RESEARCH

SRD5A2 gene polymorphism and the risk of benign prostatic hyperplasia: a meta-analysis

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ABSTRACT

The aim of this study was to undertake a pooled data analysis for assessment of the impact of *SRD5A2* polymorphisms on the risk of BPH. Literature search was performed to identify the studies that had analyzed *SRD5A2* polymorphisms in association with the risk of BPH. To pool data from published case-control studies, we undertook meta-analyses on V89L polymorphism (1116 patients and 1447 controls from five studies) and $(TA)_n$ polymorphism (548 patients and 276 controls from two studies). Moderate value of I2 for between studies genotype comparison (P heterogeneity = 0.204, Q = 7.232, df (Q) = 5, I^2 = 30.867) showed the presence of low level of true heterogeneity. The meta-analysis on V89L polymorphism using either of two analysis models suggested that there is no association of this substitution with BPH risk (fixed effect model: OR=1.119 (CI = 0.95-1.31), p-value = 0.168; random effects model: OR=1.118 (CI = 0.87-1.44), p-value = 0.389). Nevertheless, the frequency of VV was higher in the cases. Similarly, $(TA)_n$ repeats distribution showed no significant difference between cases and controls. Meta-analysis using either of the two analysis models suggested that there is no association of $(TA)_n$ repeat length with BPH risk (fixed effect model: OR=1.062 (CI = 0.73-1.54), p-value= 0.751; random effect model: OR=1.062 (CI = 0.73-1.54), p-value= 0.751). In conclusion, V89L and $(TA)_n$ repeat polymorphisms in the *SRD5A2* gene do not significantly affect the risk of BPH.

KEYWORDS: 5α-reductase type 2, benign prostatic hyperplasia, genetic polymorphism, prostate cancer, SRD5A2

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INTRODUCTION

Benign prostatic hyperplasia (BPH), a common disease of men above 50 years of age (Boyle et al., 1996), is characterized histologically by hyperplasia and hypertrophy of the prostatic cells and clinically by prostatic enlargement and lower urinary tract symptoms (LUTS). The evidence of BPH is found in 50 % of males by the age 50 and in 90 % of males by the age of 80 (Berry et al., 1984). Testosterone, a primary androgen in males, is converted into its most active form, dihydrotestosterone (DHT), by 5α-reductase type 2 (encoded by the *SRD5A2* gene) enzyme in the prostate (Wilson et al., 1993). DHT has five times higher binding affinity than testosterone for androgen receptor (Wilbert et al., 1993); the receptor-ligand complex thus formed translocates to the nucleus to trans-activate the target genes (Stanford et al. 1997; Feigelson et al.,1996). DHT is necessary for prostatic growth and development of male external genitalia. Two isoforms of 5α-reductase (Type I and II) have been reported. Type I is expressed in liver, skin, and scalp and is encoded by the SRD5A1 gene located on chromosome 5 (Suzuki et al., 2001) while the type II enzyme is encoded by the *SRD5A2* gene, which is mainly expressed in the skin and the prostate (Andersson et al., 1990). The gene encoding the type II enzyme is located on chromosome 2 (Locus 2p23) and has five exons and four introns (Thigpen et al., 1992).

The mutations/deficiencies in the *SRD5A2* gene are associated with male pseudohermaphroditism; adult males with this condition have a vestigial prostate and do not develop BPH (Wilson et al., 1993; Thigpen et al., 1992; Imperato-McGinley et al., 1979). 5α-reductase activity (conversion of testosterone to DHT) varies in different ethnic populations, and polymorphisms in the *SRD5A2* gene have been identified to affect enzyme activity (Makridakis et al., 1997; Reichardt et al., 1995; Ross et al., 1992; Makridakis et al., 1999). It is reported that higher SRD5A2 activity is found in Blacks than Asians, which parallels observed ethnic differences in the PCa risk. A49T substitution is absent in most of the populations; therefore, it was not considered for meta-analysis (Rajender et al., 2009). V89L substitution (a missense substitution of leucine for valine at codon 89 due to a G to C transversion, rs523349) results in about 30% reduction in enzyme activity both in vitro and in vivo Makridakis et al., 1997). Another polymorphism, a $(TA)_n$ dinucleotide repeat, in the 3′ UTR also affects 5α-reductase activity. Three alleles, $(TA)_0$, $(TA)_9$ and $(TA)_{18}$, are most commonly seen with frequency variation with ethnic changes; however, exact effect of this repeat on 5α-reductase activity has not been worked out.

Genetic epidemiological studies have shown large variations in the frequency of V89L, and $(TA)_n$ repeat polymorphisms and in their association with BPH/PCa risk. Meta-analysis and literature review have shown no correlation of *SRD5A2* gene polymorphisms with PCa risk, but a pooled analysis on *SRD5A2* polymorphisms in BPH has not been undertaken. Therefore, we have undertaken the present study to conduct a meta-analysis to generate a pooled estimate about the effect of *SRD5A2* polymorphisms on the risk of BPH.

MATERIALS AND METHODS

Selection of Published studies

We considered all the studies that examined V89L and $(TA)_n$ repeat polymorphisms in BPH. A computer based search in the PubMed, EMBASE, and Google Scholar databases using the following keywords: "Benign Prostatic Hyperplasia", "BPH", "Steroid 5α-reductase", "SRD5A2", "V89L", "TA repeats", "polymorphism", "Variants", and "Mutation" in different combinations was conducted to identify relevant studies. A49T was not considered for meta-analysis due to absence of polymorphism at this site in most of the populations.

Inclusion and Exclusion Criteria

The inclusion criteria for meta-analysis were; (a) independent case control studies that investigated the association of V89L and $(TA)_n$ repeats polymorphisms with the risk of BPH, (b) the purpose of all the studies and statistical methods were similar, (c) studies presented original data for calculation of odd ratio (ORs) with corresponding 95% confidence interval (95% CIs), and (d) inclusion/exclusion was done according to the standard diagnosis parameters for BPH. The exclusion criteria included: a) studies not providing enough information (raw data), and b) those not well described. Detailed information like first author, year of publication, ethnicity of population, and genotype data were gathered from the selected studies

Statistical analysis

Meta-analysis was performed using the Comprehensive Meta Analysis software (version 2). The association analysis was performed for V89L and (TA)n repeats polymorphisms in BPH against healthy controls for differences in the distribution of VV vs VL+LL genotypes at V89L locus and $(TA)_0/(TA)_0$ vs $(TA)_0/(TA)_9$ + $(TA)_9/(TA)_9$ genotypes at (TA)n repeat locus. Odds ratio and confidence interval were chosen as effect size for meta-analysis. Chi square based 'Q' test and I^2 index proposed by Higgins and Thompson were used to test for the presence of true heterogeneity (Higgins et al., 2002). A significance level of $P<0.10$ instead of traditional $P<0.05$ was used because of low power of this test and to avoid type II errors in statistical test for heterogeneity (Petitti et al., 2001). Meta-analysis was performed adopting both fixed and random effects models. Publication bias was investigated by looking at symmetry in the funnel plot and statistically by Egger's regression test of significance. Statistical tests such as fail safe N (Classic and Orwin) or Duvall and Tweedie trim and fill procedure were also performed to quantify the publication bias.

RESULTS

Pooled analysis of V89L data

Literature search retrieved a total of nine studies (Rajender et al., 2009; Li et al.,2003; Klotsman et al.,2004; Salam et al., 2005; Roberts et al.,2005; Das et al.,2008;Tong et al.,2010; Izmirli et al.,2011; Gu et al., 2013). Four studies were excluded because three studies had no relevant data for meta-analysis (Klotsman et al.,2004; Roberts et al.,2005; Tong et al.,2010) and another study was based on a very small sample size (cases=39 and controls=34). Thus, only five studies (Rajender et al., 2009; Li et al.,2003; Salam et al., 2005; Das et al., 2008; Gu et al., 2013) were found to be suitable for inclusion in meta-analysis. Two data-sets corresponding to the two populations (Hispanic and Caucasian) in the study (Salam et al., 2005) were included as separate groups in meta-analysis (Table 1). Hence, we included a total of 1116 patients and 1447 healthy controls from five studies (six data-sets).

Moderate value of I^2 for between studies genotype comparison (P heterogeneity = 0.204, Q = 7.232, df (Q) = 5, I^2 = 30.867) showed the presence of low amount of true heterogeneity. The meta-analysis on V89L polymorphism using either of two analysis models suggested that there is no association of this substitution with BPH risk (fixed effect model: OR=1.119 (CI = 0.95-1.31), p-value = 0.168; random effect model: OR=1.118 (CI = 0.87-1.44), p-value = 0.389) (Figure 1A). Nevertheless, the frequency of VV was higher in the cases. Funnel plot and Egger's regression test were used for quantification of publication bias. A symmetrical distribution of the studies on the funnel plot suggested the absence of publication bias in quantitative assessment of the pooled data (Figure 1B). The absence of publication bias was confirmed by Egger's regression intercept test (t-value = 0.228, Intercept = -0.218, SE = 0.957 and p = 0.830).

Table 1: Data extracted on V89L polymorphism in *SRD5A2* gene on BPH risk

Study	Population	Cases (%)			Controls (%)		
		Total	VV	VL+LL	Total	VV	VL+LL
Li et al., 2003	Japanese	228	64 (28.07)	164 (71.93)	243	75 (30.86)	168 (69.14)
Salam et al., 2005a	Hispanic	264	111 (42.05)	153 (57.95)	44	25 (56.82)	19 (43.18)
Salam et al., 2005b	Caucasian	62	36 (58.06)	26 (41.94)	28	10 (35.71)	18 (64.26)
Das et al., 2008	Caucasian	96	21 (21.88)	75 (78.13)	28	8 (28.57)	20 (71.43)
Rajender et al., 2009	Indian	40	12 (30)	28 (70)	96	29 (30.21)	67 (69.79)
Gu X et al., 2013*	Chinese	426	NA	NA	1008	NA	NA
Total		1116	-	-	1447	-	-

Table 2: Data extracted on $(TA)_n$ repeat length in *SRD5A2* gene on BPH risk

Study	Population	Cases (%)			Controls (%)		
		Total	$(TA)_0/(TA)_0$	$(TA)_0/(TA)_9/(TA)_9/(TA)_9$	Total	$(TA)_0/(TA)_0$	$(TA)_0/(TA)_9/(TA)_9/(TA)_9$
Salam et al., 2005	USA/Mixed	378	309 (81.75)	69 (18.25)	106	85 (80.19)	21 (19.81)
Sobti et al., 2008	Indian	170	128 (75.29)	42 (24.71)	170	134 (78.82)	36 (21.18)
Total		548	437 (79.74)	111 (20.26)	276	219 (79.35)	57 (20.65)

Pooled analysis of $(TA)_n$ data on BPH

Literature search retrieved three studies (Rajender et al., 2009; Salam et al., 2005; Sobti et al., 2008), out of which only two (Salam et al., 2005; Sobti et al., 2001) had analyzed $(TA)_n$ repeat polymorphism in relation to BPH (Table 2). Hence, we pooled data for a total of 548 patients and 276 healthy controls. Zero I^2 value for between studies genotype comparison (P heterogeneity = 0.428, Q = 0.630 df (Q) = 1, I^2 = 0.0) showed the absence of true heterogeneity. Meta-analysis using either of the two analysis models suggested that there is no association of $(TA)_n$ repeat length with BPH risk (fixed effect model: OR=1.062 (CI = 0.73-1.54), p value= 0.751; random effect model: OR=1.062 (CI = 0.73-1.54), p-value= 0.751) (Figure 2). Low number of studies (only two studies) was available to calculate the publication bias.

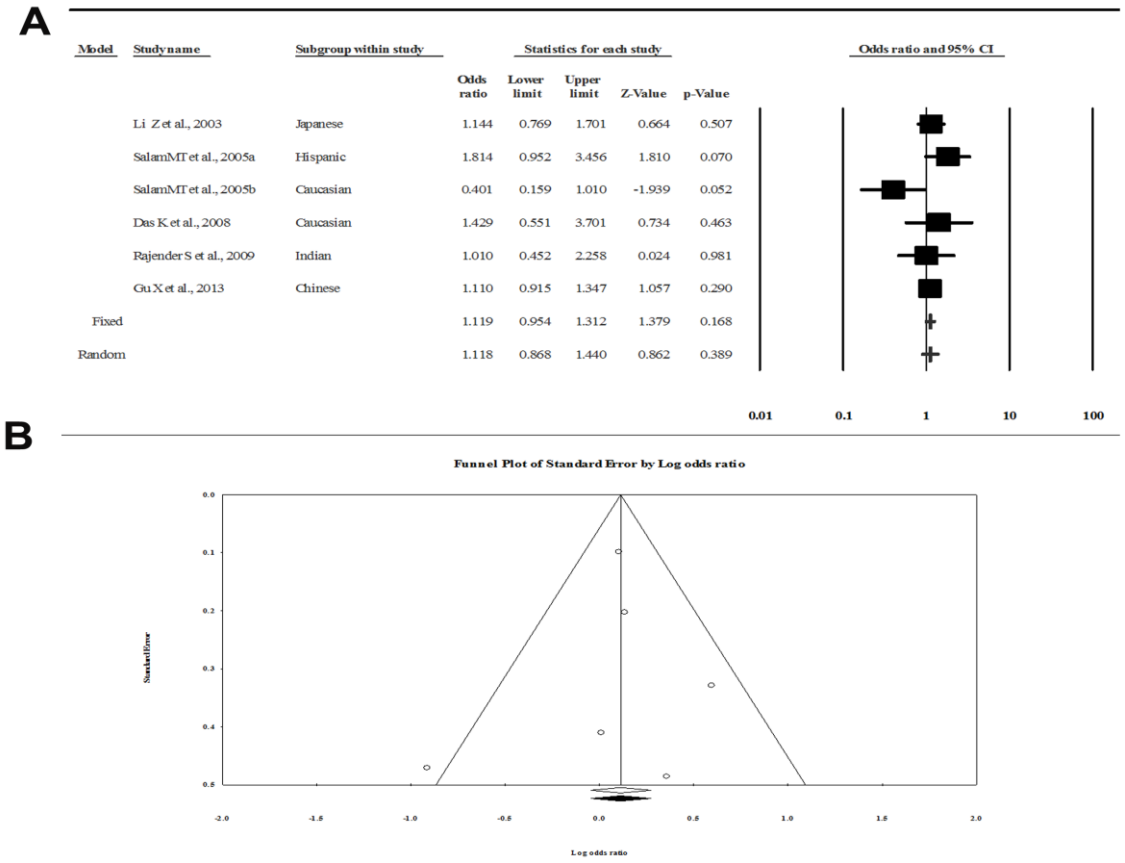

Figure 1. Meta-analysis on V89L polymorphism in *SRD5A2* gene with BPH risk; A: Forest plot showing the pooled estimates of studies, B: Funnel plot for test of publication bias across the studies.

DISCUSSION

We found V89L site to be highly polymorphic in most of the populations (Table 1). This substitution may have a protective effect against prostate problems, perhaps due to lower activity of the enzyme with 'L' variant (Allen et al.,2011). A cohort study has shown that the presence of 'LL' confers lowest 5α-reductase activity in PCa patients in an Asian population (Makridakis et al.,1997). An in vivo study has shown that V89L substitution reduced 5α-reductase enzyme activity by 39% in Asians (Makridakis et al., 1997), and by 10% in Caucasians (Makridakis et al., 1997; Allen et al., 2011). A previous meta-analysis on V89L data from thirty-three studies found no difference in genotype distribution between PCa cases and control samples (Li et al.,2011). Similarly, a review of twenty-four case-control studies showed no association of V89L polymorphism with PCa risk (Li et al., 2010). In the present study, we found that V89L substitution does not significantly correlate with BPH.

It has been reported that Caucasians have longer $(TA)_n$ repeats, which is associated with decreased transcription of the 5α- reductase, resulting in decreased 5α- reductase enzyme activity. Longer $(TA)_n$ repeats also decreased DHT level, decreasing PSA production in PCa. In our meta-analysis, pooled analysis showed no correlation of $(TA)_n$ polymorphism with BPH. At least ten alleles of $(TA)_n$ repeats, 0, 8, 9 10, 17, 18, 19, 20, 21, and 22, have been reported till date[12], but only three

$(TA)_0$, $(TA)_9$, and $(TA)_{18}$ of them are common; $(TA)_0$ being the most common in most of the populations, while $(TA)_{18}$ is rare. The pooled (meta) analysis also showed higher frequency of smaller $(TA)_n$ repeats in cases and controls; however, the difference was not statistically significant.

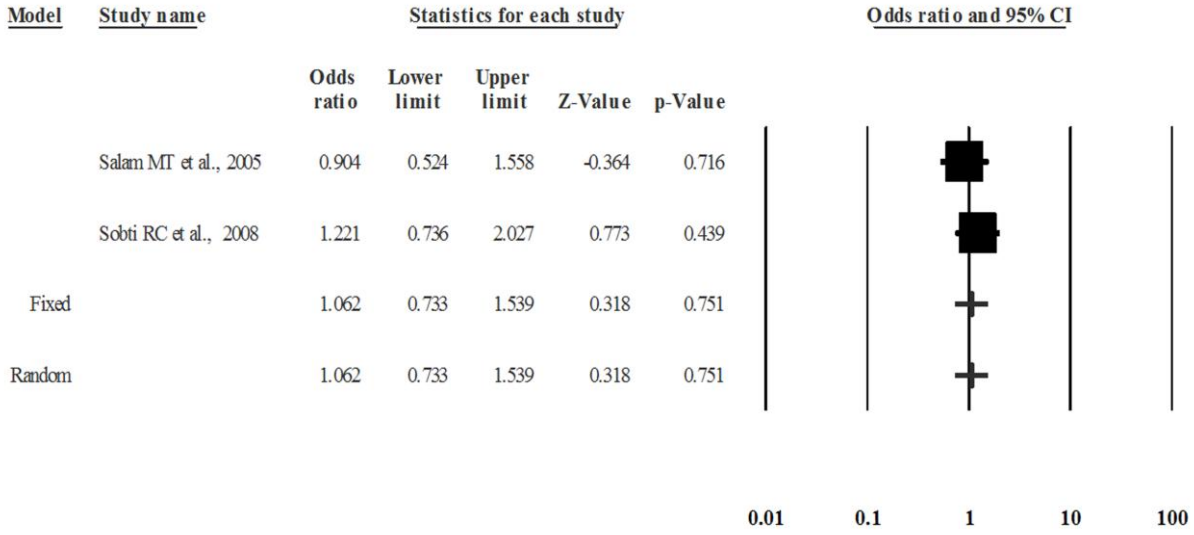

Figure 2: Meta-analysis on (TA)n repeat length in *SRD5A2* gene with BPH risk: Forest plot showing the pooled estimates of studies.

In conclusion, meta-analysis showed higher frequency of V89L substitution and shorter $(TA)_n$ repeats in the BPH cases, but without statistical significance. Therefore, *SRD5A2* polymorphisms do not appear to affect the risk of BPH. We admit the limitation that the meta-analysis included a small number of studies; therefore, inclusion of more studies in the meta-analysis in due course of time would help strengthen the conclusions. Studies on ethnically divergent populations are encouraged to unveil ethnic specific differences in the association between *SRD5A2* polymorphisms and BPH.

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Conflict of interest statement

The authors have declared that no competing or conflict of interests exists. The funders had no role in study design, writing of the manuscript and decision to publish.

Authors' contributions

VKC, SKB collected data and conducted analysis. SNS and SR conceived the idea, designed the study and supervised the project.

Declaration of originality

The author declares that he has not copied text, figure or data from a particular source without appropriately citing it.

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