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.

Demographics

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

Results

Known Neuropsychiatric risk Intervals identified in the Kunkel cohort (N=129)

Chr	Start	End	Size	Locus	CNV	In Kunkel cohort
16	29,560,000	30,110,000	550,000	16p11.2 (proximal)	gain	N=1
2	50,000,992	51,113,178	1,112,186	2p16.3 NRXN1	loss	N=1
16	28,730,000	28,960,000	230,000	16p11.2 (distal)	loss	N=1
Large CNVs seen in preliminary data subset of the Kunkel Cohort (N=129)						
2	49,003,954	53,897,139	4,893,185	FSHR, NRXN1	loss	N=1
12	22,089,466	25,146,730	3,057,264	ABCC9, CMAS, ST8SIA1, C2CD5, ETNK1, SOX5, BCAT1	loss	N=1

Results

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

CHROM	POS	Ref	Call	hetORhom	Change	Number affected	Max AF	Gene	Associated syndrome
chr19	46271631	C	T	het	A158T	N=4	4.00E-04	SIX5	BOR syndrome
chr19	46269339	C	T	het	W206X	N=1	5.64E-05	SIX5	BOR syndrome
chr19	46269896	G	A	het	P441S	N=1	9.92E-05	SIX5	BOR syndrome
chr5	44388545	T	G	het	R80S	N=3	0	FGF10	LADD syndrome

Results

- We observed a previously reported pathogenic variant in SIX5, a heterozygous c.472G>A change producing a missense variant p.A158T, segregating with disease in a large family. This same variant is known to be associated with branchiootorenal syndrome (BOR2). This variant is rare in gnomAD (checked July 27, 2020), with 26 instances of A158T in 232,976 alleles.
- A previously reported pathogenic variant in FGF10 was identified in 3 individuals. FGF10 is linked to Levy-Hollister syndrome(LADD) which can have recurrent urinary tract infections and abnormalities of the genitourinary system.
- An analysis of copy number variations in 98 patients detected a 16p11.2 deletion (N=1) and a 16p11.2 duplication (N=1). 16p11.2 CNVs are associated with congenital anomalies of the kidney and urinary tract (CAKUT).

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.