Rare known pathogenic variants for urogenital disorders in 129 exomes from severe IC/BPS patients

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Introduction & Objective

INTRODUCTION
Interstitial cystitis, also called “Bladder Pain Syndrome” (IC/BPS) is an understudied but major subset of bladder dysfunction. We have collected biological samples and phenotypic information on over 400 families with severe and/or early onset IC/BPS over the past two decades. Our hypothesis is that genetics plays a major role in IC/BPS, which is discoverable by combining rich phenotypic data with next generation sequencing.

OBJECTIVE
• To exome sequence 129 patients with early onset and severe IC/BPS
• To identify known but unrecognized Mendelian variants within the cohort

Methods
We have conducted pilot genetic analyses of whole exome sequencing data on a total of 129 IC/BPS cases. DNA from blood was extracted using standard protocols and sequenced at the Broad Institute on the Illumina platform.

Variants were analyzed using the Genomic Learning System at Boston Children’s Hospital (Boston, MA) and Codified Genomics (San Diego, CA). CNVKit (San Francisco, CA) was utilized for analyzing copy number variations from exome data.

Results

Rare missense and LoF variants identified in the Kunkel Cohort. Rows in yellow are listed in ClinVar as pathogenic AD variants

<table>
<thead>
<tr>
<th>CHROM</th>
<th>POS</th>
<th>Ref</th>
<th>Call</th>
<th>het/Or/hom</th>
<th>Change</th>
<th>Number affected</th>
<th>Max AF</th>
<th>Gene</th>
<th>Associated syndrome</th>
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<td>T</td>
<td>het</td>
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Demographics

Average age of symptom onset: 26±14
Average age of diagnosis: 36±14
Males: 28 (21%)
Females: 101 (79%)

Discussion

Prior data suggest that some patients with complex urologic disorders have unrecognized Mendelian syndromes. That may also be the case here, with genes and CNV intervals for BOR2 and CAKUT syndrome identified.

While the patients in our cohort do not have documented diagnoses of BOR2 syndrome or CAKUT, it is possible that there are mild structural anomalies that eluded detection and will be identified upon further clinical review. As an O’Brien opportunity pool project, an additional 100 exomes will be analyzed to extend and replicate these findings.