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Clinical Utility of Exon Deletion/Duplication Microarray Testing - a Children's Mercy Kansas City Two-Year Experience

Binu Porath
bporath@cmh.edu

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Porath, Binu, "Clinical Utility of Exon Deletion/Duplication Microarray Testing - a Children's Mercy Kansas City Two-Year Experience" (2019). *Research Days*. 17.

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Clinical Utility of Exon Deletion/Duplication Microarray Testing - a Children's Mercy Kansas City Two-Year Experience

Submitting/Presenting Author (must be a trainee): Binu Porath

Primary Email Address: bporath@cmh.edu

Resident/Psychology Intern

Fellow

Primary Mentor (one name only): Elena Repnikova

Other authors/contributors involved in project: Jennifer Roberts, Linda Cooley, Julie Joyce, John Herriges, Carol Saunders, Preeti Thakor, Isabelle Thiffault, Lei Zhang

IRB Number: N/A

Describe role of Submitting/Presenting Trainee in this project (limit 150 words):

Binu Porath was primarily involved in gathering and analyzing the data and writing the abstract.

Background & Objectives:

Copy number variants (CNVs) represent a large proportion of genetic variation in the human genome and contribute to a number of disorders. Traditional microarray platforms designed to detect large CNVs (>25 kb) often have suboptimal probe coverage within exonic regions of medically relevant genes, which hinders detection of smaller events. In 2016, our laboratory clinically validated exon deletion/duplication microarray (EDDM) for detection of smaller CNVs to complement non-diagnostic results from NGS-based sequencing and traditional microarray. EDDM platforms are designed with high probe coverage within the exons of genes and are more sensitive in detecting small CNVs than traditional microarray. Here, we evaluate the clinical utility of EDDM as an adjunct to NGS-based analysis and traditional microarray.

Methods/Design:

Between May 2016-November 2018, 416 consecutive patients were referred to our laboratory for EDDM testing either as a primary test based on clinical indication or as a follow-up after non-diagnostic NGS testing. The majority of these cases were also previously analyzed by traditional microarray with non-diagnostic results. DNA extracted from blood was run using the CytoSure OGT 1x1M Medical Exome or CytoScan Xon array platforms.

Results:

Of the 416 cases, 106 (25%) were ordered as single or multi-gene panel and 310 (75%) as exome-wide deletion/duplication analysis. In total, 15 diagnostic CNVs were found (13 pathogenic and 2 likely pathogenic; 12 deletions and 3 duplications), which accounts for 3.6% of all cases. The remaining cases, 96.4% (401/416) were non-diagnostic. Of these, 6 patients were found to be carriers of pathogenic autosomal or X-linked recessive CNVs, and 66 (17%) had reportable variants of uncertain significance (VUS) with 16 novel or rare CNVs not previously identified by traditional microarray.

All of the 15 diagnostic CNVs detected by EDDM [7 small (500bp-19kb) and 8 large (41kb-12.3Mb)] were associated with dominant conditions. Of these, 2 had CNVs in clinically suspected genes identified by the EDDM platform alone, 2 had CNVs in the ordered genes after negative NGS analysis of those genes and 4 had CNVs identified by exome-wide EDDM analysis after negative whole-exome sequencing (WES) results. An additional 4 cases had deletions previously detected by outside laboratories using NGS, however, EDDM was performed to clarify the breakpoints of those deletions. Finally, 3 cases had large (>2 Mb) CNVs which included a 22q11.21 duplication, a 13q12.3q14.11 mosaic deletion and a complex 1p36 duplication.

Conclusions:

Overall, the use of the EDDM platform in our laboratory yielded a diagnostic rate of ~3.6%. All of the diagnostic cases were associated with dominant conditions, although, we also identified 6 cases with CNVs indicating carrier status for autosomal and X-linked recessive diseases that appeared to be incidental. Exon-level resolution of the EDDM platform provides higher sensitivity as exemplified by several cases in which clinically relevant deletions were not detected by traditional microarray. Our experience shows that targeted EDDM analysis for specific dominant disease has high clinical utility; however overall it significantly increases costs. EDDM may be most useful in cases where there is a strong suspicion for a specific disorder.