FAMILIALITY OF LOWER URINARY TRACT SYMPTOM DISORDERS IN WOMEN

Hypothesis / aims of study
Lower urinary tract symptom (LUTS) disorders including stress urinary incontinence (SUI), urge urinary incontinence (UUI), and interstitial cystitis (IC) are common. Twin and family studies suggest some prior evidence of heritability for LUTS disorders; however, most prior studies focus on family history of a disease within close relatives (i.e., nuclear family) who often share an environment. Family history of a disease that includes both near and distant relatives is a strong predictor of an underlying genetic contribution to a disease. The objective of this study was to perform a familiality analysis looking at near and distant relatives using statewide hospital inpatient discharge data that has been record linked to a state population-based genealogy database.

Study design, materials and methods
The population-based genealogical database contains over 15 million records obtained from family history records, birth certificates and other public data and has been used to investigate the familiality of many diseases including cancer. The genealogical data have been record linked to inpatient hospital discharge data from 1991-2009; statewide outpatient data is not yet available. We used ICD-9 and CPT4 codes to identify cases and required that all cases have at least 3 generations of genealogy data. We estimated the genealogical index of familiality (GIF) statistic for all SUI, UUI, and IC cases identified. The GIF statistic compares the average relatedness of cases compared to the average relatedness of 1000 sets of matched controls based on 5-year birth cohorts, sex, and birth in/out of the state; empirical significance is assigned based on comparison of the case/control distributions. We also calculated a distant GIF (dGIF) statistic that similarly calculates average relatedness of cases and controls after excluding 1st and 2nd degree relatives in order to assess relatedness of only distant affected relatives.

Results
There were 8,036 female cases identified with SUI, 2,287 cases with UUI and 247 cases with IC in the inpatient discharge dataset who had at least three generations of relatives in the database. SUI, UUI, and IC all showed significant overall excess relatedness in cases compared to controls; however, when distant relatives were considered, only SUI and IC remained significant.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Overall Case GIF</th>
<th>Overall Control GIF</th>
<th>p-value</th>
<th>dGIF of Cases</th>
<th>dGIF of Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUI</td>
<td>5.05</td>
<td>4.60</td>
<td>&lt;0.001</td>
<td>4.30</td>
<td>4.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UUI</td>
<td>5.07</td>
<td>4.63</td>
<td>0.001</td>
<td>4.23</td>
<td>4.13</td>
<td>0.159</td>
</tr>
<tr>
<td>IC</td>
<td>7.06</td>
<td>4.50</td>
<td>0.003</td>
<td>5.01</td>
<td>4.08</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Interpretation of results
Both genetics and environment contribute to these LUTS disorders, but these risks can be difficult to tease out because families share both genes and living conditions. Significant excess relatedness observed in both close and distant relatives for SUI and IC cases strongly supports genetic factors to contribute to risk.

Concluding message
Women affected with SUI and IC are more related to each other than would be expected; they have an excess of both close and distant relatives, providing evidence for a genetic contribution to these conditions. Women affected with UUI were more related to each other than expected, but this excess was only observed in close relatives; thus, either shared genes or environment or both contribute to risk of UUI.

Disclosures
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