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Characterizing the Phenotype of Advanced Pelvic Organ Prolapse

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Abstract

Objective—Genetic studies require a clearly defined phenotype to reach valid conclusions. Our aim was to characterize the phenotype of advanced prolapse by comparing women with stage III to IV prolapse with controls without prolapse.

Methods—Based on the pelvic organ prolapse quantification examination, women with stage 0 to stage I prolapse (controls) and those with stage III to stage IV prolapse (cases) were prospectively recruited as part of a genetic epidemiologic study. Data regarding sociodemographics; medical, obstetric, and surgical history; family history; and body mass index were obtained by a questionnaire administered by a trained coordinator and abstracted from electronic medical records.

Results—There were 275 case patients with advanced prolapse and 206 controls with stage 0 to stage I prolapse. Based on our recruitment strategy, the women were younger than the controls (64.7 ± 10.1 vs 68.6 ± 10.4 years; $P < 0.001$); cases were also more likely to have had one or more vaginal deliveries (96.0% vs 82.0%; $P < 0.001$). There were no differences in race, body mass index, and constipation. Regarding family history, cases were more likely to report that either their mother and/or sister(s) had prolapse (44.8% vs 16.9%, $P < 0.001$). In a logistic regression model, vaginal parity (odds ratio, 4.05; 95% confidence interval, 1.67–9.85) and family history of prolapse (odds ratio, 3.74; 95% confidence interval, 2.16–6.46) remained significantly associated with advanced prolapse.

Conclusions—Vaginal parity and a family history of prolapse are more common in women with advanced prolapse compared to those without prolapse. These characteristics are important in phenotyping advanced prolapse, suggesting that these data should be collected in future genetic epidemiologic studies.

Keywords

pelvic organ prolapse; phenotype; genetic epidemiology; family history

Pelvic organ prolapse (POP) is a highly prevalent condition in women¹ with demonstrated negative impact on patients' quality of life² and considerable cost associated with management and treatment.^{3,4} Good evidence exists to suggest POP has a genetic etiology. Several studies suggest a familial predisposition or transmission of POP.^{5,6} Further evidence of a genetic contribution to POP was identified in a linkage analysis,⁷ a genomewide association study,⁸ and several candidate gene association studies.^{9–11}

Despite multiple studies providing evidence for a genetic etiology for POP, a clearly established phenotype for POP has not yet been defined. In clinical medicine, the term *phenotype* is rarely used; however, in genetic studies, a clearly defined phenotype is a critical component. Phenotype is defined as the observable traits or characteristics of an organism.¹² Defining a phenotype relies on a systematic selection of distinct features that may be the result of genetic influences. The more recent focus on understanding the genetic etiology of complex diseases underscores the importance of carefully defining phenotypes of disease. In fact, the National Institutes of Health has funded the PhenX Toolkit to provide standard measures, phenotypic traits, and environmental exposures of complex diseases for the use of investigators in genomics-based studies.¹³

Several studies have evaluated risk factors for POP. Most often, POP is described as having a multifactorial etiology, and a multitude of factors have been identified that affect the risk of prolapse including age, race, family history, number of vaginal births, body mass index, connective tissue disease, and chronic constipation.^{14–17} In general, however, data from formal phenotyping studies regarding POP is quite limited. Given this knowledge gap, the aim of this study was to characterize the phenotype of advanced POP by comparing women with stage III to stage IV prolapse to women with stage 0 or I prolapse.

MATERIALS AND METHODS

This is a case-control study comparing the phenotypic characteristics of women with advanced POP to those with none to minimal prolapse. We prospectively recruited subjects from an academic urogynecologic practice from February 2009 to December 2010 after institutional review board approval. Cases were defined as women with stage III to stage IV prolapse based on the POP quantification (POP-Q) examination, and controls were women with stage 0 to stage I prolapse and no history of prolapse surgery. We excluded pregnant women, women with a gynecologic malignancy, or those with connective tissue diseases, including Marfan or Ehlers-Danlos syndromes.

This is a secondary analysis of clinical data obtained prospectively for a genetic epidemiologic study.¹⁸ Because the primary investigation was to investigate candidate genes for advanced prolapse,⁹ we attempted to concentrate on the genetic effect by recruiting more extreme phenotypes, which is a common approach in genetic epidemiologic studies. For example, we did not include stage II prolapse in our definition of cases or controls to evaluate advanced versus none/minimal prolapse. In addition, although we recruited subjects of all ages with advanced prolapse, we preferentially enrolled younger subjects with more advanced disease to select a “high risk” group with a presumably higher genetic load.^{18–20} We also preferentially recruited older women as controls given the higher prevalence of prolapse with increasing age. This strategy was used to avoid younger controls that are still at risk for developing prolapse, but they have not yet reached a sufficient age to manifest the disease. Whereas we did not have specific age cutoffs for controls or cases, as a general rule, we opted to recruit controls who were postmenopausal, and ideal cases were those who were premenopausal.

For this analysis, we focused on the nongenetic data of our cases and controls. Information regarding sociodemographics, family history of prolapse or hernia, obstetrical history, medical history, and surgical history were obtained directly from participants using a questionnaire, which was administered by a trained coordinator and completed at the time of enrollment. With regard to family history, subjects were specifically asked, “Did your mother have any problems with prolapse or undergo any surgeries for prolapse?” Similarly, the subjects were asked if they had sisters and if so, “Does/did your sisters have any problems with prolapse or undergo any surgery for prolapse?” Subjects were then asked, “Does/did anyone in your family have any problems with a hernia or undergo surgery for a hernia?” and if yes, which family member had a hernia or hernia surgery. Responses were then characterized as to whether or not the history of hernia was reported in a first-degree relative.

Medical history questions were aimed at obtaining data for calculation of a Charlson comorbidity index, a validated questionnaire.²¹ Subjects were also asked specifically about a medical history of chronic constipation, chronic cough, and smoking history. Data regarding prior hysterectomy, prior prolapse repair, and prior surgery for urinary incontinence were also obtained. Medical and surgical history details were supplemented with information from electronic medical record and operative reports when appropriate. Physical examination characteristics, including POP-Q examination, height and weight, were abstracted from electronic medical records. Each vaginal compartment was characterized independently, such that advanced prolapse in the anterior compartment was defined as Aa or Ba points +1 or greater, advanced prolapse in the posterior compartment was defined as Ap or Bp points +1 or greater, and advanced prolapse in the apical compartment was defined as C or D points +1 or greater.

We compared the sociodemographics, family history, obstetrical history, medical history, surgical history, and body mass index (BMI) between cases and controls using the χ^2 , Fisher exact, Student *t*, and Mann-Whitney *U* tests where appropriate. A multivariate logistic regression was also performed using white race, chronic constipation, vaginal parity, POP in mother and/or sister, hernia in first-degree relative, and mean BMI (kg/m²) as covariates. All statistical analyses were performed using IBM SPSS (version 19.0, Chicago, IL) and significance was defined as *P*<0.05.

RESULTS

A total of 481 subjects were recruited and enrolled in the genetic epidemiologic study. Data from all subjects participating in the primary study were included. Of these, 275 subjects (57.2%) were cases of advanced prolapse, and 206 (42.9%) were controls with none to minimal prolapse (Table 1). On physical examination, 84.7% of the cases had advanced anterior prolapse, 40.1% had advanced apical prolapse, and 34.7% had advanced posterior prolapse.

As expected, based on the recruitment strategy of the primary study, cases were younger than controls, with mean±SD ages of 64.7±10.1 years versus 68.6±10.4 years (*P*<0.001), respectively (Table 2). No difference existed between cases and controls with regard to race, with the predominant race in both groups being white. In addition, no differences existed between cases and controls in mean BMI (27.9±5.1 vs 28.9±6.7 [*P*=0.07], respectively), constipation, current tobacco use, or history of surgery for urinary incontinence. Most cases had a history of prior prolapse surgery (77.8%). Cases were more likely than controls to be parous (96.0% vs 90.8%; *P*=0.02) and specifically to have had 1 vaginal delivery or more (vaginal parity; 96.0% vs 82.0%; *P*<0.001; Table 2).

Regarding family history, cases were more likely to report prolapse in their mother and/or sister (44.8% vs 16.9%; $P<0.001$). Specifically, a significantly greater proportion of women with advanced prolapse reported prolapse history in their mother (33.5% vs 11.3% [$P<0.001$], respectively) and their sister(s) compared to controls (15.2% vs 4.6% [$P<0.001$], respectively). No difference was demonstrated in the history of hernia in first-degree relatives between cases and controls, respectively (34.7% vs 26.8%; $P=0.09$). In a logistic regression model, which adjusted for white race, BMI, constipation, vaginal parity, family history of prolapse, and family history of hernias, vaginal parity (odds ratio, 4.05; 95% confidence interval, 1.67–9.85) and family history of a mother and/or sister with prolapse (odds ratio, 3.74; 95% confidence interval, 2.16–6.46) remained significantly associated with advanced POP (Table 3).

DISCUSSION

A well-established phenotype is a necessary component of any genetic study. Given the recent focus and development of genetic studies into the etiology of POP, formally defining the phenotype of POP is an important factor in the continued growth and expansion of this area of research. Our findings suggest that in defining a POP, family history is an important factor. In addition, our work supports the idea that POP is likely multifactorial in etiology, as evidenced by vaginal parity and family history of prolapse, both being more common in women with advanced prolapse compared to those without prolapse.

Prior studies have also demonstrated that family history is a risk factor for POP.^{5,6,22} Our data support this theory, however, within the contextual framework of a genetic epidemiologic study aimed at formally defining the phenotype of advanced prolapse. Specifically, this was achieved by selecting more extreme phenotypes, which allowed us to identify associations. Our results subsequently underscore the role of family history in the POP phenotype as well as the importance of capturing family history data when performing genetic epidemiologic studies of POP.

Parity and vaginal parity have previously been reported as risk factors for POP.²² In one large population study of women ages 40 to 69 years, one or more vaginal deliveries were found to have 3- to 5-fold higher odds of symptomatic prolapse compared to women without a history of vaginal parity.²³ Our data demonstrated a similar effect in that subjects with advanced prolapse were more likely to have a history of parity and vaginal parity than those without advanced prolapse.

Although several other studies have suggested additional risk factors for POP, including age, race, body mass index, connective tissue disease, and chronic constipation,^{14–17} no significant associations were identified in this investigation. One factor explored in this study, but not typically included in the list of risk factors for prolapse, is family history of hernia. Although not found to have a statistically significant association with prolapse in our analysis, Lammers et al²⁴ reported that subjects with prolapse had a higher rate of collagen-associated disorders defined as inguinal hernia, umbilical hernia, arterial aneurysm, cardiac valve prolapse, varicose veins, intervertebral disc displacement, joint hypermobility, and rectal prolapse.²⁴ Further exploration into collagen-associated disorders as a group and how this may factor into a prolapse phenotype may prove valuable.

This study has several unique strengths. Primarily, this is a novel approach to clinically phenotyping prolapse based on sound genetic study design principles. In addition, despite several studies suggesting a genetic etiology or contribution to prolapse, a clearly defined phenotype for prolapse has not been established. Scientific investigation into the establishment of an advanced prolapse phenotype has been limited. Furthermore, no

phenotyping data on prolapse exists on the National Institutes of Health supported PhenX catalog despite the high prevalence of this disorder. Finally, this study purposefully included subjects with more advanced prolapse groups, stage III and stage IV, to represent cases. This strategy ensured that prolapse consistently believed to be symptomatic was included, whereas omission of subjects with only stage II prolapse, avoided the considerable variability in the degree of bother associated with less severe prolapse.

A limitation of our study was that family history data were obtained through the individual subject. Medical records or operative reports were not used to confirm these data; therefore, this could affect the reliability of our data. Further, the degree of prolapse in family members was not included nor was the type or number of procedures sought for correction of prolapse. In addition, it is likely that the presence of prolapse may have been underreported by family members given the personal nature of the disease. Similar limitations are likely to exist in the accuracy of reporting on family history of hernias. Another potential limitation is that our study population was particularly homogenous with regard to race. Several studies have reported on varying rates of and risk factors for POP in different racial/ethnic groups.^{23,25} As such, the external validity of our results may be somewhat limited. Furthermore, our population was also recruited from a urogynecology practice, where patients are more likely to have pelvic floor disorders compared to the general population. Finally, although our data suggest that family history, parity, and vaginal parity are important components of the prolapse phenotype, misclassification due to a poorly defined phenotype can lead to a type I or type II error. This underscores the need for further investigation to better define the phenotype of prolapse.

In conclusion, phenotyping disease is crucial to the advancement of genetic studies. Our work suggests that parity and family history of prolapse are important components of an advanced POP phenotype. With a more standardized prolapse phenotype, the probability of identifying genetic risk factors in genetic epidemiologic studies will be improved, such that one day, physicians may be able to use this genetic information to risk stratify patients. Although genetic risk factors for prolapse are nonmodifiable, identification of high-risk patients would allow providers the opportunity to advise patients on preventive measures or specific treatment options. Future directions for expanding our understanding of the genetic components of prolapse may include exploring the interplay between genetic and environmental factors that impact prolapse, as well as family history with considerations made for racial and ethnic differences. Finally, given the importance of family history in the prolapse phenotype, valuable future investigations should explore ideal methods for obtaining and characterizing family history for the use in genetic epidemiologic studies of this highly prevalent condition, which significantly affects quality of life.

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TABLE 1

Pelvic Examination Findings

	<u>Cases</u>	<u>Controls</u>
Prolapse Description	n=275	n=206
Stage of POP, n (%)		
0	–	121 (58.7)
I	–	85 (41.3)
II	–	–
III	256 (93.1)	–
IV	19 (6.9)	–
Advanced anterior prolapse (Aa or Ba +1)	232 (84.7)	0 (0)
Advanced apical prolapse (C or D +1)	110 (40.1)	0 (0)
Advanced posterior prolapse (Ap or Bp +1)	95 (34.7)	0 (0)

TABLE 2**Sociodemographic Characteristics, Medical History, and Family History**

Characteristic	Cases	Controls	P
	n=275	n=206	
Mean age, yrs	64.7±10.1	68.6±10.4	<0.001
White race	247 (89.8)	190 (92.2)	0.36
Mean BMI, kg/m ²	27.9±5.1	28.9±6.7	0.07
Charlson comorbidity index	0 (0, 1)	0 (0, 1)	0.90
Constipation	60 (22.2)	34 (17.0)	0.16
Current tobacco use	18 (6.6)	9 (4.4)	0.29
Prior prolapse surgery	214 (77.8)	0 (0)	<0.001
Prior incontinence surgery	107 (39.1)	76 (36.9)	0.63
Parous	264 (96.0)	187 (90.8)	0.02
Vaginal parity	263 (96.0)	169 (82.0)	<0.001
Prolapse in mother and/or sister	86 (44.8)	26 (16.9)	<0.001
Prolapse in mother	63 (33.5)	18 (11.3)	<0.001
Prolapse in sister	40 (15.2)	9 (4.6)	<0.001
Hernia in first-degree relative	82 (34.7)	44 (26.8)	0.09

* Data are presented as n (%), mean ± SD, or median (IQR).

TABLE 3**Subjects' Characteristics in a Multivariate Logistic Regression**

Characteristic	Adjusted Odds Ratio (95% CI)	P
White race	0.68 (0.28–1.68)	0.40
Chronic constipation	0.90 (0.49–1.62)	0.71
Vaginal parity	4.05 (1.67–9.85)	0.002
POP in mother and/or sister	3.74 (2.16–6.46)	<0.001
Hernia in first-degree relative	1.21 (0.72–2.02)	0.48
Mean BMI, kg/m ²	0.98 (0.94–1.02)	0.34

CI, Confidence interval.