Copy Number Variants, Aneuploidies, and Human Disease

Christa Lese Martin, PhD*, Brianne E. Kirkpatrick, MS,
David H. Ledbetter, PhD

KEYWORDS

- Copy number variant • CNV • Chromosomal microarray
- Noninvasive prenatal testing • Genomic databases • Aneuploidy • Prenatal
- Neonatal

KEY POINTS

- Copy number variants (CNVs) are a common cause of a wide range of human disorders, accounting for ~15% of neurodevelopmental disorders, cardiac abnormalities, and other congenital anomalies.
- Various methods are available to detect CNVs, including those that can identify CNVs across the entire genome and those that only target specific regions of the genome (eg, the common aneuploidies involving chromosomes 13, 18, 21, X, and Y).
- Accurate clinical interpretation of CNVs requires incorporation of genotype plus phenotype information.
- Identifying a genetic cause for a patient's phenotype can help to define targeted interventions and clinical management.

INTRODUCTION

In the perinatal setting, chromosome abnormalities span a wide range of genomic imbalance, from polyploidy (the presence of 3 [triploidy] or 4 [tetraploidy] copies of every chromosome), to whole-chromosome aneuploidy (typically involving only a single chromosome), to submicroscopic deletions and duplications that can only be detected by DNA-based copy number methods, such as fluorescence *in situ* hybridization (FISH) or chromosomal microarray (CMA). As technologies have improved to

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Geisinger Health System, Autism & Developmental Medicine Institute, 120 Hamm Drive, Lewisburg, PA 17837, USA
* Corresponding author.
E-mail address: clmartin1@geisinger.edu

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detect smaller and smaller copy number variants (CNVs) across the genome, clinicians are learning the high frequency and important role that this type of genomic variation plays in human health and development.

CNVs have been identified as a common cause of several human diseases, many of which present in the neonatal period and/or early childhood. These diseases include neurodevelopmental disorders (such as autism, intellectual disability, and epilepsy), congenital heart defects, and other congenital anomalies.[1–3] However, not all CNVs are disease causing: some CNVs have been identified in apparently normal individuals.[4,5] Whether a CNV is disease causing or not depends on many factors, such as gene content (eg, a CNV that is gene rich is more likely to cause a phenotype than one containing few or no genes).[6] Therefore, understanding the corresponding phenotypic effects of particular CNVs is becoming increasingly important in clinical medicine so clinicians can define which CNVs cause a clinical phenotype versus those that are part of normal variation.

This article highlights key aspects of copy number detection during the prenatal and neonatal periods. Many infants presenting to neonatology services for a possible genetic diagnosis may have had prenatal testing; it is important to understand which test was performed to interpret the results and know whether additional genetic testing is warranted. In contrast, if prenatal testing was not done, then decisions need to be made about which genetic tests are most appropriate to order. To make informed test ordering decisions, it is important for neonatologists and other providers to understand the limitations and benefits of the various laboratory technologies. Therefore, this article compares methods for CNV detection. It also explores some of the most common CNVs associated with disease and how interpretation of CNVs is accomplished through the use of various resources, including online genomic databases. Given that CNVs are now appreciated as one of the most frequent causes of a broad spectrum of human disorders, early diagnosis and accurate interpretation is important to implement timely interventions and targeted clinical management.

METHODS FOR THE DETECTION OF COPY NUMBER VARIANTS

Various methods have been developed over the years for the detection of chromosomal deletions, duplications, and rearrangements. As shown in **Fig. 1**, some of these methods allow genomewide analyses, in which the entire chromosome complement is being interrogated, whereas others are targeted analyses and only examine specific regions of the genome. In addition, methods differ in their level of resolution (ie, how small an imbalance can be detected) and the type of sample that can be analyzed. **Table 1** summarizes the most commonly used cytogenetic methods for the detection of chromosome abnormalities and compares the benefits and limitations of each.

Of the techniques listed in **Table 1**, Giemsa-banded (G-banded) chromosome analysis and CMA are the only ones that are considered genomewide analyses, in which the entirety of each chromosome is being analyzed. However, the resolution of CMA far exceeds that of G-banding; genomic imbalances that could only be approximated by G-banding analysis can now be measured with precision by CMA based on the ability to link the probes contained on a microarray with the underlying DNA sequence coordinates. For these reasons, and others detailed later, CMA has become the first-tier test for clinical cytogenetic testing in the pediatric setting.

Most genomewide microarrays used for clinical CMA now also include single-nucleotide polymorphism (SNP) probes in addition to probes used for copy number detection. The addition of SNP probes offers several advantages. For example, SNP probes allow the detection of triploidy and some cases of tetraploidy.[7] These