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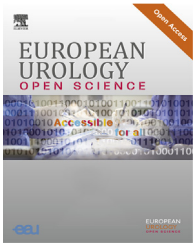

Review – Benign Prostatic Hyperplasia

Genetic Predisposition to Benign Prostatic Hyperplasia: Where Do We Stand?

Martin Hennenberg *, *Sheng Hu, Alexander Tamalunas, Christian G. Stief*

Department of Urology, LMU University Hospital, LMU Munich, Munich, Germany

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Abstract

Background and objective: Genetic predisposition is a factor in 40–70% of cases of benign prostatic hyperplasia (BPH) and voiding symptoms. However, informal reviews summarizing genes and variants imparting genetic disposition to BPH are not yet available.
Methods: We conducted an informal narrative review of genes and variants associated with BPH or voiding symptoms in candidate gene studies, genome-wide association studies (GWAS), and Mendelian randomization studies. A literature search of PubMed was performed using the terms "BPH heritability", "LUTS heritability", "BPH risk variant", "LUTS genetic risk", "GWAS BPH", and "genome-wide BPH".
Key findings and limitations: Candidate gene studies focused on variants related to the vitamin D receptor, steroid metabolism, detoxification, inflammation, cytokines, and growth factors, which were previously found to be associated with prostate cancer. Despite overall limited conclusiveness of candidate gene approaches, some recent studies point to population-dependent contributions of single variants to genetic BPH predisposition. Four GWAS and two Mendelian randomization studies for BPH identified correlation of BPH and voiding symptoms with variants related to testosterone, prostate-specific antigen, progesterone, transcription factors, the cell cycle, neuronal organization, and thyroid-stimulating hormone.
Conclusions and clinical implications: The drug targetability of most of the genes identified in the BPH setting is precluded by predictable unbalanced side effects, low efficacy, unknown organ specificity, and a lack of characterization in the prostate. Meta-analyses of GWAS are not yet available for BPH. Unless calculated using quantitative approaches, specific contributions of the risk variants identified to the overall risk of BPH remain uncertain.
Patient summary: While age is a risk factor for benign enlargement of the prostate in all affected patients, genetic factors may be involved in 39–72% of patients. Research has identified a number of possible risk genes, but is still at a very early stage. It is unlikely that drugs could be used to target these genes because of expected side effects that would be tolerated for cancer treatment, but not for benign diseases, or low efficacy in previous clinical trials.

* Corresponding author. Urologische Klinik und Poliklinik, Marchioninistrasse 15, 81377 München, Germany. Tel. +49 89 440074868.
E-mail address: martin.hennenberg@med.uni-muenchen.de (M. Hennenberg).

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1. Introduction

According to family and twin studies, heritability can explain benign prostatic hyperplasia (BPH) and voiding symptoms in 39–72% of affected patients [1,2]. This proportion decreases with the age of the study population, as age is the most important nongenetic risk factor for BPH [3]. Rather than simply causing BPH or symptoms, genetic predisposition appears to account for earlier BPH onset, including a larger prostate volume (PV) among younger patients. A number of candidate gene studies in BPH addressed variants previously identified in prostate cancer (PCa). Though investigation of preselected variants does not allow identification of key genes, recent candidate gene studies pointed to population-dependent contributions of single variants to genetic BPH. Four genome-wide association studies (GWAS) and two Mendelian randomization studies for BPH have been conducted, but no meta-analyses are yet available.

2. Candidate gene studies

Most candidate gene studies in BPH addressed variants related to the vitamin D receptor (VDR), steroid metabolism, inflammatory responses, and cytokine activity (Table 1). The first meta-analysis of candidate gene studies summarized 74 studies, including 70 genes examined in BPH (Table 1) [4]. Quantitative synthesis was possible for 35 variants related to 24 genes, with five variants meeting the statistical significance level. The epidemiological credibility was highest, albeit moderate, for a VDR variant protective against lower urinary tract symptoms (LUTS). The epidemiological credibility was rated as weak for the four other variants, related to angiotensin-converting enzyme (ACE, protective against LUTS and BPH surgery), ELA2 (PCa risk gene, symptomatic BPH), GSTM1 (carcinogen detoxification) and TERT (apoptosis-delaying telomerase, LUTS). Subsequent original studies and four further meta-analyses confirmed correlations for further VDR variants and for polymorphisms related to ACE, steroid metabolism, 5α-reductase, growth factors, the androgen receptor, and prostate-specific antigen (PSA) with histologically confirmed BPH, voiding symptoms, or a need for surgery (Table 1) [5–8]. Two candidate gene studies addressed the estrogen receptor and reported correlations between three ESR2 polymorphisms and voiding symptoms (International Prostate Symptom Score [IPSS] >8, maximum urinary flow rate <15 ml/s, PV >30 ml; n = 173; odds ratio [OR] 1.94–2.18), and between one ESRa variant and histologically confirmed BPH (n = 482; OR 6.3) [9,10].

3. Epidemiological approaches: GWAS and Mendelian randomization studies

Four GWAS and two Mendelian randomization studies have been performed for BPH (Table 2). The studies identified contributions of testosterone, PSA, progesterone, transcription factors, genes with purported functions in the cell cycle and neuronal organization, and thyroid-stimulating hormone (TSH) to genetic BPH predisposition. A strong correlation was found between PSA and LUTS/BPH, paralleled by identification of 23 significant variants in patients who received medical or surgical treatment for LUTS suggestive of BPH [11]. Induction of BPH by genetically elevated testosterone was been confirmed in a Mendelian randomization analysis that included 149 single-nucleotide polymorphisms [12]. Another GWAS identified significant correlations of 35 variants [13]. In a validation cohort, four of the variants were significantly associated with BPH diagnosis or treatment, including variants of the progesterone receptor, RBMS1 (RNA/DNA binding in cell cycle/death), MPPED1 (metallophosphoesterase), and NPAP1 (tissue-specific imprinting, spermatogenesis). Top hits in a GWAS based on codes for BPH diagnosis included variants in SYN3 (synaptogenesis and neurotransmission), GCLC (glutathione synthesis), UNC13A, DCC, BTBD3 (dendritic organization), and ELVOVL3 [14]. The authors estimated that genetic factors account for 60% of the phenotype variation in BPH.

Table 1 – Meta-analyses of candidate gene studies in BPH

Study	Population	Genes/SNP	Findings
Cartwright 2014 [4]	LUTS	70 genes; quantitative synthesis for 35 variants related to 24 genes	Moderate epidemiological credibility across 5 studies: VDR rs731236 is protective for LUTS (OR 0.64).Weak credibility for pooled associations: ACE rs4340 (protects against LUTS and surgery: OR 0.66), ELAC2 rs5030793 (symptomatic BPH: OR 1.75), GSTM1 null allele (LUTS: OR 2.08), TERT rs2736098 (LUTS, OR 1.25)
Zeng 2014 [7]	BPH	4 VDR polymorphisms	No association for Taq-I, Bsm-I, Apa-I, and Fok-I without stratification of the study population.
Zeng 2017 [6]	BPH	3 polymorphisms (SRD5A2 rs523349, rs9282858)	rs9282858 OR 2.51; rs523349 depends on ethnicity and allele (protective or promoting in Caucasians).
Su 2017 [5]	BPH	PSA-158G/A	OR 0.47 for Caucasians, OR 1.63 for Asians; no association overall.
Lin 2022 [12]	BPH	VDR, ACE, CYP17	Polymorphism association positive for ACE, negative for CYP17 and VDR (several variants); partly depends on ethnicity.

ACE = angiotensin-converting enzyme; BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms; OR = odds ratio; SNP = single-nucleotide polymorphism; VDR = vitamin D receptor.

Table 2 – GWAS and MR studies in BPH

Study	Population	Design	Findings
Na 2017 [15]	3 populations: CLUE II (IPSS >8, or PV >30 ml, *n* = 3103); REDUCE (treatment for LUTS/BPH, IPSS >15, *n* = 32 898); confirmation in 485 BPH cases (clinically confirmed LUTS) and 475 controls	GWAS	One GATA3 variant significant in all 3 populations (OR 1.13, 1.3, 1.55); transcription factor, cell differentiation and function
Gudmundsson 2018 [11]	20 621 patients treated for LUTS/BPH (medical or surgical) and 280 541 controls; European setting	GWAS	Strong correlation with PSA and LUTS/BPH (rg 0.77); 23 further significant variants for 14 loci: BCL11A, CLPTM1L, TERT, STARD4, H2AFY, HIST1H2BL, DNAJC1, EBLN1, FGFR2, WED11, ODF3, TBX5, TBS3, DLEU1, RNASEH2B, HNF1B, GATA5, -6, CTAGE1, THEG5; low ORs (0.85–1.12) for 21/23 variants; OR 0.67 for GATA5 variant, OR 1.27 for DNAJC1 variant.
Hellwege 2019 [14]	2656 BPH cases (codes for diagnosis) and 7763 controls	GWAS	Genetic factors account for 60% of phenotype variation in BPH. Top-hit variations in SYN3 (OR 0.69; synaptogenesis, neurotransmission), GCLC (OR 1.24; glutathione synthesis), UNC13A, DCC, BTBD3 (8 variants, dendritic organization), and ELOVL3.
Li 2021 [13]	Discovery cohort: 1942 BPH cases, 4730 controls from eMERGE; validation cohort: 5109 BPH cases, 16 1911 controls from the UK Biobank	GWAS	Of 35 significant variants (22 loci) in the discovery cohort, 4 were significant in the validation cohort: progesterone receptor (OR 1.36 in discovery cohort), RBMS1 (OR 1.29; RNA/DNA binding in cell cycle/death), MPPED1 (OR 0.72; metallophosphoesterase), and NPAP1 (OR 0.66; tissue-specific imprinting, spermatogenesis)
Lin 2023 [12]	participants from previous GWAS	MR	Genetically elevated bioavailable testosterone induces BPH
Huang 2023 [16]	289 980 participants from thyroid studies, 13 118 BPH patients (digital health care data), and 72 799 controls	MR	Genetically predicted elevated TSH and hypothyroidism reduce the risk of BPE (ORs 0.885, 0.864, 0.912 for overt hypothyroidism, subclinical hypothyroidism, TSH)

BPE = benign prostatic enlargement; BPH = benign prostatic hyperplasia; GWAS = genome-wide association studies; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MR = Mendelian randomization; OR = odds ratio; PSA = prostate-specific antigen; PV = prostate volume; rg = genetic correlation; TSH = thyroid-stimulating hormone

Na et al [15] found that a GATA3 variant (transcription factor, cell differentiation, cell function) was significantly related to voiding symptoms in three independent populations, including cohorts with IPSS >8 or PV >30 ml, treatment for LUTS/BPH and IPSS >15, and clinically confirmed LUTS. In this and other studies, clinical endpoints were often very broad in trials addressing variants associated with genetic predisposition to BPH, and varied greatly by study. It is arguable whether IPSS >8 or PV >30 ml is clinically meaningful, and the criteria "treatment for LUTS/BPH" and "clinically confirmed LUTS/BPH" cover a wide range of conditions.

A Mendelian randomization study with data from participants in thyroid studies, patients with BPH, and control participants revealed that genetically elevated TSH and hypothyroidism were associated with a lower risk of benign prostatic enlargement [16]. Although not a GWAS, an integrative approach that included sequencing arrays, profiling, and database analyses suggested mTOR as a potential therapeutic target, which was validated by decreases in PV for patients treated with mTOR inhibitors [17].

4. Translational aspects

The translational value of many of the genes identified may be limited by unbalanced side effects that might be tolerated in cancer treatment, but not in benign diseases. This may apply to variants related to transcription factors, the cell cycle, detoxification, cytokines, and growth factors. Many of the genes identified are poorly understood, so translation to clinical practice will depend on functional characterization in the prostate and on organ specificity, including genes functionally involved in neuronal organization, as well as genes with testis-specific or sperm-specific expression. For findings related to steroid metabolism, the options for innovative drugs are limited, as 5α-reductase inhibitors are routinely used. Similar limitations apply to progesterone, considering that gestonorone was discontinued decades ago because of low efficacy. The relevance of other variants may be limited by the low efficacy of relevant drugs. Vitamin D analogs were rated as disappointing after initial preliminary clinical trials. The VDR agonist BXL-628 significantly reduced PV after 12 wk of treatment in a placebo-controlled phase 2 study, which was possibly too short for urodynamic improvements [18], while addition of cholecalciferol to tamsulosin prevented recurrent urinary tract infections and reduced the postvoid residual urine volume and PSA [19]. ACE inhibitors are widely used antihypertensive agents, but no effect on BPH or LUTS has ever become apparent. Use of mTOR inhibitors for BPH treatment may be precluded not only by unbalanced side effects but also by their high cost. The contribution of the estrogen receptor to genetic BPH predisposition is an interesting issue. The balance of estrogens to androgens is of higher utility than androgen levels alone. The estrogen receptor may be targeted by isoflavone phytoestrogens, which have been examined in epidemiological studies and in preclinical and clinical trials [20].

5. Conclusions

Unless calculated via quantitative approaches, specific contributions of single variants to the overall genetic risk of BPH remain uncertain. It is unlikely that a single key gene imparting genetic predisposition to BPH exists. Rather, the genetic risk for BPH may represent the sum of many variants. Meta-analyses of GWAS and other epidemiological approaches are required to confirm the relevance of key variants that have been identified, but no such analyses are yet available for BPH. Post-GWAS strategies have been

used for PCa [21], including computational methods, functional validation, and clinical post-GWAS trials to confirm causal contributions. Analog programs and the druggability of variants identified in BPH will depend on functional characterization and organ specificity, as unbalanced side effects may be tolerated in oncology, but not for the treatment of benign diseases. Gene ontology analyses could be applied to attractive candidates for experimental characterization identified in both candidate gene studies and GWAS, such as TERT.

Author contributions: Martin Hennenberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hennenberg, Stief
Acquisition of data: Hennenberg, Hu, Tamalunas.
Analysis and interpretation of data: Hennenberg, Hu.
Drafting of the manuscript: Hennenberg.
Critical revision of the manuscript for important intellectual content: Hu, Tamalunas, Stief.
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