Genomics in Urologic Health and Disease

Genetic and Environmental Influences on Urinary Conditions in Men: A Classical Twin Study

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OBJECTIVE   To evaluate the genetic and environmental relationship among prostatitis and other urological conditions, including benign prostatic hyperplasia (BPH) and prostate cancer (CaP), a classical twin design and biometric modeling was used. While prostatitis—characterized by pain and voiding symptoms, no clear etiology, and functional and quality of life impairments—co-occurs with other urinary conditions, the degree of shared overlapping etiologic processes among them remains unclear. We examined the contribution of genetic and environmental factors to these conditions and the etiology of their associations at the level of genetic and environmental influences.

METHODS   4380 monozygotic and dizygotic male twin pairs from the Vietnam Era Twin Registry reported lifetime physician-diagnosed prostatitis (combined acute and chronic), bladder problems, enlarged prostate/BPH, and CaP. Multivariate biometrical modeling estimated the magnitude of genetic and environmental influences for each condition, as well as their genetic and environmental covariance. The common pathway model tested the assumption that covariation among these urinary conditions is determined by a single latent factor.

RESULTS   Overall prevalence of prostatitis was 2.7%. Heritability estimates ranged from 19% for bladder problems to 42% for CaP. Significant shared environmental influences were present for CaP (12%), enlarged prostate/BPH (10%) but were smaller than genetic influences. A reduced one factor common pathway model provided the best fit, suggesting that covariation among the conditions is determined by a shared latent factor.

CONCLUSION   We identified a common, genetically-influenced factor that accounts for much of the comorbidity among these 4 disease conditions. Nonshared environmental factors also make a significant contribution.   UROLOGY 129: 54−59, 2019. © 2019 Elsevier Inc.

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) accounts for most prostatitis cases and is characterized by urological pain that

may be associated with various urinary or sexual disturbances.[1] CP/CPPS affects 1.8%-10.4% of men in different populations[2,3] and is the leading reason for urological outpatient consultations for men under age 50.[4] Measures of functional status including ability to perform daily tasks and maintain well-being is lower in patients with CP/CPPS than their counterparts with severe diabetes or congestive heart failure,[5] and similar to patients with Crohn's disease, angina, or myocardial infarction.[6]

Infection, inflammation, neurologic and immune dysfunction,[7] oxidative stress, prostatic obstruction, and edema have been linked to CP/CPPS,[8] but none of these represents the etiology of most cases. Studies have found high levels of comorbidity between CP/CPPS with other urological and nonurological syndromes, such as benign prostatic hyperplasia (BPH), and prostate cancer (CaP).[2,9,10] The reason for this comorbidity is likely multifaceted, and may stem, in part, from a common etiology among the conditions due to shared genetic influences, overlapping physiology, or common environmental factors.

The multivariate application of the classical twin design represents a powerful approach to evaluate sources of common etiology. Previous twin studies demonstrated moderate levels of heritability ("h^2" or proportion of variation attributable to genetic effects) for bladder problems, enlarged prostate/BPH, and CaP, suggesting that genetic factors play an important role.[11,12] Genetic factors have been implicated in CP/CPPS,[13] however, no study has evaluated the degree to which genetic factors contribute to the comorbidity of prostatitis with other prostatic and urinary conditions. Evaluating the overlap of genetic and environmental factors common or unique to these conditions can improve our understanding of their etiology.

The present study used multivariate biometric modeling of a unique sample of middle-aged male-male twins to: (a) estimate the heritability of prostatitis and other urological conditions, and (b) examine genetic and environmental covariance among these conditions. Based on the literature, we expected that a moderate portion of the variance in each condition would be due to genetic factors. Because these conditions co-occur at high rates, and each has been shown to be at least partially genetically influenced, evaluating the overlap in genetic effects and their contribution to the co-occurrence of these conditions can yield information about their shared etiology. We hypothesized that the covariation between prostatitis and other conditions results in part from common genetic and environmental factors.

MATERIALS AND METHODS

Participants
The Vietnam Era Twin Registry is a community-based sample of male twins born between 1939 and 1957 who both served in the US military at some point between 1965 and 1975.[14] With approximately 7500 twin pairs, the Vietnam Era Twin Registry is one of the largest twin registries in United States. Initial contact of registry members occurred in 1987. The registry has been described in detail previously.[15]

Procedures
Between 2010 and 2012, participants were contacted regarding Veterans Administration (VA) Cooperative Study #569—"The course and consequences of post-traumatic stress disorder in Vietnam-era veteran twins." A mailed questionnaire evaluated wide ranging physical and mental health issues, including prostatic and urinary conditions. Inclusion of questions on these conditions resulted from a site-specific study in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network.[16] Because of the size and scope of the study, data collection was done under contract by Abt SRBI, Inc. The VA Central Institutional Review Board and the Research and Development Committee at VA San Diego Healthcare System approved the study. All participants provided written informed consent.

Measures
Demographics and Zygosity. Age, race, and Hispanic ethnicity were available from the Registry database. Zygosity was assigned using an algorithm based on childhood similarity questions shown to be more than 95% accurate.[17] Current marital status and years of education were obtained from the questionnaire.

Self-reported Prostatitis and Urinary Conditions. Twins were asked to report lifetime conditions, specifically, "Have you ever been told by a doctor or other health professional that you had . . ." followed by a list of conditions including acute prostatitis, CP, bladder problems, enlarged prostate, BPH, and CaP. CP is a general diagnostic category; approximately 90% of patient with this label have CP/CPPS.[18] Chronic and acute prostatitis were highly correlated in our sample, $r = 0.89$ (95% CI: 0.89-0.99, $P < .001$) and were therefore combined into 1 "prostatitis" variable for all subsequent analyses. Enlarged prostate and BPH questions represented the same condition, and were similarly combined.

Statistical Analyses
In the classical twin design, monozygotic (MZ) and dizygotic (DZ) twins are compared to partition the variance of each phenotype into additive genetic influences (A), shared environmental influences (C), and nonshared environmental influences (E). This variance decomposition, or "ACE model," is accomplished by evaluating the similarity of MZ twins (sharing 100% of their genes) with DZ twins (sharing, on average, 50% of their segregating genes). Additive genetic influences are inferred when MZ correlations are greater than DZ correlations. Shared environmental effects increase similarity between members of a twin pair (eg, family environment) and are inferred when DZ correlations are greater than half the MZ correlations.[19] Nonshared environmental effects contribute to differences between twin pair members, and include measurement error. When 2 or more conditions are correlated, multivariate biometric models decompose the covariance between conditions into genetic and environmental components, thus estimating the source and magnitude of the overlap in the form of genetic and environmental correlations.

To evaluate variance components for noncontinuous traits (ie, diagnostic categories) it is assumed that the liability to develop the condition is normally distributed,[19] and that 1 or more thresholds subdivides the population into the observed diagnostic categories. The relative contribution of genetic and environmental factors to this liability is estimated using maximum likelihood.

Multivariate Models. We fit a series of multivariate biometric models to evaluate the relative contribution of genetic and environmental factors to the liability of each condition, and their covariance. First, we fit a Cholesky decomposition (Supplementary Fig. 1A)—the most saturated model of genetic and environmental relationships among conditions—that provides estimates of genetic and environmental influences on each condition, and the genetic and environmental covariance among them.[19] The Cholesky provides a summary of the data without imposing a structure.

Next, we examined the relative fit of 2 multivariate models applied to the 4 conditions; the independent pathway and the common pathway models. The independent pathway model[20] (Supplementary Fig. 1B) specifies direct paths from genetic and environmental factors common to all conditions and as well as A, C, and E factors specific to each trait. In the independent model, common genetic and environmental influences partially explain the phenotypic covariance, along with specific genetic and environmental influences. The common pathway model[21] (Supplementary Fig. 1C) tests the assumption that covariation among conditions is determined by 1 latent (unobserved) factor.

The latent factor is influenced by A, C, and E factors that reflect the relative contribution of genetic and environmental factors to this underlying trait. The effect of the latent factor on the observed conditions is expressed by factor loadings. Additionally, each condition is influenced by specific A, C, and E factors that decompose the residual variance of each variable. Thus, the common model allows estimation of genetic and environmental influences contributing to the latent trait and of those unique to each condition. To further improve model fit, the best multivariate model was reduced by removing insignificant paths.

The magnitude of genetic overlap among variables, and whether they are likely to share the same genes, can be expressed in terms of a genetic correlation (rg). These correlations estimate the degree to which the same genetic (or environmental) factors influence 2 variables and are more informative than characteristic correlations by isolating the source of the association.[19] In other words, genetic correlations estimate overlap in genetic signal rather than all sources of variance and covariance.

Models were fit in OpenMx[22] version 2.3.1 using full information maximum-likelihood that utilizes information from all cases regardless of missing data to yield less-biased estimates than list-wise or pair-wise deletion methods. Model fit was evaluated by comparing −2 times the natural log likelihood (−2lnL) and Akaike's Information Criterion (AIC), calculated as $\Delta \chi^2 - 2 \times \Delta df$, between nested models. Lower AIC values represent a better balance between goodness of fit and parsimony. In addition to determining the best model, the magnitude of A, C, and E can be estimated with 95% confidence intervals.

RESULTS

7079 twins completed questionnaires (67% response rate). The analytical dataset included 6824 individuals with known zygosity; 6156 with prostatitis data, and 4680 members of complete pairs (1457 MZ pairs, 883 DZ pairs). Consistent with the Registry sample, participants were middle-aged (mean = 61.1 years, range 53-73), white (92.9%), and non-Hispanic (97%). Most were married or widowed (79.7%) and had completed an average 14.1 (SD = 2.2) years of education.

Prevalence and Correlations

There were 168 cases with prostatitis for a prevalence of 2.7% (Table 1). Prevalence rates did not vary across zygosity (all $P > .05$). Positive correlations were observed, particularly prostatitis with enlarged prostate/BPH ($r = 0.61$; 95% CI: 0.55; 0.67).

Biometric Modeling

Multivariate model fitting results are reported in Table 2. Our baseline model was the ACE Cholesky decomposition (standardized variance components and correlations are presented in Supplemental Table 1). There was no significant loss in fit between the independent pathway model (Supplemental Fig. 2) and the Cholesky. The common pathway model also did not produce a decrease in fit compared to the independent pathway model. This model is consistent with the hypothesis that a single latent factor accounts for the close relationship of prostatitis with the other conditions. The common pathway model was further reduced by removing insignificant paths including the shared environmental influence on the common factor, the specific shared environmental influences on prostatitis and bladder problems, and the specific genetic influence on bladder problems and enlarged prostate/BPH. The reduced common factor model (Table 2, model 4) produced the lowest AIC, suggesting an optimal balance between model fit and parsimony.

Overall variance component estimates from the best-fitting reduced common pathway model showed that all 4 conditions had significant genetic influences with heritabilities ranging from $h^2 = 0.19$ for bladder problems to $h^2 = 0.42$ for CaP (Table 3). Shared environmental influences were significant for enlarged prostate/BPH ($c^2 = 0.10$) and CaP ($c^2 = 0.12$). The remaining variance for each condition was due to nonshared environmental influences.

The strongest genetic correlation was between enlarged prostate/BPH and bladder problems $rg = 0.99$ (95% CI: 0.99, 0.99, Table 4). Genetic correlations among prostatitis, bladder problems, and enlarged prostate/BPH were all positive and high ($rg = 0.87-0.99$), while the genetic correlations between CaP and the other conditions were lower (0.48−0.55). No shared environmental correlation was observed. Nonshared environmental correlations ranged from $re = 0.39$ (0.35; 0.50) for CaP and bladder problems to $re = 0.54$ (95% CI: 0.50, 0.66) for enlarged prostate/BPH and prostatitis.

The reduced common pathway model (Fig. 1) found that genetic influences account for 40% of the variance in the common factor with nonshared environmental influences accounting for 60%. The common factor accounted for 69% (obtained by squaring the path: $0.83 \times 0.83 = 0.69 \times 100\% = 69\%$) of the variance in prostatitis, 52% in enlarged prostate/BPH, 49% in bladder problems, and 33% in CaP. Trait-specific genetic variance ranged from 28% for CaP (obtained by squaring the specific genetic path: $0.53 \times 0.53 = 0.28 \times 100\% = 28\%$) to 0% for bladder problems and enlarged prostate/BPH. Trait-specific shared environmental influences ranged from 12% for CaP to 0% for enlarged prostate/BPH and bladder problems, and trait specific

Table 1. Life-time prevalence of self-reported, physician-diagnosed urinary conditions and tetrachoric correlations (bootstrapped 95% confidence intervals)

Diagnosis	Prevalence (N = 6,824)	Prostatitis	Bladder Problems	Enlarged Prostate/BPH	Prostate Cancer
Prostatitis	2.7%	1			
Bladder problems	8.2%	0.53 (0.47; 0.60) n = 6132	1		
Enlarged prostate/BPH	18.8%	0.61 (0.55; 0.67) n = 6150	0.50 (0.46; 0.55) n = 6145	1	
Prostate cancer	4.9%	0.52 (0.43; 0.60) n = 6147	0.44 (0.36; 0.51) n = 6150	0.37 (0.31; 0.42) n = 6162	1

BPH, benign prostatic hyperplasia.
All correlations significant at $P < .001$.

Table 2. Comparative model fit

Model	−2lnL	Df	AIC	Δ−2lnL	Δdf	*P*
1 Cholesky ACE decomposition	8566.51	17036	−25505.49	—	—	—
2 Independent pathway	8572.21	17042	−25511.79	5.7	6	.4576
3 Common pathway	8576.29	17048	−25519.71	9.78	12	.6354
4 Common pathway reduced	**8576.49**	**17053**	**−25529.51**	**9.98**	**17**	**.9044**

AIC, Akaike information criterion; df, degrees of freedom; lnL, log-likelihood.
Δ−2LL and Δdf are relative to the Cholesky decomposition. Best-fitting model in bold.

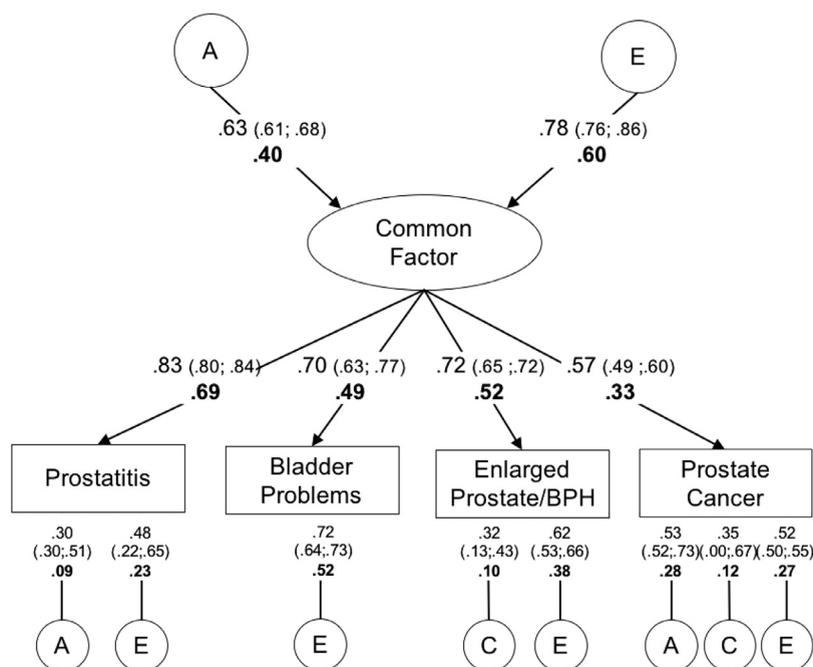**Table 3.** Standardized variance components estimates from the best-fitting reduced common pathway model

Component	a^2	c^2	e^2
Prostatitis	0.36 (0.33; 0.54)	—	0.64 (0.50; 0.81)
Bladder problems	0.19 (0.17; 0.21)	—	0.81 (0.79; 0.87)
Enlarged prostate/BPH	0.20 (0.13; 0.27)	0.10 (0.09; 0.16)	0.70 (0.61; 0.78)
Prostate cancer	0.42 (0.09; 0.65)	0.12 (0.12; 0.45)	0.47 (0.35; 0.61)

a^2, genetic variance; BPH, benign prostatic hyperplasia; c^2, shared environmental variance, e^2, nonshared environmental variance.
95% confidence intervals are presented in the parentheses. Results are derived from the multivariate reduced common pathway model.

Table 4. Genetic and environmental correlations (95% confidence intervals) from best-fitting reduced common factor model

Component	Prostatitis	Bladder Problems	Enlarged Prostate/BPH
Genetic Influences			
Prostatitis	—		
Bladder problems	0.87 (0.72; 0.90)	—	
Enlarged prostate/BPH	0.87 (0.67; 0.91)	0.99 (0.99; 0.99)	—
Prostate cancer	0.48 (0.33; 0.99)	0.55 (0.38; 0.58)	0.55 (0.49; 0.72)
Nonshared environmental influences			
Prostatitis	—		
Bladder problems	0.48 (0.46; 0.51)	—	
Enlarged prostate/BPH	0.54 (0.50; 0.66)	0.41 (0.35; 0.41)	—
Prostate cancer	0.52 (0.48; 0.67)	0.39 (0.35; 0.50)	0.43 (0.39; 0.54)

BPH, benign prostatic hyperplasia.
Results are derived from the multivariate reduced common pathway model.

Figure 1. Reduced common pathway model path diagram with standardized path coefficients (95% confidence intervals). Variance components presented in bold.

nonshared environmental influences ranged from 52% for bladder problems to 23% for prostatitis.

COMMENT

We used a classical twin design with multivariate genetic analyses to explore the genetic and environmental sources of overlap among prostatitis and urinary conditions. Though these conditions frequently co-occur, a biometric evaluation of the common and unique etiology responsible for this association has not been previously conducted. The level of comorbidity in our data is consistent with existing research on the relationship of prostatitis and other conditions.[9] Supporting our hypotheses, each condition was moderately heritable (19%-42%), consistent with previous estimates.[11,12] The covariation among the conditions was primarily due to genetic factors, with nonshared environmental factors making smaller but meaningful contributions.

Most importantly, our biometric analyses support the hypothesis that prostatitis, bladder problems, enlarged prostate/BPH, and CaP are in part different expressions of a single underlying pathology that is genetically influenced. Sizable genetic correlations indicate that the same set of genetic factors contribute to expression of the 4 diagnoses, suggesting they are not simply related, but instead manifestations of the same underlying genetic and environmental influences. Together, our findings support theories of a common biological etiology.

Previous research proposed several etiologic risk factors that may account for our findings. Inflammatory processes, for example, have been implicated in both CP/CPPS[8] and regulation of cellular events in CaP.[23] Post-infection inflammation may contribute to the development of BPH in the presence of androgen dysfunction,[24] a finding in line with the association of androgen signaling gene polymorphisms with risk of CaP and BPH.[25] Obesity has been shown to increase the risk of CaP[26] and BPH[27] but not CP/CPPS.[28] Though infectious pathogens have been linked with CaP, efforts to identify potential microbiome differences in CP/CPPS are ongoing and inconclusive.[29] The biometric analyses conducted in this study distinguish between the influence of genetic and environmental factors (such as environmental trauma, deployment, and pathogen exposure) to the development of these conditions, and this influence is captured by the estimates of nonshared environmental influence (e^2). Further investigation could evaluate the nature of these environmental factors (similarly, specific genetic variants) and explore the genetic-environmental interplay in the development of these conditions. Taken together with our current findings, these observations highlight the need for future studies to determine etiologic overlap and common pathogenetic mechanisms among these conditions.

We found that although CaP is associated with the other conditions, a sizable amount of variance in CaP is independent of the common factor. Thus, CaP appears to show less genetic and environmental overlap with other conditions; while shared etiology is present, unique genetic and environmental factors (independent of prostatitis, BPH, enlarged prostate, and bladder problems) also contribute to CaP etiology. Specific gene variants, oxidative stress, diet, hormones, infection, and exposure to environmental agents have been linked to CaP.[30] While we tested various models to clarify sources of co-occurrence among these urinary conditions, different models may also further illuminate these relationships. For example, future models may incorporate possible causal influences between prostatitis and CaP. Based on our findings, exploring the differential impact of these potential causes on CaP is advised.

This study has important limitations. Not all of these conditions can be considered equivalent in terms of the ease with which they can be diagnosed, and some, like bladder problems could capture conditions of multiple etiologies. Use of self-reported diagnoses may have led to low prevalence estimates for prostatitis, a particularly difficult condition to diagnose. Despite this, overall prevalence and heritability estimates are consistent with previous studies suggesting that our data are representative.[28] Twins in this sample were, on average, 61 years old and may not have passed through the risk period for prostatitis, which becomes more prevalent with age.[9] Thus, comorbidity and prevalence may increase with time. While receiving specialized care following an initial urinary diagnosis may slightly increase the rates of comorbidity among these conditions, it is not likely to inflate the genetic relationship and genetic correlations among them. We lacked longitudinal data that would give us the natural history and progression of these conditions and further inform the nature of the comorbidity relationship. Future studies may want to validate our findings with confirmed diagnostic data and examine the association of prostatitis and other urinary conditions over time, and in the context of severity and treatment. Evaluating age of diagnosis across twins would also be helpful in understanding the development of these conditions. Despite these limitations, use of this genetically-informative sample and robust statistical approaches substantially extends the work to date by examining the sources of variance and etiology in these important urological conditions.

CONCLUSION

In summary, we identified a common, genetically-influenced factor that accounts for much of the comorbidity among these conditions. Along with genetic influences, nonshared environmental factors also make a significant contribution. Because our results suggest the presence of common etiologic influences, further research should focus on identifying explanations for this common cause and sources of unique etiology. Further biometric and molecular genetic research can target common biological mechanisms, explore changes in genetic influences over the life course, and the interplay of genetic and environmental

factors. Understanding the nature of this common etiology may have implications for diagnosing and treating prostatitis and other urological conditions.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.04.005.

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