

Editorial



Chromosomal Microarray: Application for Congenital Heart Diseases

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Conflict of Interest

The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

► See the article "Array Comparative Genomic Hybridization as the First-line Investigation for Neonates with Congenital Heart Disease: Experience in a Single Tertiary Center" in volume 48 on page 209.

Chromosomal microarray (CMA) is a technology used to determine if there are microduplication or microdeletion pieces of genetic information. The prefix 'Micro-' indicates that less than 5 Mb sized genomic regions which has not been identified by conventional karyotyping using the G-band technique. These small gains and losses are called copy number variants (CNVs). A CNV is detected by CMA can not only be pathogenic resulting in physical and/or intellectual consequence, but also be of no medical consequence.^{1,2)}

In 2010, the first consensus statement for CMA from American Society of Human Genetics mentioned that CMA is a first-tier clinical diagnostic test for individuals with developmental disabilities, autism spectrum disorders or multiple congenital anomalies including congenital heart diseases.¹⁾ This report also showed that CMA offers a much higher diagnostic yield (15–20%) in these patients than a conventional karyotype (up to 3%). This discrepancy of diagnostic yield is due to CMA's higher sensitivity for submicroscopic deletions and duplications. Therefore, CMA allows to identify the underlying etiology of an individual's disability and/or congenital anomalies and ends the diagnostic odyssey without other unnecessary diagnostic tests. Additionally, the rapid and accurate diagnosis can facilitate access to necessary medical services and offer more appropriate genetic counseling to patients and their high-risk family members.¹⁻⁴⁾

On the other hands, there are some important limitations in CMA for clinical settings. Completely balanced translocations of chromosomes and low-level mosaicism (<30%) are not usually detectable by CMAs. Conventional karyotype using G-banding technique still has clinical meaning as a diagnostic method for balanced chromosomal translocations. However, completely balanced translocations of chromosomes are generally not associated with abnormal or disease phenotypes, and patients with low-level of chromosomal mosaicism manifest milder clinical phenotypes than non-mosaic patients.^{1,4)}

CMA encompasses all types of array-based genomic CNV analyses including bacterial artificial chromosome (BAC), cDNA, oligonucleotide, and single nucleotide polymorphism (SNP) arrays. Originally, targeted microarray was constructed from BAC for the clinical laboratory due to its ability to clearly identify CNV in discrete regions of the human genome

already known to play a role in specific genetic diseases.⁵⁾ Usually 2,000 to 30,000 BAC probes can be contained on the whole genome BAC array platforms. Oligonucleotide array platforms consists of up to 1 million of single-stranded 25 to 85 bp oligonucleotide clones.⁶⁾ There have been significant evidence that oligonucleotide array offers higher resolution and outperform BAC array in measuring size of CNVs and increasing sensitivity to detect smaller CNVs in clinical implementation.⁷⁾ SNP array, the newest CMA platform, can also be used for detection of uniparental isodisomies and genetic identity by descent, in addition to detection of CNVs.⁸⁾ Oligonucleotide and SNP arrays lead to increase resolution as low as 100 kb. The higher resolution platform we use, the more variant of unknown significance we find. So, choosing an appropriate method is important in clinical setting, considering to cost- or time-effectiveness and minimizing uncertainty in interpretation of the results.

In this article,⁹⁾ authors chose BAC array (including only 1,440 probes) as the method for CMA in patients with congenital heart anomalies. The location of each probes is targeted to specific chromosomal locations associated with well-known genetic syndromes. The results showed that diagnostic yield of 13.5%. However, it may be due to inclusion of very well-known genetic syndromes (trisomy 21, trisomy 13, 22q11.2 deletion syndrome), which can be also confirmed by more basic genetic studies such as conventional karyotypes without help of CMA. Moreover, the other very famous and common microdeletion, Williams syndrome (7q11.23 microdeletion) is not detected by the BAC array method used in this study. This is an important technical fault for this platform used in this study and should be complemented. Other representative genetic syndromes associated with congenital heart diseases including Noonan syndrome, Marfan syndrome, and Alagille syndrome are rarely caused by CNVs, but mainly by sequence variations in causing genes which are not detected by any CMA platforms. Therefore, clinical phenotyping is still most important and is required to prior to choose the most suitable method for diagnosis of underlying diseases in patients with congenital heart diseases.

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