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RISK OF ASSOCIATED CONDITIONS IN RELATIVES OF SUBJECTS WITH INTERSTITIAL CYSTITIS

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Abstract

Objectives—Urological chronic pelvic pain syndrome (UCPPS) includes interstitial cystitis/painful bladder syndrome (IC/PBS), a chronic, bladder pain condition of unknown etiology. IC/PBS can co-occur with a number of associated conditions such as irritable bowel syndrome and fibromyalgia. The purpose of this study is to estimate the heritability of approximately 20 associated conditions in first-, and if appropriate second-, and third-degree relatives of IC/PBS cases to identify shared genetic contributions for the disease combinations.

Methods—We used the Utah Population Database (UPDB), a unique population-based genealogical database that has been linked to electronic health records for the University of Utah Health Science Center back to 1994. IC/PBS probands were identified by ICD-9 code for chronic interstitial cystitis and had genealogy information for 12 of their 14 immediate ancestors. We calculated excess risk of an associated condition in relatives of IC/PBS cases using relative risk estimates.

Results—We identified 248 IC/PBS probands. We found that two associated conditions, myalgia and myositis/unspecified (fibromyalgia) and constipation, were in significant excess in IC/PBS cases themselves, their first-degree relatives and their second-degree relatives. The excess risk among relatives between IC/PBS and these associated conditions also held in the converse direction. Excess risk of IC/PBS was observed in first- and second-degree relatives in probands with myalgia and myositis/unspecified (fibromyalgia) and in probands with constipation.

Conclusion—These results suggest myalgia and myositis/unspecified (fibromyalgia) and constipation are likely to share underlying genetic factors with IC/PBS.

Keywords

Urological chronic pelvic pain syndrome (UCPPS); interstitial cystitis/painful bladder syndrome (IC/PBS); comorbid conditions; familial risk

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Introduction

Urological chronic pelvic pain syndrome (UCPPS) is a global term that includes Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). IC/PBS is a chronic, bladder pain condition that includes urgency, frequency, and/or nocturia. The underlying etiology for IC/PBS is poorly understood and it is often considered a heterogeneous disease. The prevalence of the IC/PBS in females in the United States based on self-report ranges between 2.7% and 6.5% based on definitions of high specificity and sensitivity, respectively.[1] In males, the prevalence of IC/PBS ranges between 1.9% and 4.2% based on high specificity and sensitivity definitions.[2] IC/PBS greatly impacts quality-of-life, employment, and relationships.[3]

IC/PBS often presents with the co-occurrence of other conditions including irritable bowel syndrome, fibromyalgia, and migraines (e.g., [4–9]). A few studies have investigated the risk of associated conditions in relatives of IC/PBS cases for identification of a potential syndrome [10–12]. These studies provide evidence that co-occurrence of IC/PBS and other associated conditions takes place not only within IC/PBS cases but also across their relatives. However, these studies have typically focused on a limited number of families, required a self-report of symptoms, required subject/family participation, and have studied only a limited number of associated conditions.

In this study, we estimate the relative risk of approximately 20 associated conditions in IC/PBS cases and their first-degree relatives (and if appropriate, second- and third-degree relatives) based on uniform physician-diagnosis codes (i.e., ICD-9 codes). We hypothesize that study of the heritability of IC/PBS and associated conditions will identify shared genetic contributions for the disease combinations and may lead to identification of more homogeneous subgroups of IC/PBS which will be very useful for future genetic studies.

Materials and Methods

Utah Population Database (UPDB)

We used the Utah Population Database (UPDB), a unique population-based, computerized genealogical database for the state of Utah. The UPDB was originally comprised of genealogical records of Utah, compiled by members of The Church of Jesus Christ of Latter-day Saints, and submitted to the Genealogical Society of Utah.[13, 14] The original genealogy had approximately 1.6 million individual records for 186,000 three-generation families. Utah birth certificate information (mother, father, and child) has since been linked to extend the genealogy to the present day. The UPDB now includes nearly 15 million records; some pedigrees are up to 11 generations. The UPDB is one of only two such population-based genealogy databases in the world, the other being in Iceland. Electronic patient records for the University of Utah Health Science Center (UHHSC) have been linked to the UPDB genealogy information back to 1994 for 1.7 million patients. Rates of medical record linking to the UPDB vary slightly according to sex (e.g., women because of surname changes with marriage are more difficult to link), diagnosis, birthplace (e.g., individuals born outside of Utah are more difficult to link) and year of birth, but have averaged 50% for

hospital data. Diagnosis data stored in the UUHSC electronic medical record are coded to ICD-9 and CPT-4 codes.

Our study was approved by the University of Utah Institutional Review Board and the Utah Resource for Genetic and Epidemiological Research (RGE). Informed consent was waived in order to protect the privacy of subjects; names and other identifying information were not available to the authors of the study.

Diagnosis Codes for IC and Associated Conditions of Interest

IC/PBS probands were identified by the ICD-9 code of 595.1 (chronic interstitial cystitis). We selected associated conditions that may share some of the possible underlying causes of IC/PBS, including neuropathic pain, inflammatory dysfunction, abnormality of the bladder epithelium, and mast cell activation. We chose associated conditions that have been observed by others to co-occur with IC/PBS [8, 15, 16] as well as other conditions of interest. Associated conditions were required to have at least 200 UUHSC patients who met the genealogy requirement to be included in our list. Table 1 lists associated conditions of interest, corresponding ICD-9 codes used for this study, and the number of subjects with the condition.

Estimation of Relative Risk (RR)

The Relative Risk (RR) is an estimation of the risk of a disease among relatives of a set of probands compared to the general population, and it provides a way of determining the significance of familial clustering. For a heritable disease or heritable composite of diseases, the risk of the disease(s) will be higher among relatives compared to the general population.

For all subjects involved in this study, we required them to have genealogy information available for parents, all four grandparents, and six of eight great grandparents (i.e., 12 of their 14 immediate ancestors or at least three generations of genealogy information). This genealogy requirement helps to ensure that genealogy quantity and quality are matched in cases and controls. There were 354,738 UUHSC patients who met our strict genealogy requirement and were used in this analysis.

We compared the observed number of cases with an associated condition in relatives of a IC/PBS case to the expected number with the associated condition in relatives, based on population rates. Only relatives who were also patients at UUHSC were considered in this analysis. The number of observed cases with an associated condition was counted, without duplication, in the IC/PBS cases and in their first-degree relatives. Risk of the associated condition was estimated in second- and third-degree relatives if the risk in first-degree relatives was found to be significant. To estimate the expected number of cases, population rates for each associated condition were required. Population rates for each associated condition were based on assigning all individuals in the UPDB who linked to electronic health records at the UUHSC into 137 cohort specific bins based on sex, birth place (Utah or elsewhere), and 5-year birth cohorts [34 birth-year cohort bins*2 sex bins*2 birthplace bins=136 bins +1 unknown sex bin]. Cohort specific rates for each associated condition were estimated by dividing the number with the associated condition in each cohort by the total number in the cohort. The RR was estimated among relatives of cases as the ratio of

observed to expected number of cases with the associated condition. The RR is assumed to follow a Poisson distribution with the mean value equal to the number of expected cases with the associated condition among relatives of IC/PBS cases. We have used this methodology for the study of multiple diseases.[17–22]

Results

We identified 248 subjects with a diagnosis of chronic interstitial cystitis; 228 females and 20 males. Table 2 shows the relative risk estimates for each associated condition in the 248 subjects with chronic interstitial cystitis. As can be seen, all associated conditions except diabetes type 1 and lupus erythematosus were found to be in significant excess in the IC/PBS cases. Table 3 lists the relative risk estimates for each associated condition in 761 first-degree relatives, who were also patients at UUHSC, of the 248 subjects with chronic interstitial cystitis. Four of the associated conditions were found to be in significant excess in first-degree relatives. The four associated conditions were irritable bowel syndrome; myalgia and myositis/unspecified (Fibromyalgia); constipation; and anxiety and panic disorder. We also investigated the risk of IC/PBS among first-degree relatives of the IC/PBS probands and observed no cases of IC/PBS, although 0.67 cases were expected.

We further explored the heritability of these four associated conditions in 1,382 second- and 3,091 third-degree relatives of the IC/PBS cases who were also patients at UUHSC; results are shown in Table 4. Myalgia and myositis/unspecified (Fibromyalgia), and constipation were found to be in significant excess in second-degree relatives, but not in third-degree relatives. As constipation can occur with irritable bowel syndrome, we looked for overlap of first- and second-degree relatives who had both constipation and irritable bowel syndrome. Among first-degree relatives, we identified 5 relatives who had both irritable bowel syndrome (5/18 total diagnosed with irritable bowel syndrome) and constipation (5/36 total diagnosed with constipation). Among second-degree relatives, we identified 9 relatives who had both irritable bowel syndrome (9/19 total diagnosed with irritable bowel syndrome) and constipation (9/59 total diagnosed with constipation). Among both first- and second-degree relatives, the majority of those with constipation or irritable bowel syndrome had been diagnosed with only one of the conditions.

As a further test for the strength of the familial relationships of IC/PBS with the two associated conditions, myalgia and myositis/unspecified (fibromyalgia) and constipation; we estimated risk of IC/PBS among first-, second-, and third-degree relatives of probands with each condition, respectively. Results are presented in Table 5. First- and second-degree relatives of probands with myalgia and myositis/unspecified (fibromyalgia) were significantly at increased risk of IC/PBS as were first- and second-degree relatives of probands with constipation.

Discussion

We have examined the familial clustering of IC/PBS with approximately 20 associated conditions. We found that two associated conditions, myalgia and myositis/unspecified (fibromyalgia) and constipation, are in significant excess in IC/PBS cases themselves, their

first-degree relatives and their second-degree relatives. Moreover, the familial relationship between IC/PBS and these two associated conditions holds even in the converse direction. Excess risk of IC/PBS was observed in first- and second-degree relatives in probands with myalgia and myositis/unspecified (fibromyalgia), and in probands with constipation.

It is recognized that IC/PBS is likely to have an underlying genetic component based on first-degree relative studies.[23–25] Excess clustering of a disease in relatives suggests that shared environmental and/or shared genetic factors contribute to the disease process. Excess clustering of a disease in distant relatives, who are less likely to share immediate environments, suggests a genetic contribution. As we observed an excess risk of IC/PBS and these two associated conditions in second-degree relatives who are less likely to share immediate environments, there may be an underlying genetic contribution to the combination of diseases. Perhaps genetic abnormalities behind one condition may cause other seemingly unrelated disorders. However, we cannot rule out shared environmental factors which may also contribute to the combination of the diseases.

The relationship of IC/PBS with fibromyalgia [15, 16, 26, 27] is well established within patients themselves. However, to our knowledge, the risk of these associated conditions in first-, second- and third-degree relatives has not been previously described. As the etiology of IC/PBS is unknown, these associated conditions may lead us to hypothesize the various mechanisms by which these seemingly unrelated conditions co-occur. For example, IC/PBS and fibromyalgia may share common central neurophysiologic mechanisms such as abnormalities in sensory processing, autonomic function, and the hypo-pit-adrenal axis [27] such that these physiological similarities could be attributable to the same genetic etiology. The co-occurrence of constipation with IC/PBS has been assumed to occur because of a joint diagnosis of irritable bowel syndrome and IC/PBS or because of use of medications prescribed to treat IC/PBS (e.g., tricyclic antidepressants). Peters et al. identified constipation in childhood and adolescence as a condition of interest in the natural history of IC/PBS.[28] As we have shown an excess familiarity of IC/PBS and constipation, there may be some shared underlying genetic factors that contribute pathologically to the function of the hypogastric plexus resulting in generalized pelvic pain originating from the bladder and the descending colon. Further understanding of IC/PBS may be gained by taking a multidisciplinary approach to this complex condition, including genetic, bowel, and nerve/muscle specialists.

There are two other studies that examined risk of associated conditions in relatives of IC/PBS cases. Weissman et al. investigated a potential panic disorder syndrome composed of panic disorder, kidney or bladder problems (possibly IC/PBS), serious headaches, thyroid problems, and/or mitral valve prolapse in 34 families ranging in size from 4–34 individuals. [11, 12] We observed an increased risk of chronic headaches, mitral valve prolapse and anxiety and panic disorder in the IC/PBS cases, but only anxiety and panic disorder were observed to be in significant excess among first-degree relatives of IC/PBS cases. Eaton et al. using Danish health registers examined risk of autoimmune disorders among individuals with schizophrenia and their parents and found five autoimmune disorders that appeared more frequently in patients with schizophrenia and their parents: thyrotoxicosis, intestinal malabsorption, acquired hemolytic anemia, IC/PBS, and Sjögren's syndrome.[10] We also

observed an excess risk of Sjögren's syndrome in subjects with IC/PBS but not in their first-degree relatives; we did not investigate any of the other autoimmune disorders. While there may be specific families in our Utah dataset who meet the definition for the panic disorder syndrome described by Weissman et al.[11, 12] or the syndrome of schizophrenia and autoimmune disorders as described by Eaton et al.[10], the majority of our subjects do not fit either syndrome profile.

We are not the first to see that IC/PBS is associated with multiple comorbid conditions. Keller et al. compared 32 medical comorbidities for 9,269 subjects with IC/PBS based on ICD-9 diagnosis codes with 46,345 randomly selected comparison subjects.[7] They found that subjects with IC/PBS had significantly higher prevalence of all comorbid conditions studied, except metastatic cancer. Both our study and the study by Keller et al. show that individuals diagnosed with IC/PBS are likely to be diagnosed with other comorbid conditions. Perhaps because of the difficulty in diagnosing IC/PBS, patients with IC/PBS encounter more physicians and are more likely to be diagnosed with clinically asymptomatic comorbidities. It is also possible because of more physician visits, patients with IC/PBS are more likely to report comorbid conditions than patients without IC. As we have shown in this analysis it is difficult to study comorbid conditions in IC cases themselves. A family approach in studying comorbid conditions as was used here is a means to identify diseases that might share genetic underpinnings.[29]

There are limitations of our study. Our sample size of IC/PBS cases is unexpectedly small. This could be due to several reasons. There are no urologists or urogynecologists at UUHSC who specialize in treating IC/PBS; patients with IC/PBS symptoms may seek treatment elsewhere or we may have many patients at UUHSC with undiagnosed IC/PBS. Despite our small sample size, we have opted to not use broader diagnosis criteria for IC/PBS, and instead use the single specific ICD-9 code (595.1, chronic interstitial cystitis) to define IC/PBS for a more homogeneous sample. We used ICD-9 codes to identify IC/PBS cases and all associated conditions analyzed as part of this study. ICD-9 codes are primarily used as billing codes and a patient may be assigned an ICD-9 code as part of 'ruling-out' a diagnosis, or in error. Because IC/PBS and some of these associated conditions can be difficult to diagnosis, this may be particularly problematic for patients with IC/PBS who encounter physicians often and must have various diseases 'ruled-out'. There may also be additional patients who have IC/PBS or one of the associated conditions who have been censored from this analysis. This includes, for example, individuals who have not sought medical attention, or who received medical care at another facility than UUHSC, or individuals not included in the genealogy data. This type of censoring will primarily result in an underestimation of the true incidence of IC/PBS or any of the associated conditions and relative risk estimates may be conservative. For this study, we analyzed only the risk of one associated condition at a time among relatives of IC/PBS probands. There may be potential syndromes that include a combination of IC/PBS and associated conditions in IC/PBS cases and their family members. Although others have observed an excess familiarity of IC/PBS among first-degree relatives,[24, 25] we did not observe an excess. We attribute the lack of excess familiarity findings for IC/PBS due to our small sample size of cases. Finally, the founding population of Utah originated from northern and western Europe; our results apply to other populations of similar descent.

In conclusion, IC/PBS is most likely a multifactorial disease with genetic and environmental components. We have identified two associated conditions, myalgia and myositits/ unspecified (fibromyalgia) and constipation, that co-occur with IC/PBS, appear more often in extended relatives, and may share underlying genetic factors. Further study of extended families with a significant excess number of cases of these associated conditions and IC/PBS may further our knowledge about IC/PBS etiology.

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Table 1

Associated conditions of interest

	ICD-9	Number with condition and
Irritable bowel syndrome	564.1	2,998
Chronic fatigue syndrome	780.71	827
Sjögren's syndrome/ Sicca syndrome	710.2	744
Myalgia and myositis, unspecified (Fibromyalgia)*	729.1	8,216
Sleep apnea	327.23, 780.51, 780.57	6,725
Chronic headache/migraine	346	9,035
Seizure disorder	345.9, 780.39	6,357
Lupus erythematosus	695.4	374
Endometriosis	617	1,664
Asthma, chronic airway obstruction	493, 496	14,422
Pelvic organ prolapse	618, 569.1	2,471
Stress incontinence	599.81, 599.82, 625.6, 788.33	2,873
Urge urinary incontinence	596.51, 596.54, 596.59, 788.31, 788.33	5,474
Hernia	550–553	7,255
Constipation	564.0	10,713
Hemorrhoids	455.0–455.7	4,684
Diabetes Type 1	250.X1, 250.X3 (where X=0–9)	3,735
Diabetes Type 2	250.X0, 250.X2 (where X=0–9)	15,648
Major depression	296.2, 296.3	8,152
Anxiety and panic disorder	300.00, 300.01, 300.02, 300.09, 300.21	15,071
Mitral valve prolapse	424.0	4,214

* The ICD-9 code used for fibromyalgia is myalgia and myositis, unspecified.

Table 2

Relative Risk (RR) estimates for associated conditions in 248 subjects with IC

	Observed	Expected	RR (95% CI)	p
Irritable bowel syndrome	32	3.44	9.31 (6.37–13.14)	<0.0001
Chronic fatigue syndrome	8	0.92	8.74 (3.77–17.21)	<0.0001
Sjögren's syndrome/ Sicca syndrome	8	1.01	7.89 (3.41–15.54)	<0.0001
Myalgia and myositis, unspecified (Fibromyalgia)	59	9.02	6.54 (4.98–8.44)	<0.0001
Sleep apnea	14	4.72	3.00 (1.62–4.98)	0.0004
Chronic headache/migraine	34	9.20	3.70 (2.56–5.17)	<0.0001
Seizure disorder	14	3.83	3.65 (2.00–6.13)	<0.0001
Lupus erythematosus	<5	0.47	-	-
Endometriosis	17	2.18	7.79 (4.54–12.47)	<0.0001
Asthma, chronic airway obstruction	34	10.92	3.11 (2.16–4.35)	<0.0001
Pelvic organ prolapse	53	4.24	12.49 (9.36–16.34)	<0.0001
Stress incontinence	52	4.73	10.99 (8.21–14.42)	<0.0001
Urge urinary incontinence	84	5.57	15.08 (12.03–18.67)	<0.0001
Hernia	18	5.55	3.25 (1.92–5.13)	<0.0001
Constipation	46	7.92	5.81 (4.25–7.75)	<0.0001
Hemorrhoids	12	4.50	2.67 (1.38–4.66)	0.0024
Diabetes Type 1	5	2.87	1.74 (0.56–4.06)	0.221
Diabetes Type 2	26	14.61	1.78 (1.16–2.61)	0.005
Major depression	37	7.39	5.01 (3.52–6.90)	<0.0001
Anxiety and panic disorder	66	14.28	4.62 (3.57–5.88)	<0.0001
Mitral valve prolapse	15	4.06	3.69 (2.07–6.09)	<0.0001

Table 3

Relative Risk (RR) estimates for associated conditions in 761 first-degree relatives of 248 subjects with IC who are also patients at UUHSC

	Observed	Expected	RR (95% CI)	p
Irritable bowel syndrome	18	7.59	2.37 (1.41–3.75)	0.0009
Chronic fatigue syndrome	<5	2.17	1.38 (0.28–4.03)	0.731
Sjögren's syndrome/ Sicca syndrome	5	2.10	2.38 (0.77–5.56)	0.062
Myalgia and myositis, unspecified (Fibromyalgia)	33	21.73	1.52 (1.05–2.13)	0.019
Sleep apnea	23	17.61	1.31 (0.83–1.96)	0.231
Chronic headache/migraine	26	21.53	1.21 (0.79–1.77)	0.388
Seizure disorder	12	12.38	0.97 (0.50–1.69)	1.00
Lupus erythematosus	<5	1.03	0.97 (0.02–5.42)	1.00
Endometriosis	<5	3.99	0.25 (0.006–1.40)	0.202
Asthma, chronic airway obstruction	35	31.63	1.11 (0.77–1.54)	0.593
Pelvic organ prolapse	11	7.06	1.56 (0.78–2.79)	0.182
Stress incontinence	8	8.13	0.98 (0.43–1.94)	1.00
Urge urinary incontinence	10	12.62	0.79 (0.38–1.46)	0.499
Hernia	19	18.61	1.02 (0.61–1.59)	1.00
Constipation	36	21.51	1.67 (1.17–2.32)	0.0029
Hemorrhoids	17	12.93	1.31 (0.77–2.10)	0.263
Diabetes Type 1	11	8.88	1.24 (0.62–2.22)	0.498
Diabetes Type 2	45	43.02	1.05 (0.76–1.40)	0.819
Major depression	29	20.34	1.43 (0.95–2.05)	0.059
Anxiety and panic disorder	63	36.88	1.71 (1.31–2.19)	0.00006
Mitral valve prolapse	5	10.8	0.46 (0.15–1.08)	0.091

Table 4

Selected Relative Risk (RR) estimates for associated conditions in 1,382 second-degree relatives and 3,091 third-degree relatives of 248 subjects with IC who are also patients at UUHSC

	Observed	Expected	RR (95% CI)	p
Irritable bowel syndrome				
2 nd degree relatives	19	12.39	1.53 (0.92–2.39)	0.064
3 rd degree relatives	24	26.44	0.91 (0.58–1.35)	0.698
Myalgia and myositis, unspecified (Fibromyalgia)				
2 nd degree relatives	50	34.22	1.46 (1.08–1.93)	0.0085
3 rd degree relatives	68	72.45	0.94 (0.73–1.19)	0.639
Constipation				
2 nd degree relatives	59	41.76	1.41 (1.08–1.82)	0.0089
3 rd degree relatives	100	95.76	1.04 (0.85–1.27)	0.683
Anxiety and panic disorder				
2 nd degree relatives	57	60.94	0.94 (0.71–1.21)	0.654
3 rd degree relatives	119	129.49	0.92 (0.76–1.10)	0.379

Table 5
Risk of IC among relatives of irritable bowel syndrome, myalgia and myositis/unspecified (Fibromyalgia), and constipation probands

	Number of relatives	Observed	Expected	RR (95% CI)	p
Myalgia and myositis, unspecified (Fibromyalgia) (N=8,216)					
1 st degree relatives	23,929	31	20.14	1.54 (1.05–2.19)	0.019
2 nd degree relatives	40,944	45	29.82	1.51 (1.10–2.02)	0.0067
3 rd degree relatives	77,269	61	58.00	1.05 (0.80–1.35)	0.743
Constipation (N=10,713)					
1 st degree relatives	26,616	33	20.33	1.62 (1.12–2.28)	0.0066
2 nd degree relatives	47,718	51	36.80	1.39 (1.03–1.82)	0.021
3 rd degree relatives	96,318	81	70.46	1.15 (0.91–1.43)	0.210