Incidence and Clinical Significance of Small Copy Number Variants Detected by Chromosomal Microarray Testing

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Objective: Chromosomal microarray (CMA) is a first-tier clinical test in the evaluation of individuals with autism spectrum disorders, developmental delay, intellectual disability, and multiple congenital anomalies. Testing for our tertiary-care pediatric institution is currently performed at a reference laboratory via high-resolution CMA designed to detect and report changes down to 100 base pairs. In 2014, the first commercial CMA platform received premarket approval from the United States Food and Drug Administration. The approval required the system to filter out results for losses smaller than 25 kilobases (kb) or gains of less than 50 kb. In this study, we assessed the incidence and clinical significance of small (losses <25 kb and gains <50 kb) copy number variants (CNVs) in our patient population. Methods: All CMA test results from September 2011 to 2012 were reviewed to identify reports with small CNVs. To determine the clinical significance of these variants, cases were evaluated via in-depth chart review by a genetics counselor, medical geneticist, and pathologist. The CNVs were then classified as causative (i.e., a known pathogenic variant), likely causative, unknown, unlikely causative, or not causative of the patient’s phenotype. Follow-up parental studies and ancillary genetic tests were included in the assessment whenever available. Results: Of the 440 CMA cases reviewed, 214 (48.6%) had one or more CNVs, while 226 (51.4%) had no reported findings. The majority of patients tested had developmental delay or other neurologic phenotypes (344 cases, 78.2%). Overall, 46 cases (approximately 10.5%) had small CNVs. Five patients harbored two different small CNVs. Thus, there were a total of 51 instances of small CNVs — 21 copy number losses (ranging from 0.2 to 23 kb) and 30 copy number gains (ranging from 0.1 to 43 kb). The overall incidence of small CNVs relative to all CNVs was 18.7% (51 out of 273 CNVs total). We then classified whether these small CNVs were causative of the patient’s phenotype. We found that none were causative or likely causative, 28 were unlikely to be causative, 19 were not causative, and 4 were of unknown or unclear significance. In contrast, 37 (13.5%) large (losses >25 kb and gains >50 kb) CNVs were causative or likely causative. Discussion: Almost half of the tested patient population had an abnormality found on CMA analysis; 18.7% of these were small CNVs. However, our analysis found no small CNVs that were clinically significant. Conclusions: In our patient population, high-resolution microarrays designed to detect small CNVs did not lead to improved diagnostic yield. While the analytical capabilities of various platforms may be different, a lack of small CNV detection does not appear to be a diagnostic liability.