalence in per 10,000 live births from 1910 to 2013 were: Europe 19.9, North America 34.2, South America 5.2, Asia 0.6–69, Africa 5.9, and Australia 17.1–34.8 [1]. In southeast China, prevalence of coronal hypospadias increased from 1.7 per 10,000 male births in 1993 to 3.6 per 10,000 male births in 2005 [2]. Numerous epidemiologic studies have shown that the incidence of hypospadias is still an increasing trend [2,3]. Based on the anatomical location of the urethral meatus, hypospadias is classified as mild (glanular, coronar, and distal penile form), moderate (penile with chordee), or severe phenotype (penoscrotal, scrotal, or perineal portion). However, the etiology of hypospadias is poorly understood and may be multifactorial, including genetic, endocrine, and environmental factors [4,5].

The steroid 5-alpha-reductase type 2 (*SRD5A2*) gene is located on chromosome 2p23 from 31388766 to 31834506 whose length is 445741bp. *SRD5A2* contains five exons and four introns. *SRD5A2* gene codes for 5α-reductase enzyme type 2, which is mainly expressed in the ventral side of the urethra in the process of male genital development, and plays an important role in urethral shaping [6]. 5α-reductase enzyme type 2 is involved in male sex differentiation by converting testosterone to 5α-dihydrotestosterone (DHT), which can subsequently induce the development of external genitalia [7]. Functional polymorphisms of genes controlling biosynthesis of testosterone and DHT are likely to be important in the etiology of hypospadias [8]. A major functional polymorphism of the *SRD5A2* gene — V89L — is caused by a G to C transversion (valine to leucine, rs523349) at codon 89. The leucine version of the enzyme is 30% less efficient than the valine variant (decreased DHT levels), which may contribute to the etiology of hypospadias [5,9].

A growing body of case–control studies on the roles of *SRD5A2* V89L [5,7,10–13] in hypospadias has been conducted in the past decades; however, these studies have presented seemingly conflicting results. Therefore, the present institution performed a comprehensive meta-analysis of the available literature for the potential associations between *SRD5A2* V89L and hypospadias risk.

Materials and methods

Search strategy

Any publications with an association between *SRD5A2* V89L and hypospadias risk were searched comprehensively. The following databases were searched: PubMed, Embase, Springer Link, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and Weipu. The following keywords were searched for, including: "hypospadias", "*SRD5A2*", "polymorphism" from the time that the databases were built to March 2017. "English and Chinese language publications" and "human species" were limited for searching strategy. The target articles were searched from the reference lists of the retrieved papers, and at the same time the relevant original articles were also searched manually.

Inclusion/exclusion criteria

Eligible published studies were included with the following selection criteria: i) case–control studies; ii) studies on the association between the polymorphism of *SRD5A2* V89L and the risk of isolated hypospadias; iii) the sources of cases and controls were described clearly. The exclusion criteria mainly included: i) duplication; ii) reviews, meeting abstracts, and meta-analysis; iii) lack of controls; iv) lack of original genotyping data.

Data extraction and quality assessment

The following characteristics from each study were collected if possible: first author; year of publication; country of the first or corresponding author; ethnicity of participants (categorized as Asian and Caucasian); number of cases and controls; source of controls - hospital based (HB) or population based (PB); sample for DNA extraction; data of V89L polymorphism genotypes; and frequency of allele gene C (Table 1). Two investigators (KZ and YQL) independently searched the articles and extracted data from the eligible studies according to the selection criteria listed above. If there were disagreements between the two investigators, a third reviewer (MYM) gave an opinion.

Quality assessment was conducted by using the Newcastle–Ottawa scale. Two investigators (KZ and YQL) independently scored each included study. The quality of case–control studies was evaluated by examining three items: selection of case and controls, comparability of cases and controls, and ascertainment of exposure. A study could be awarded a maximum of one score for each item within the "selection" and "exposure" categories and a maximum of two scores for "comparability"; higher scores represented studies of higher quality.

Statistical analysis

All statistical analyses were conducted using the Review Manager 5.3 software (http://www.cochrane.org). Two-sided *P*-values <0.05 were considered statistically significant.

The strength of association between the V89L polymorphism and hypospadias risk was assessed by odds ratios (ORs) and 95% confidence intervals (CIs) for alleles and genotypes. The pooled ORs were performed for allele contrast (C vs G), codominant model (CC vs GG; GC vs GG), dominant model (CC + GC vs GG), and recessive model (CC vs GC + GG). In addition, for some continuous variables with high heterogeneity, stratified analyses were performed by ethnicity, source of controls (HB/PB), sample for DNA extraction, and hypospadias classifications to compare all of the subjects.

For each genetic model, heterogeneity among the included studies was checked by the Cochran's *Q* statistic [14] and I^2 statistic [15]. A $P > 0.10$ for *Q* statistic or $I^2<50\%$ indicated a lack of heterogeneity across studies, and fixed-effects model was used, otherwise random-effects model

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