# Association of Variants in Genes Related to the Immune Response and Obesity with Benign Prostatic Hyperplasia in CLUE II

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## Abstract

**BACKGROUND**—Chronic inflammation and obesity may contribute to the genesis or progression of benign prostatic hyperplasia (BPH) and BPH-associated lower urinary tract symptoms (LUTS). The influence of variants in genes related to these states on BPH has not been studied extensively. Thus, we evaluated the association of 17 single nucleotide polymorphisms (SNPs) in immune response genes (*IL1B, IL6, IL8, IL10, TNF, CRP, TLR4, RNASEL*) and genes involved in obesity, including insulin regulation (*LEP, ADIPOQ, PPARG, TCF7L2*), with BPH.

**METHODS**—BPH cases (N=568) and age-frequency matched controls (N=568) were selected from among adult male CLUE II cohort participants who responded in 2000 to a mailed

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questionnaire. BPH was defined as BPH surgery, use of BPH medications, or symptomatic BPH (American Urological Association Symptom Index Score ≥ 15). Controls were men who had not had BPH surgery, did not use BPH medications, and whose symptom score was ≤ 7. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression.

**RESULTS**—None of the candidate SNPs was statistically significantly associated with BPH. However, we could not rule out possible weak associations for *CRP* rs1205 (1082C>T), *ADIPOQ* rs1501299 (276C>A), *PPARG* rs1801282 (-49C>G), and *TCF7L2* rs7903146 (47833T>C). After summing risk alleles, men with ≥ 4 had an increased BPH risk compared with those with ≤ 1 (OR, 1.78; 95% CI, 1.10-2.89; $P_{trend}$=0.006).

**CONCLUSION**—SNPs in genes related to immune response and obesity, especially in combination, may be associated with BPH.

## Keywords

benign prostatic hyperplasia; risk; genes

## INTRODUCTION

Dietary and lifestyle factors likely contribute to the development and progression of benign prostatic hyperplasia (BPH) and BPH-associated lower urinary tract symptoms (LUTS) in older men.[1] The precise mechanisms by which these factors may influence this complex condition are not well-understood, but several lines of evidence suggest that risk of BPH and LUTS could be increased by chronic inflammation[2] and obesity-associated perturbations in energy and insulin regulation.[3] More specifically, cytokines and reactive species elaborated during a chronic inflammatory state may damage prostate cell membranes and DNA leading to increased cellular replication to replaced damage cells, and thus increasing the risk of hyperplasia.[4] Obesity is also a state of increased oxidative stress and the metabolic perturbations that accompany obesity tend to be growth-promoting, again possibly leading to hyperplasia and increased risk of BPH.[5, 6]

In addition to modifiable factors, genetics likely plays a role in BPH. A twin study estimated that genetic factors contributed 72% to high-moderate/severe LUTS risk.[7] Because the immune response and energy regulation are influenced by genetic variation, we hypothesized that single nucleotide polymorphisms (SNPs) in genes involved in these pathways would influence BPH. Candidates include genes encoding pro- (interleukin [IL] 1β, IL-6, IL-8, tumor necrosis factor-α) and anti- (IL-10) inflammatory cytokines and a non-specific acute phase protein (C-reactive protein) produced during an inflammatory response[8], a receptor (toll-like receptor 4) involved in innate immune recognition of invading bacteria and viruses that activates signaling cascades that lead to the induction of proinflammatory cytokines[9], and an endoribonuclease (RNase L) that mediates apoptosis in response to viral infections.[10] Other candidates include genes encoding adipokines (leptin and adiponectin) produced by adipose that have important functions in energy regulation and insulin sensitivity[11], a transcription factor (peroxisome proliferator-activated receptors) expressed in adipose that regulates lipid and glucose metabolism that is known to be insulin-

sensitizing[12], and a transcription factor (transcription factor-7-like 2) that influences insulin secretion, genetic variation in which has been associated with type 2 diabetes risk.[13]

Thus, we evaluated the association of 17 SNPs in immune response genes (*IL1B, IL6, IL8, IL10, TNF, CRP, TLR4, RNASEL*) and genes involved in obesity, including insulin regulation (*LEP, ADIPOQ, PPARG, TCF7L2*) with BPH in a case-control study nested in the community-based CLUE II cohort.

## METHODS

### Study Population

Men in this study were participants in the CLUE II cohort, established in May 1989. 32,894 volunteers were recruited in Washington County, Maryland and neighboring areas. At baseline, a brief medical history, blood pressure, a food frequency questionnaire[14], and 20 mL of blood were collected. Heparinized blood was collected, chilled until centrifuged, aliquotted into plasma, red blood cells, and buffy coat, and frozen at -70ºC. Participants updated lifestyle, medical, and exposure histories by mailed questionnaire in 1996, 1998, and 2000. Men were eligible for the BPH study if they responded to the 2000 follow-up questionnaire (on which we assessed LUTS and BPH medications), did not have a cancer diagnosis prior to 2000 (except possibly non-melanoma skin cancer), and had not undergone a transurethral resection of the prostate (TURP) or prostatectomy before 1989. Based on these criteria 4,086 men aged 40 years formed the source population. The Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health approved the study.

### BPH Case and Control Selection

On the 2000 questionnaire, men were asked if they had ever had a TURP (and the date), or if they had regularly taken medications to treat an enlarged prostate or to treat the urinary symptoms of BPH (e.g., finasteride, alpha-blockers). Among those who had not had a TURP and who were not using BPH medications, we identified men with LUTS using a slightly modified version (to fit the constraints of our questionnaire) of the American Urological Association (AUA) Symptom Index.[15] Using the AUA Symptom Index algorithm, we assigned 0 to 5 points to the 0 to 100% frequency of symptoms and the 0 to 5+ times per night that a man gets up to urinate. We summed points across all symptoms and nocturia to obtain a score ranging from 0 to 35. For this study, we considered men with scores of 0-7 to be asymptomatic, 8-14 to have low-moderate symptoms, 15-19 to have high-moderate symptoms, and 20-35 to have severe symptoms. Three case groups were identified for the 568 BPH cases: Group 1–Surgery for BPH since 1989 irrespective of BPH medication use in the past two years or current symptoms (N=102); Group 2–Use of BPH medications in the past two years by men who never had BPH surgery and irrespective of current symptoms (N=310); and Group 3–High-moderate to severe symptoms on the AUA Symptom Index in men who never had BPH surgery and who did not use BPH medications (N=156). We frequency matched 568 controls to the 568 cases on baseline age (±5 years). Controls were defined as men who never had BPH surgery, did not use BPH medications in the past two years, and currently had no or low symptoms ( 7).

## SNP Assessment

Buffy coat DNA was extracted using the AutoPure DNA analyzer from Qiagen (Valencia, CA). Genotyping was performed using the Applied Biosystems Taqman 5′ exonuclease assays, Taqman Universal PCR Master Mix, No AmpErase UNG, and 2.5 nanograms of genomic DNA. The thermal cycling conditions consisted of an initial hold at 95°C denaturing step and a 1 min 60°C annealing and extension step. The ABI Prism 7900HT Sequence Detection System was used to detect the nucleic acids and the Sequence Detection Software v2.2 was used to discriminate alleles and call genotypes (Applied Biosystems, Foster City, CA). Laboratory personnel were masked to case-control status.

We performed SNP selection in two stages, candidate gene and follow-up haplotype tagging SNPs (tagSNPs). In stage 1, we genotyped 17 candidate SNPs in 12 genes (IL1B, IL6, IL8, IL10, TNF, CRP, TLR4, RNASEL, LEP, ADIPOQ, PPARG, TCF7L2,). The majority of the selected SNPs were located in the gene promoter region.[16] Candidates were selected based on allele frequency ( 5% minor allele frequency in whites) and functional data related to gene expression or association with health conditions. Three SNPs–*TLR4* rs4986790 (896A>G, Asp299Gly), *RNASEL* rs486907 (-1385G>A, Arg462Gln], and *PPARG* rs1801282 (-49C>G, Pro12Ala)–were non-synonymous. Genotyping was successful for 93-99% of the men for each candidate SNP.

After observing possible associations for SNPs in *IL10, CRP,* and *TLR4* for prostate[17] and colorectal[16] cancers in this cohort, in stage 2 we selected tagSNPs for these genes. TagSNPs were selected using Tagger to cover most of the variation in these genes (http://www.broad.mit.edu/mpg/tagger/server.html). The targeted regions encompassed 10 kb before the transcription start site to 5 kb after the transcription end site based on the National Center for Biotechnology Information NCBI Build 35 and the phased HapMap release 21 CEU population panel. The selection criteria were a pairwise $r^2$ 0.8 and a minor allele frequency 5%. Seven tagSNPs were chosen for *IL10*, four for *CRP*, and eight for *TLR4*. Genotyping was successful for >95% of *IL10* and *CRP* tagSNPs, but success was lower for *TLR4* tagSNPs.

## Covariate Assessment

Self-reported age, race, marital status, education, weight, height, cigarette smoking, and treatment for high blood pressure and high cholesterol were collected at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Participants were asked whether they had used any medications in the 48 hours before blood donation. We classified sulfonylurea, other glucose-lowering medications, and insulin as diabetes medications. We classified over-the-counter and prescription aspirin, ibuprofen, and other non-aspirin non-steroidal anti-inflammatory agents (NSAIDs) as NSAIDs. Blood pressure was measured three times by a study nurse with a blood pressure cuff while the participant was in a seated position; the third blood pressure value was recorded. Hypertension was defined as a systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg or report of treatment for high blood pressure. Plasma total cholesterol concentration in the non-fasting blood specimens was measured previously using an enzymatic method[18].

## Statistical Analysis

Baseline characteristics were compared between cases and controls using the chi-square test (categorical) and *t* test (continuous). Hardy-Weinberg equilibrium was tested among controls using the chi-square test. D′ and r$^2$ were used to estimate pairwise linkage disequilibrium for the *IL10, CRP,* and *TLR4* tagSNPs using PROC ALLELE in SAS Genetics (SAS Institute, Cary, NC).

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). ORs were estimated assuming a co-dominant or a dominant model of inheritance. Tests for trend were conducted by entering into the model an ordinal variable with values corresponding to number of variant alleles; its coefficient was evaluated by the Wald test. In *post-hoc* analyses we summed number of risk alleles for the subset of SNPs for which there were possible associations with BPH. Then, we estimated the association between number of risk alleles and BPH using indicator variables with ≤1 risk alleles as the reference group.

Analyses were conducted stratifying by level of potentially modifying factors (obesity, hypertension, NSAIDs use). Tests for interaction were done by entering into the model an ordinal variable for genotype, a binary variable for the potentially modifying factor, and a term for their product; the coefficient for this latter term was evaluated by the Wald test. Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC). *P*-values are from two-sided tests.

Haplotypes were reconstructed from unphased genotyped data using the computer program Haplo Stats on the R statistical package (http://www.mayo.edu/hsr/Sfunc.html). Haplotype frequencies were estimated using the Expectation-Maximization algorithm.[19] We used a global score test for differences in haplotype frequency distribution between cases and controls[20]; permutated *P*-values were calculated from an empirical distribution created from a minimum 10,000 permutated data sets. The association between each haplotype and BPH was estimated by regression substitution assuming additive association in Haplo Stat.

# RESULTS

BPH cases and controls did not differ significantly on their characteristics, with the possible exception of cases having a higher prevalence of NSAIDs use (Table 1). In controls, all genotypes were distributed in accordance with Hardy-Weinberg equilibrium, except for two candidate SNPs (*TLR4* rs11536889 [11381G>C], *P*=0.05; *IL10* rs1800896 [-1082A>G], *P*=0.02) and one tagSNP rs3024496 [*IL10* 7951C>T], *P*=0.01). We retained these SNPs because the deviations from the expected genotype frequencies did not appear great.

## Candidate SNPs

None of the candidate SNPs was statistically significantly associated with total BPH (Table II). Possible weak, non-statistically significant associations were observed for *CRP* rs1205 (1082C>T), *ADIPOQ* rs1501299 (276C>A), *PPARG* rs1801282 (−49C>G), and *TCF7L2* rs7903146 (47833T>C). These patterns were generally similar across the BPH case definitions (data not shown). Men with ≥4 risk alleles had a statistically significant 78% higher risk of BPH when compared with those with ≤1, and risk increased across number of

risk alleles ($P_{trend}$=0.006; Table III). Similar associations were observed for each BPH case definition (Table III).

### Effect Modification

Among obese men (BMI ≥ 30 kg/m$^2$), *IL10* rs1800896 (−1082G>A) was positively associated with total BPH (vs A/A, A/G + G/G: OR, 1.83; 95% CI, 1.03–3.25), whereas in non-obese men (BMI <30 kg/m$^2$) the association was inverse (OR, 0.73; 95% CI, 0.53–1.00; $P_{interaction}$=0.01). In hypertensive men, *PPARG* rs1801282 (−49C>G) was inversely associated with total BPH (vs C/C, C/G + G/G: OR, 0.53; 95% CI, 0.34–0.81), but in men without hypertension this association was null (OR, 1.10; 95% CI, 0.74–1.63; $P_{interaction}$=0.04). NSAIDs use did not modify any associations (data not shown).

### Haplotype Analyses

The tagSNPs were not associated with total BPH or the three case definitions (data not shown). We observed five common haplotypes (>5%) for *IL10,* four for *CRP*, and four for *TLR4*. However, neither the distributions of haplotypes between cases and controls ($P_{global}$=0.20, 0.57, and 0.76, respectively), nor individual haplotypes (versus the most common) were associated with total BPH (Table IV).

## DISCUSSION

In this case-control study nested in CLUE II, none of 17 candidate SNPs in 12 genes involved in the immune response and obesity was statistically significantly associated with total BPH. However, when we combined risk alleles for four SNPs that were possibly weakly associated with total BPH (*CRP* rs1205 [1082C>T], *ADIPOQ* rs1501299 [276C>A], *PPARG* rs1801282 [-49C>G], *TCF7L2* rs7903146 [47833T>C]), we found that the greater the number of risk alleles carried, the greater the BPH risk. The 19 tagSNPs and their haplotypes did not provide any additional information about the association of *IL10, CRP,* and *TLR4* with BPH. Our findings suggest that variation in genes related to the immune response and obesity, especially in combination, may be associated with BPH.

No prior studies have evaluated *CRP* rs1205 (1082C>T), *ADIPOQ* rs1501299 (276C>A), *PPARG* rs1801282 (-49C>G), and *TCF7L2* rs7903146 (47833T>C) with BPH. Some studies have investigated circulating concentrations of C-reactive protein and adiponectin with BPH. Three large studies have reported that higher levels of C-reactive protein, a non-specific inflammatory marker whose circulating levels are influenced by *CRP* variants[21], were positively associated with BPH/LUTS.[22-24] Adiponectin, an insulin-sensitizing cytokine secreted by adipocytes, was inversely associated with incident BPH in a nested case-control study[25], but not significantly associated with BPH in a small Greek case-control study.[26] Although there is no direct evidence that *PPARG*[27] and *TCF7L2* influence risk of BPH, variants in these genes are associated with diabetes[28, 29], a purported risk factor for BPH.[30]

The remaining candidate SNPs in genes involved in the immune response (*IL1B, IL6, IL8, IL10, TNF, TLR4,* and *RNASEL*) and obesity (*LEP*) were not associated with total BPH. Our results are largely consistent with a community-based prospective study that showed no

significant association of *IL10* (rs1800896) or *IL8* (rs4073) [or a SNP in *IL1B* (rs16944) that we did not study] with clinical measures of BPH.[31] In that study the AA genotype of *TNF* (rs1800629) was inversely associated with impaired peak urinary flow rate.

We also considered whether the association between the SNPs and BPH differed by strata of modifiable factors relevant to the pathways of interest. We observed a positive association for the *IL10* (rs1800896) -1082 G allele in obese men, but a possible inverse association in non-obese men. We had expected that the G allele, which results in greater levels of this anti-inflammatory cytokine than the A allele[32], would be inversely associated with BPH. It is unclear why in obese men the association was in the opposite direction. Consistent with the overall finding and the inverse association between the *PPARG* (rs1801282) −49 G allele and diabetes[12], in hypertensive men, we found an inverse association for the G allele and BPH, but a positive association in men without hypertension. Although we did not find effect modification by NSAIDs use, our ability to detect interaction may have been limited by our assessment of NSAIDs use only for the 48 hours prior to blood donation.

Aspects of our study warrant discussion. We sampled cases and controls from a community-based cohort and doing so helped to ensure that allele frequencies in controls reflected those in the source population. We used several BPH definitions and the results were generally consistent, which helps to support that the associations that we observed were capturing the same underlying complex condition. Our BPH case definition was based on symptoms, including treatment for symptoms, and our control definition was based on lack of symptoms, a parallel comparison. However, we cannot rule out that some controls and cases may have had an enlarged prostate that did not lead to symptoms or was not the cause of their symptoms, respectively. The BPH surgery cases were incident; that is the men had their TURPs months to years after the donation of blood used for genotyping. However, these men likely had symptomatic enlarged prostate for some time prior to their surgery. We asked the men to report whether they had a TURP, but not other far less common procedures to treat BPH; thus, we could have missed some BPH cases. The cases defined based on BPH medications use or LUTS were prevalent. We collected LUTS information only once, thus, we could not study whether SNPs are associated with LUTS progression.

We used a hypothesis-driven approach to select the genes for study. We chose SNPs based on known or suspected functionality. For three genes, we inferred haplotypes based on tagSNPs. We did not correct for multiple testing for either the candidate SNPs or tagSNPs because none of their main effects was statistically significant. The evaluation of the association for number of risk alleles was conducted *post hoc*, that is, the SNPs we included for summing of risk alleles were those for which we noted minimal evidence for an association with BPH. For this *post-hoc* analysis and using the prevalence of the number of risk alleles that we observed in the controls, we had 70% power for a two-sided test with α=0.05 to detect a statistically significant trend across number of risk alleles when the OR comparing ≥4 to ≤1 risk alleles was 1.78 or greater. These findings from this analysis require evaluation in other studies.

In conclusion, our findings suggest that polymorphisms in genes related to the immune response and obesity weakly influence BPH risk. That we found an increasing odds of BPH

with increasing number of risk alleles suggests that multiple genes and/or pathways together may affect the development of BPH.

## ACKNOWLEDGMENTS

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**Table I**

Baseline characteristics of age-frequency matched[*] men with BPH and controls in the CLUE II cohort of Washington County, Maryland, 1989

| Characteristic | Controls (N=568) | Total BPH (N=568) | BPH Case Groups | | | P[†] |
| --- | --- | --- | --- | --- | --- | --- |
| | | | Surgery (N=102) | Medication Use (N=310) | Symptoms (N=156) | |
| Age (y), mean (SD) | 55.6 (10.5) | 55.6 (10.6) | 61.3 (8.2) | 56.0 (10.2) | 51.1 (11.0) | Matched |
| White, % | 98.8 | 98.8 | 100.0 | 98.4 | 98.7 | -- |
| Marital status | | | | | | |
| Never married, % | 1.8 | 3.4 | 1.0 | 2.3 | 7.1 | 0.23 |
| Married, % | 90.7 | 88.7 | 96.1 | 91.3 | 78.8 | |
| Other, % | 7.6 | 8.0 | 2.9 | 6.4 | 14.1 | |
| 12 years of education, % | 81.7 | 82.0 | 85.3 | 80.3 | 83.3 | 0.87 |
| BMI (kg/m$^2$) | | | | | | |
| Mean (SD) | 27.8 (3.8) | 27.5 (3.8) | 27.3 (3.8) | 27.8 (3.9) | 27.2 (3.7) | 0.15 |
| Normal (<24.9), % | 23.2 | 25.5 | 23.5 | 25.8 | 26.3 | 0.28 |
| Overweight (25–29.9), % | 51.6 | 53.2 | 59.8 | 49.0 | 57.0 | |
| Obese ( 30), % | 25.2 | 21.3 | 16.7 | 25.2 | 16.7 | |
| Cigarette smoking status | | | | | | |
| Never, % | 37.3 | 37.3 | 38.2 | 37.7 | 35.9 | 0.32 |
| Former, % | 49.0 | 51.8 | 50.0 | 54.5 | 47.4 | |
| Current, % | 13.7 | 10.9 | 11.8 | 7.8 | 16.7 | |
| Use of NSAIDs in past 48 hr, % | 27.8 | 32.6 | 36.3 | 34.5 | 26.3 | 0.08 |
| Use of diabetes medication in past 48 hr, % | 2.5 | 2.6 | 4.9 | 1.9 | 2.6 | 0.85 |
| Hypertension[‡], % | 48.2 | 48.4 | 53.9 | 51.9 | 37.8 | 0.95 |
| Plasma total cholesterol (mg/dL), mean (SD) | 209.0 (33.4) | 206.4 (35.3) | 207.3 (39.2) | 206.3 (33.4) | 206.1 (36.3) | 0.21 |

Abbreviations: SD, standard deviation; BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs.

[*] Age-frequency matching only between total BPH cases and controls.

[†] Comparing total BPH cases and controls using the t-test for continuous variables and chi-square for categorical variables.

[‡] Systolic blood pressure 140 mm Hg, diastolic blood pressure 90 mm Hg, or treatment for hypertension.

**Table II**

Odds ratios and 95% confidence intervals of BPH for 17 candidate single nucleotide polymorphisms in the CLUE II cohort of Washington County, Maryland

| Genotype | Cases, N | Controls, N | OR (95% CI)[*] |
|---|---|---|---|
| *IL10* | | | |
| −592C>A (rs1800872) | | | |
| C/C | 306 | 298 | 1.00 (Reference) |
| A/C | 194 | 209 | 0.90 (0.70-1.16) |
| A/A | 23 | 25 | 0.89 (0.50-1.61) |
| $P_{trend}$ [†] | | | 0.43 |
| A-carrier | 217 | 234 | 0.90 (0.71-1.15) |
| −1082A>G (rs1800896) | | | |
| A/A | 147 | 138 | 1.00 (Reference) |
| A/G | 285 | 303 | 0.88 (0.66-1.17) |
| G/G | 116 | 110 | 0.99 (0.69-1.40) |
| $P_{trend}$ [†] | | | 0.88 |
| G-carrier | 401 | 413 | 0.91 (0.69-1.19) |
| *CRP* | | | |
| 1082C>T (rs1205) | | | |
| C/C | 250 | 273 | 1.00 (Reference) |
| C/T | 237 | 225 | 1.15 (0.89-1.47) |
| T/T | 58 | 47 | 1.34 (0.88-2.05) |
| $P_{trend}$ [†] | | | 0.11 |
| T-carrier | 295 | 272 | 1.18 (0.93-1.50) |
| 1059G>C (rs1800947) | | | |
| G/G | 500 | 495 | 1.00 (Reference) |
| C/G | 52 | 50 | 1.03 (0.68-1.54) |
| C/C | 0 | 1 | Not estimated |
| $P_{trend}$ [†] | | | 0.96 |
| C-carrier | 52 | 51 | 1.01 (0.67-1.51) |
| *TLR4* | | | |
| 11381G>C (rs11536889) | | | |
| G/G | 396 | 399 | 1.00 (Reference) |
| C/G | 134 | 128 | 1.05 (0.79-1.39) |
| C/C | 15 | 18 | 0.84 (0.41-1.69) |
| $P_{trend}$ [†] | | | 0.99 |
| C-carrier | 149 | 146 | 1.02 (0.78-1.34) |
| 896A>G [Asp299Gly] (rs4986790) | | | |
| A/A | 489 | 491 | 1.00 (Reference) |

| Genotype | Cases, N | Controls, N | OR (95% CI)[*] |
|---|---|---|---|
| A/G | 62 | 58 | 1.07 (0.73-1.56) |
| G/G | 2 | 3 | 0.67 (0.11-4.02) |
| $P_{trend}$[†] | | | 0.86 |
| G-carrier | 64 | 61 | 1.05 (0.72-1.52) |
| **IL6** | | | |
| −174G>C (rs1800795) | | | |
| G/G | 177 | 177 | 1.00 (Reference) |
| C/G | 254 | 269 | 0.94 (0.72-1.23) |
| C/C | 99 | 86 | 1.15 (0.80-1.64) |
| $P_{trend}$[†] | | | 0.58 |
| C-carrier | 353 | 355 | 1.00 (0.77-1.28) |
| −572G>C (rs1800796) | | | |
| G/G | 482 | 478 | 1.00 (Reference) |
| C/G | 43 | 57 | 0.74 (0.49-1.13) |
| C/C | 2 | 2 | 1.00 (0.13-7.07) |
| $P_{trend}$[†] | | | 0.21 |
| C-carrier | 45 | 59 | 0.75 (0.50-1.13) |
| −597G>A (rs1800797) | | | |
| G/G | 182 | 189 | 1.00 (Reference) |
| A/G | 261 | 266 | 1.02 (0.78-1.32) |
| A/A | 98 | 80 | 1.27 (0.88-1.82) |
| $P_{trend}$[†] | | | 0.25 |
| A-carrier | 359 | 346 | 1.08 (0.83-1.38) |
| **IL1B** | | | |
| −31C>T (rs1143627) | | | |
| T/T | 233 | 236 | 1.00 (Reference) |
| C/T | 232 | 241 | 0.97 (0.75-1.25) |
| C/C | 72 | 68 | 1.07 (0.73-1.56) |
| $P_{trend}$[†] | | | 0.83 |
| C-carrier | 304 | 309 | 1.00 (0.78-1.26) |
| **IL8** | | | |
| −251A>T (rs4073) | | | |
| T/T | 151 | 145 | 1.00 (Reference) |
| A/T | 254 | 284 | 0.85 (0.65-1.14) |
| A/A | 132 | 109 | 1.16 (0.82-1.63) |
| $P_{trend}$[†] | | | 0.46 |
| A-carrier | 386 | 493 | 0.94 (0.72-1.23) |

| Genotype | Cases, N | Controls, N | OR (95% CI)[*] |
|---|---|---|---|
| **_TNF_** | | | |
| −308G>A (rs1800629) | | | |
| G/G | 361 | 377 | 1.00 (Reference) |
| A/G | 158 | 150 | 1.10 (0.84-1.43) |
| A/A | 17 | 16 | 1.11 (0.55-2.22) |
| $P_{trend}$[†] | | | 0.48 |
| A-carrier | 175 | 166 | 1.10 (0.85-1.42) |
| **_RNASEL_** | | | |
| −1385G>A [Arg462Gln] (rs486907) | | | |
| G/G | 213 | 224 | 1.00 (Reference) |
| A/G | 244 | 242 | 1.06 (0.81-1.37) |
| A/A | 74 | 69 | 1.12 (0.77-1.64) |
| $P_{trend}$[†] | | | 0.51 |
| A-carrier | 318 | 311 | 1.08 (0.84-1.37) |
| **_PPARG_** | | | |
| −49C>G [Pro12Ala] (rs1801282) | | | |
| C/C | 427 | 408 | 1.00 (Reference) |
| C/G | 103 | 125 | 0.78 (0.58-1.05) |
| G/G | 7 | 10 | 0.66 (0.25-1.77) |
| $P_{trend}$[†] | | | 0.08 |
| G-carrier | 110 | 135 | 0.77 (0.58-1.03) |
| **_TCF7L2_** | | | |
| 47833T>C (rs7903146) | | | |
| C/C | 250 | 261 | 1.00 (Reference) |
| C/T | 222 | 224 | 1.03 (0.80-1.33) |
| T/T | 52 | 38 | 1.42 (0.90-2.24) |
| $P_{trend}$[*] | | | 0.22 |
| T-carrier | 274 | 262 | 1.09 (0.85-1.39) |
| **_ADIPOQ_** | | | |
| 276C>A (rs1501299) | | | |
| C/C | 271 | 281 | 1.00 (Reference) |
| A/C | 209 | 213 | 1.01 (0.79-1.31) |
| A/A | 59 | 48 | 1.27 (0.84-1.93) |
| $P_{trend}$[*] | | | 0.36 |
| A-carrier | 268 | 261 | 1.06 (0.83-1.35) |
| **_LEP_** | | | |
| −19G>A (rs2167270) | | | |
| G/G | 211 | 201 | 1.00 (Reference) |

| Genotype | Cases, N | Controls, N | OR (95% CI)[*] |
|---|---|---|---|
| A/G | 248 | 272 | 0.86 (0.67-1.12) |
| A/A | 74 | 66 | 1.06 (0.72-1.56) |
| $P_{trend}$[*] | | | 0.87 |
| A-carrier | 322 | 338 | 0.90 (0.70-1.16) |

[*] From a logistic regression model adjusting for age. Cases and controls frequency-matched on age.

[†] From a logistic regression model with number of variant alleles entered as an ordinal variable.

**Table III**

Association between number of risk alleles for *CRP*, *ADIPOQ*, *PPARG*, and *TCF7L2*, and BPH in the CLUE II cohort of Washington County, Maryland

| Number of risk alleles | Controls, N* | Cases, N* | Total BPH OR (95% CI) | BPH Case Groups Surgery | Medication Use | Symptoms |
|---|---|---|---|---|---|---|
| 1 | 59 | 42 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 2 | 199 | 174 | 1.23 (0.79-1.92) | 1.50 (0.62-3.63) | 1.14 (0.67-1.93) | 1.31 (0.61-2.76) |
| 3 | 158 | 167 | 1.49 (0.95-2.34) | 1.57 (0.64-3.86) | 1.47 (0.87-2.50) | 1.52 (0.71-3.23) |
| 4 | 91 | 115 | 1.78 (1.10-2.89) | 2.60 (1.04-6.52) | 1.52 (0.86-2.70) | 1.90 (0.86-4.18) |
| $P_{trend}$† | | | 0.006 | 0.03 | 0.05 | 0.07 |

*Missing: controls=61; total BPH cases=70.

†From a logistic regression model with number of risk alleles entered as an ordinal variable and adjusting for age.

Table IV Odds ratios and 95% confidence intervals of BPH for *IL10, CRP,* and *TLR4* haplotypes in the CLUE II cohort of Washington County, Maryland

| Haplotype[¶] | Haplotype frequency | | OR (95% CI)[**] |
|---|---|---|---|
| | **Cases** | **Controls** | |
| ***IL10*[†]** | **N=465** | **N=472** | |
| A-C-A-C-C-C-A | 0.327 | 0.321 | 1.00 (Reference) |
| T-C-A-C-C-T-G | 0.221 | 0.211 | 1.04 (0.80-1.34) |
| T-C-A-C-C-T-A | 0.166 | 0.145 | 1.13 (0.86-1.50) |
| A-C-A-T-C-C-A | 0.125 | 0.119 | 1.03 (0.75-1.40) |
| A-C-C-T-C-C-A | 0.051 | 0.066 | 0.73 (0.48-1.11) |
| $P_{global}$[††] | | | 0.20 |
| ***CRP*[*]** | **N=487** | **N=494** | |
| T-T-T-A | 0.342 | 0.309 | 1.00 (Reference) |
| T-A-T-A | 0.313 | 0.315 | 0.89 (0.71-1.12) |
| C-T-C-A | 0.271 | 0.296 | 0.83 (0.66-1.04) |
| T-T-T-C | 0.067 | 0.070 | 0.85 (0.59-1.23) |
| $P_{global}$[††] | | | 0.57 |
| ***TLR4*[‡]** | **N=351** | **N=358** | |
| A-T-A-G-G-G-T-C | 0.657 | 0.658 | 1.00 (Reference) |
| G-C-G-A-T-C-C-A | 0.130 | 0.140 | 0.91 (0.66-1.25) |
| G-C-G-A-T-G-T-C | 0.107 | 0.110 | 0.97 (0.69-1.37) |
| G-T-G-G-T-G-T-C | 0.061 | 0.060 | 1.02 (0.65-1.60) |
| $P_{global}$[††] | | | 0.76 |

[†]TagSNPs: rs1800890, rs1800894, rs3021094, rs1554286, rs3024509, rs3024496, and rs3024498

[*]TagSNPs: rs2794521, rs1417938, rs2808630, and rs3093077

[‡]TagSNPs: rs2737190, rs10116253, rs1927914, rs1927911, rs2149356, rs7873784, rs11536891, and rs11536898

[¶]Haplotypes shown if present in 5% of men; haplotypes were missing due to missing genotype for one or more SNPs for *IL10* – cases 18.1%, controls 16.9%; *CRP* – cases 14.3%, controls 13.0%; and *TLR4* – cases 18.1%, controls 16.9%.

[**]From a generalized linear model using regression substitution adjusted for age.

[††]From a global score test of differences in distribution of haplotype frequencies between cases and controls adjusting for age.