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Systematic Review and Meta-analysis of Candidate Gene Association Studies of Lower Urinary Tract Symptoms in Men

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Abstract

Context: Although family studies have shown that male lower urinary tract symptoms (LUTS) are highly heritable, no systematic review exists of genetic polymorphisms tested for association with LUTS.
Objective: To systematically review and meta-analyze studies assessing candidate polymorphisms/genes tested for an association with LUTS, and to assess the strength, consistency, and potential for bias among pooled associations.
Evidence acquisition: A systematic search of the PubMed and HuGE databases as well as abstracts of major urologic meetings was performed through to January 2013. Case-control studies reporting genetic associations in men with LUTS were included. Reviewers independently and in duplicate screened titles, abstracts, and full texts to determine eligibility, abstracted data, and assessed the credibility of pooled associations according to the interim Venice criteria. Authors were contacted for clarifications if needed. Meta-analyses were performed for variants assessed in more than two studies.
Evidence synthesis: We identified 74 eligible studies containing data on 70 different genes. A total of 35 meta-analyses were performed with statistical significance in five (*ACE, ELAC2, GSTM1, TERT*, and *VDR*). The heterogeneity was high in three of these meta-analyses. The rs731236 variant of the vitamin D receptor had a protective effect for LUTS (odds ratio: 0.64; 95% confidence interval, 0.49–0.83) with moderate heterogeneity

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(I^2 = 27.2%). No evidence for publication bias was identified. Limitations include wide-ranging phenotype definitions for LUTS and limited power in most meta-analyses to detect smaller effect sizes.
Conclusions: Few putative genetic risk variants have been reliably replicated across populations. We found consistent evidence of a reduced risk of LUTS associated with the common rs731236 variant of the vitamin D receptor gene in our meta-analyses.
Patient summary: Combining the results from all previous studies of genetic variants that may cause urinary symptoms in men, we found significant variants in five genes. Only one, a variant of the vitamin D receptor, was consistently protective across different populations.

1. Introduction

Lower urinary tract symptoms (LUTS) in men are categorized into storage symptoms (increased daytime urinary frequency, nocturia, urgency, and incontinence), voiding symptoms (slow stream, splitting or spraying, intermittent stream, hesitancy, straining, and terminal dribble), and postmicturition symptoms (feeling of incomplete emptying and postmicturition dribble) [1,2]. LUTS are highly prevalent and often bothersome. They are strongly associated with both age and obesity [3–5], which is therefore likely to increase future associated costs and burden.

Particularly when considering older men, a variety of terms have been used historically to describe LUTS including symptomatic benign prostatic hyperplasia (BPH), symptomatic benign prostatic enlargement (BPE), or symptomatic bladder outlet obstruction [6]. However, only a minority of men with histologic evidence of BPH develop significant bothersome LUTS, and among men presenting with LUTS, only a minority have obstruction [6]. With increasing focus on medical therapies targeting either the bladder or prostate [7], the non–organ-specific term LUTS has therefore been recommended, emphasizing the multiple potential etiologies for these symptoms.

There is substantial evidence of familial aggregation of male LUTS. Early reports identified very large excess risks for the surgical treatment of LUTS among men with so-called familial BPH [8]. However, subsequent work has suggested more modest familial risks for the symptoms themselves [9,10]. In the Olmsted County study, having either a father or a brother with a history of diagnosed BPE was associated with an odds ratio (OR) of 1.5 (95% confidence interval [CI], 1.1–1.7) for moderate to severe LUTS at baseline [9]. In the Krimpen study, reporting any first- or second-degree relative with a diagnosis of prostate cancer was associated with a hazard ratio of 1.7 (95% CI, 1.1–2.5) for incident LUTS over a median of 6.5 yr of follow-up [10]. Such risks seem to be cumulative, with two or more affected relatives conferring greater risk [11].

Twin studies provide estimates of heritability that are less confounded by environmental or lifestyle factors that may be shared within families. In a study of 256 twin pairs enrolled in the US military, heritability was estimated at 49% using a case definition corresponding to diagnosis and/or treatment for BPH [12]. In a population-based study of 83 twin pairs, the heritability of the American Urological Association Symptom Index (AUA-SI) was estimated at 39% overall, but with a higher heritability of 83% for men >50 yr of age [13]. In a further population-based study of 3446 elderly male twins, heritability of moderate to severe LUTS (again assessed using the AUA-SI) was estimated at 72% [14]. Taken together, these twin studies suggest similar heritability as for many complex diseases for which the genetic architecture is well understood, including prostate cancer, where heritability has been estimated at between 42% [15] and 58% [16].

Many of the studies available for this review aimed primarily to explore the molecular genetics of prostate cancer rather than LUTS, but they included men with and without LUTS as separate subgroups of controls. It remains unclear whether LUTS or BPH might be risk factors for prostate cancer. There is conflicting data regarding any association of a diagnosis of LUTS/BPH with a subsequent diagnosis of prostate cancer [17–20]. Evidence of a consequent increase in high-risk cancers or prostate cancer mortality is also mixed. Those studies that have suggested a positive association may be unable to exclude detection bias and unmeasured confounding from shared environmental or genetic risk factors.

With pharmaceutical options for the prevention of prostate cancer and LUTS [21], and an expanding array of conservative options for managing LUTS, clinical risk stratification may become more relevant than ever. Robustly replicated genetic variants associated with LUTS would provide useful information in assessing both prognosis and potentially treatment response. Equally importantly, new insights into the molecular genetics of LUTS could help explain the underlying pathogenesis and also offer future routes toward new drug targets.

The aim of this systematic review was to assess which candidate polymorphisms and/or candidate genes had been tested for an association with LUTS in men, and to assess the strength, consistency, and potential for bias among pooled associations.

2. Evidence acquisition

2.1. Eligibility criteria

The review protocol was prospectively registered (PROSPERO 2011: CRD42012001985). We prespecified inclusion of both case-control and cross-sectional designs, with both population-based samples and other sampling methods. We included association studies testing for any genetic

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