Molecular Diagnostic Analysis Reveals High Diagnostic Rate in Congenital Obstructive Uropathy

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Background

- Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) constitute a very heterogeneous group of birth defects encompassing conditions with very different prevalence and severity. As a result, the reported diagnostic yield in CAKUT is extremely variable, likely because of ascertainment bias and the diverse phenotypic composition of the cohorts studied.
- Congenital Obstructive Uropathy (COU) is a subset of CAKUT and is the most frequent urinary tract anomaly occurring in up to 2% of pregnancies, constituting a leading cause of pediatric chronic kidney disease. The precise genetic architecture of COU is mostly unknown.
- Here we aimed to define the contribution of point mutations (SNVs) and structural variants (SVs) or CNVs to the diagnosis of COU based on an exome sequencing (ES) study of 822 COU cases, encompassing three main classes of congenital urinary obstructions: a) Ureteropelvic Junction Obstruction (UPJO; N = 338), b) Ureterovesical Junction Obstruction (UVJO; N = 217), and c) COU not otherwise specified (COU-NOS; N = 267).

Cohort Selection & Methods

- The cohort subjects were described in Table 1.
- ES was conducted on the entire cohort of 822 COU cases; Illumina DNA microarray for CNV analysis was performed for a subset 461 COU individuals.
- Clinical annotation to identify candidate diagnostic/pathogenic Mendelian mutations and structural variants was conducted based on the American College of Medical Genetics and Genomics (ACMG) guidelines for clinical variant interpretation.

Table 1. Baseline clinical characteristics of our COU cohort. 101 of the 822 COU cases had reported extrarenal phenotypes.

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<th>Phenotype</th>
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| Male                          | 557 | 67.76%
| Female                        | 265 | 32.24%
| Total                         | 822 | 100.00%
| Clinical Phenotype            |     |       |
| Ureteropelvic Junction Obstruction (UPJO) | 338 | 41.12%
| Ureterovesical Junction Obstruction (UVJO) or Congenital Megacalycus | 217 | 26.40%
| COU not otherwise specified (COU-NOS) | 267 | 32.48%
| Total                         | 822 | 100.00%
| Extrarenal Phenotype          |     |       |
| Renal                         | 18  | 2.19%
| Craniodental                  | 12  | 1.46%
| Cardiac                       | 17  | 2.07%
| Musculoskeletal               | 21  | 2.55%
| Gastrointestinal              | 23  | 2.80%
| Genital                       | 15  | 1.82%
| General Developmental Delay   | 5   | 0.61%
| Total                         | 101 | 12.29%

Results

- Overall, 6.2% of 822 COU individuals carried a pathogenic genotype at a CAKUT Mendelian gene by ES analysis
- 4.1% of 416 COU individuals with DNA microarray available carried a pathogenic CNV, for a combined yield of 8.5% (Fig. 2)
- Incomplete CNV analysis (361 individual under analysis of CNVs from ES) suggest a lower overall penetrance of the total COU cases; COU
- Similarities and differences among the 3 COU subcategories are shown in Fig. 2 and Tab. 2.

Conclusions, Limitations, and Future Directions

This study show a high diagnostic yield for COU, with important ramifications for diagnosis, counselling and risk stratification. While the diagnostic yield appears to be slightly higher for the UVJO group compared to UPJO and COU-NOS, this study had highlighted ample genetic overlap between COU subtypes supporting comprehensive approaches for genetic identification in COU. Completion of CNV analysis by ES-CN

References