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ORIGINAL ARTICLE

The familiality of pelvic organ prolapse in the Utah Population Database

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Abstract
Introduction and hypothesis Pelvic organ prolapse (POP) in women is a common condition whose etiology is poorly understood. There is increasing evidence that POP is heritable. The aim of our study was to define and evaluate familial clustering of POP.
Methods Using a population-based Utah genealogy linked to more than a decade of hospital data, we calculated relative risks (RR) of POP in female relatives of women with POP using age- and birth year-specific rates of POP. We compared the average pairwise relatedness of all POP cases to the population using a measure of genetic distance.
Results We identified 1,292 women with diagnostic and procedure codes for POP. The RR of POP was significantly elevated in first- and third-degree female relatives (RR 4.15, $p<0.001$; RR 1.24, $p=0.05$). The average pairwise relatedness for all individuals with POP was significantly higher than expected ($p<0.001$).
Conclusions These results strongly support a significant heritable contribution to POP.

Keywords Familiality · Pelvic organ prolapse · Family history · Genetics · Population database · Genital prolapse

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Introduction

Pelvic organ prolapse (POP) is common in women, and mild degrees of prolapse to just above the vaginal opening occur in half of middle-aged women [1]. The health care cost of surgical treatment for POP in the USA alone totals more than US$1 billion annually [2]. Little is known about the etiology or prevention of this condition, and most research has focused on childbirth injury to the muscles, connective tissue, and nerves of the pelvis [3]. While vaginal delivery is the best known risk factor, cesarean delivery does not completely prevent the development of pelvic floor disorders later in life [4]. Many questions remain about why some women develop POP after a single vaginal delivery, while other highly parous women do not develop prolapse [5].

Preliminary studies suggest that family history may be second only to childbirth as a risk factor for POP [4, 6], but there may be ascertainment bias in studies collecting information from the proband alone [7] (women with these conditions may be more likely to know about relatives who have the same condition compared to women without). Studies using independent, self-reported information have demonstrated a familial contribution to POP [4], single family transmission has been reported [8], and a biologically plausible genetic variation suggested [9]. We have recently reported linkage to chromosome 9 in families with two or more women surgically treated for POP [10].

Population databases represent another path to exploring the familiality of complex conditions and have been used to

study the familial and genetic contributions to breast cancer [11] and some gynecological conditions [12]. The aim of this study was to investigate familial clustering in POP using a large Utah population database linked to genealogy records; we hypothesized that we would observe excess relatedness among women with POP.

Materials and methods

The Utah Population Database

We used a powerful and unique population-based resource called the Utah Population Database (UPDB) that links genealogy information to medical diagnosis data; this allows us to study the familial and genetic contribution to multiple diseases including many cancers [13]. The UPDB includes the genealogy of the original Utah pioneers and their descendants, computerized and record-linked in the 1970s, with additional genealogy data obtained from Utah birth and death certificates going forward. Over 2.2 million individuals in the UPDB have at least 3 generations of genealogy data, ranging from 3 to 10 generations. The genealogical data have been record-linked to the medical diagnoses and procedures for 1.5 million Utah individuals treated at the University of Utah Health Sciences Center (UUHSC) from 1994 to the present. We have previously presented the data and methods used here to describe the familial and genetic contribution to multiple different diseases [13–15].

Identification of case subjects

We used specific ICD-9 diagnosis codes for POP and CPT-4 procedure codes for surgical repair of prolapse to identify women with POP who also have genealogy data: these are listed in Appendix 1. The database is continually updated for changes in international diagnostic and procedure coding. Because the University of Utah is a tertiary care referral center, most diagnostic codes indicate POP severe enough to warrant treatment, usually surgery. Cases were required to have at least three generations of genealogy to be included in the analysis.

Controls

We randomly selected matched control individuals who were also hospital patients and who had linked genealogy data and who were not POP cases. Although all University of Utah hospital patient records have been linked to the UPDB genealogy, only a selected subset of these records can be accessed at any time due to privacy concerns. A set of randomly selected hospital patients was identified, representing 20 % of all University of Utah hospital/clinic patients who also have linked genealogy data, and controls were randomly selected from this larger set. To allow appropriate matching for sex, age, and quality and quantity of genealogy data, we created cohorts to which all UPDB genealogy members (and also all hospital controls) were assigned. All 2.2 million individuals with genealogy data in the UPDB were assigned to 1 of 264 cohorts. These cohorts are based on sex, birth year, birthplace (Utah or not), and presence of ancestral genealogy data (or not). One thousand sets of cohort-matched controls were chosen randomly from this set of hospital controls to match the POP cases for the Genealogical Index of Familiality (GIF) analysis; two matched controls were selected for the relative risk (RR) analysis.

Calculation of RR in relatives

We estimated the RR of POP by comparing the observed number of affected women among relatives of POP cases to the expected number. The expected number of affected women was estimated by counting the number of affected women among two sets of matched controls. We randomly selected two matched hospital controls for each POP case and counted the number of affected relatives of these matched controls without duplication. We estimated the RR among first-, second-, and third-degree relatives of cases as the classic case-control odds ratio of observed/expected (OR). The significance of the test of the null hypothesis $RR=1.0$ was determined by a Fisher's exact test for the 2×2 table. Confidence intervals (CI) for the RR were estimated as given by Agresti [16]. One-sided probabilities for the alternative hypothesis test of $RR>1.0$ were calculated under the null hypothesis $RR=1.0$, under the assumption that the number of observed cases follows a Poisson distribution with the mean equal to the expected number of cases. All female relatives of the POP case and her matched controls, who had been diagnosed or treated at the University based on POP ICD-9 and CPT-4 codes, would be identified in this method. While some relatives and controls will have been treated for POP at other institutions, the power of the UPDB is in the size of the genealogy in this database: each affected individual and her controls will have similar likelihoods of having been treated at our institution or elsewhere, as will their relatives.

Calculation of the GIF

Another tool used in population databases to assess familiality is the GIF statistic. This statistic, developed for use with the UPDB, measures the average pairwise relatedness of all possible pairs of individuals in a group (e.g., POP cases) and compares the measure to the average relatedness

expected in this population [13, 17, 18]. The GIF statistic uses the Malécot coefficient of kinship, which measures the probability that a pair of individuals share a homologous piece of a chromosome identical by descent from a common ancestor. The average pairwise relatedness of the set of cases (women with POP) is compared to the distribution of the average pairwise relatedness statistic estimated for 1,000 independent sets of matched controls to provide an empirical test of significance. The 1,000 sets of matched controls are chosen randomly from the set of 2.2 million individuals with genealogy data in the UPDB, matched on sex, 5-year birth year, and birthplace (Utah or not).

The GIF test determines whether the average relatedness of cases is significantly greater than expected, using all relationships observed among the POP cases. Because both close and distant relationships are observed, the GIF statistic will show excess relatedness in the presence of genetic effects, but also in the presence of familial, but nongenetic effects. For this reason, we also tested the hypothesis of no excess relatedness with a modified GIF statistic, which ignores all close relationships (first- and second-degree relatives). A significant result for this "distant" GIF test provides evidence for excess relatedness in distant relatives only and strongly supports the hypothesis of a genetic contribution to the trait studied.

No patient identifiers were used in this study; all analysis of genetic relationships between affected individuals is nonidentifiable. The University of Utah Institutional Review Board and the Resource for Genetic and Epidemiologic Research (RGE), which oversees all research involving the UPDB, approved this study.

Results

We identified 1,292 individual women with POP who were patients in the UUHSC between 1994 and 2005 and who also record-linked to at least 3 generations of genealogy data in the UPDB. Of the POP cases, 1,132 had at least one child and 160 had no record of any children in the UPDB.

Estimated RR in female first-degree relatives of POP cases are shown in Table 1, including the number of female first-degree relatives, observed and expected number of POP cases among these relatives, and the 95 % CI and one-sided significance. RR in all first-degree relatives combined and in each subset of first-degree relatives (mothers, sisters, and daughters) are significantly elevated. Estimated risks for second- and third-degree relatives of POP cases are shown in Table 2. RR for both second- and third-degree relatives are elevated, but only the risk to third-degree relatives is significantly elevated.

We tested the hypothesis of no excess average relatedness among POP cases using the GIF statistic; results are summarized in Table 3. The average relatedness of women with POP is significantly higher than expected ($p<0.001$). When close relationships are ignored (to reduce the effect of shared environment), the cases still show significantly higher relatedness than expected ($p<0.001$). Because number of offspring is a recognized risk factor for POP, and because this factor might also be associated with average relatedness, we also performed the GIF analysis for the subsets of POP cases with and without offspring. The results for these two subsets of POP cases are also shown in Table 3; both subsets show results similar to the group of all POP cases.

As discussed in the Materials and methods section, the GIF statistic analyzes all pairs of POP cases. The contribution of "relatedness" for each pair of relatives contributes to the overall GIF statistic. We can consider the contribution from each different type of relative pair (from close relatives to distant) by displaying the contribution to the GIF by the genetic distance between the pair of relatives ('1'- parent/offspring, '2'-sisters, '3'- aunts/nieces, etc.). The genetic distance differs from, but is correlated with, degree of relationship. Figure 1 illustrates the contribution to the GIF statistic by the genetic distance between pairs for all relationships observed, for cases compared to 1,000 sets of matched controls. The figure illustrates the results of Table 2 and shows that POP cases have relatives with POP who are both close and distant, in excess of what is expected in this population. An excess of pairs of more distant relatives is clear for genetic path lengths 4-7.

Discussion

Using the UPDB, we observed evidence for a significant heritable contribution to POP. There was increased risk of POP in female relatives of women diagnosed and treated for

Table 1 RR estimates in first-degree relatives of 1,292 POP cases

Relationship	Number of relatives	Observed	Expected	RR	One-sided significance	95 % CI
All first-degree	11,430	55	13.2	4.15	<0.001	3.13–5.41
Mothers	2,391	13	2.2	5.85	<0.001	3.12–10.01
Sisters	4,843	30	7.9	3.80	<0.001	2.56–5.42
Daughters	4,261	14	3.2	4.40	<0.001	2.40–7.38

Table 2 RR estimates for second- and third-degree relatives of 1,292 POP cases

Relationship	Number of relatives	Observed	Expected	RR	One-sided significance	95 % CI
Second-degree	35,020	25	20.3	1.28	0.12	0.84–1.88
Third-degree	70,581	63	50.7	1.24	0.05	0.95–1.59

POP, in both close and distant relatives, as estimated by familial RR and a comparison of average relatedness (GIF statistic).

It is difficult to discriminate between shared genes and environment when considering first-degree relatives only. Significantly elevated risks in first-degree relatives may be indicative of genetic factors, but may also only represent shared environment, or some mixture of both factors, since first-degree relatives share both genes and environment. By considering multiple degrees of relatedness, the UPDB represents a unique instrument to explore relationships between genetics and disease. Using the UPDB, we were able to additionally consider more distant genetic relationships in our exploration of a genetic predisposition to POP. We observed significantly increased risk for POP even in distant relatives, suggesting that genetic factors contribute to at least some POP cases.

In our population, the RR for second-degree relatives of women with POP is elevated, but not significantly. This may represent the small window of view we have to identify POP diagnoses, since our hospital data are only available from 1994 to 2005. This limitation is likely the result of underascertainment of relationships that cross generations, such as grandmother/granddaughter or aunt/niece relationships, generations that have yet to develop conditions such as POP. While most second-degree relationships cross generations (except half siblings), third-degree relatives, in contrast, are mostly in the same generation (cousins). Increased RR estimates in third-degree relatives, who are unlikely to have cohabited, is indicative of a genetic, rather than just "familial," risk for POP.

Strengths of our study include the largest genealogy population database available for study, with a heterogeneous European population generalizable to much of the US population [17–19]. Linking of genealogy data with clinical diagnostic code data for POP began in 1994, and the validity of our phenotyping is strengthened by the fact that one senior urogynecologist made most of these diagnoses at the University of Utah (PAN). Given that most POP cases were identified by surgical coding, our findings may underestimate the strength of the association we might have found had we been able to examine all subjects. A limitation of using a population database is that it can be used to estimate genetic associations, but such a database does not replace the estimates made in conventional clinical investigations.

POP is likely a multifactorial condition, with inciting and promoting risk factors that ultimately determine whether prolapse develops to a bothersome degree in any individual woman [20]. Studies examining risk factors for POP often do not include family history. First-degree relatives are often the only relationships examined, because information for more distant relatives can be difficult to collect and potentially unreliable because of underreporting or ascertainment bias. The UPDB has been used for important genetic advances such as identification of high-risk families which ultimately resulted in finding mutations in the *BRCA1* and *BRCA2* genes resulting in breast cancer and the *APC* gene mutation in colon cancer [21–23]. In other multifactorial conditions, including Parkinson's disease [24], asthma [25], irritable bowel syndrome [26], endometriosis [27], and nonpolyposis colon cancer [28], heritability has proven to be an important risk factor. The UPDB represents US families with European ancestry and has been shown to be a non-inbred population representative of the Caucasian population in the USA [29].

Potential uses of this information include evidence for familiality as a major risk factor in POP, potential identification of a high-risk population for epidemiology and prevention studies, and risk assessment in treating individuals with POP. These results become especially relevant in terms of prevention of POP. Women around the world are requesting and getting cesarean deliveries to protect the pelvic floor, even though their specific risk may be unknown [30]. The long interval between the occurrence of known

Table 3 GIF test for excess relatedness of POP cases

					Ignoring close relatives		
Cases	*n*	Case GIF	Mean control GIF	*p*	Case GIF	Mean control GIF	*p*
POP	1,292	3.84	2.76	<0.001	2.77	2.43	<0.001
POP with children	1,132	3.81	2.23	<0.001	2.75	1.95	<0.001
POP without children	160	3.76	2.07	0.034	3.76	1.84	0.001

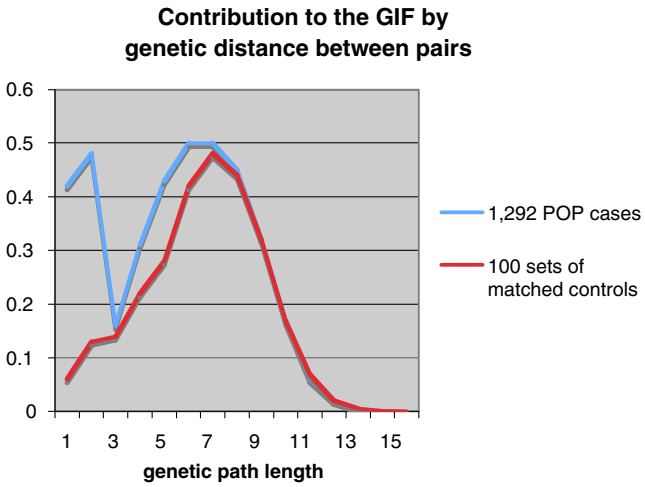

Fig. 1 Contribution to the GIF statistic for POP by genetic distance between all pairs

risk factors for POP and the end-stage clinical presentation has hampered study of its natural history. Instead, we can use the knowledge that POP is familial to identify at-risk women to study for prevention and treatment efforts; the fact that such women are at increased risk for POP makes such research more efficient, e.g., studies have more power to assess and compare various treatments. The results reported here strongly suggest genetic contributions to risk for POP; studies of the high-risk pedigrees represented in this report can identify candidate genes and test preventive mechanisms in high-risk women; genetic research may play an important role in decreasing the lifelong burden of POP.

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Appendix 1

ICD-9 diagnostic codes:

All genital prolapse codes (618 series)

CPT-4 procedure codes:

Colpocleisis (57120)
Pessary (57160)
Anterior colporrhaphy (57240)
Posterior colporrhaphy (57250)
Combined anterior and posterior colporrhaphy (57260)
Combined anterior and posterior colporrhaphy, with vaginal repair of enterocele (57265)
Vaginal repair of enterocele (57268)
Abdominal repair of enterocele (57270)
Abdominal repair of vaginal vault prolapse, abdominal sacrocolpopexy (57280)
Vaginal repair of vaginal vault prolapse, extraperitoneal approach (57282)
Vaginal repair of vaginal vault prolapse, intraperitoneal approach (57282)
Paravaginal repair (57284)

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