The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis

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KEYWORDS

• Prenatal array • Chromosomal microarray • Prenatal diagnosis • Array CGH

KEY POINTS

- Copy number variants of well-defined clinical significance not identifiable by standard karyotype are not associated with maternal age and occur in 1% to 1.7% of routine pregnancies and in 6% of pregnancies with ultrasound anomalies.
- Chromosomal microarray analysis (CMA) is the currently recommended primary test for cytogenetic analysis of all pregnancies undergoing invasive testing after identification of a fetal ultrasound abnormality.
- All women having invasive testing for routine indications such as maternal age, anxiety, and abnormal serum screening can be offered microarray as an option.
- For any patient pursuing CMA, pretest counseling is imperative for them to understand the benefits and limitations, and to make an appropriate decision regarding testing.
- For patients with abnormal CMA results, including those with variants of uncertain significance, posttest counseling should be in-depth and be conducted by a practitioner with full knowledge of the implications of the result, such as a genetic counselor or clinical geneticist.

INTRODUCTION

Prenatal cytogenetic diagnosis has expanded over the past several years from karyotype and fluorescence in situ hybridization to chromosomal microarray analysis (CMA). This evolution to CMA occurred simultaneously with the realization that many childhood anomalies and developmental disorders are secondary to small deletions and duplications previously unrecognized by standard karyotype. Many of

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these explained the causes of previously described syndromes, whereas others were identified as the previously unsuspected cause of neurocognitive disabilities. **Table 1** lists many of the common microdeletion syndromes and copy number variants (CNVs) associated with neurocognitive disorders such as autism and intellectual disability.

In pediatrics, CMA has rapidly become a mainstay for diagnosis in children with developmental delay or intellectual disability, autism spectrum disorders, and/or multiple congenital anomalies. It is now recognized as the first-tier test (superseding karyotype) for these disorders.[1] Approximately 15% of such cases will demonstrate a causative CNV despite a normal karyotype.[2]

In 2013, the American Congress of Obstetricians and Gynecologists (ACOG) along with the Society for Maternal Fetal Medicine (SMFM) released recommendations that CMA replace or supplement karyotype for prenatal evaluation of fetuses with major structural anomalies. They also suggested that either karyotype or CMA is appropriate for women with structurally normal fetuses undergoing diagnostic prenatal testing. In addition, they clarified that microdeletions or duplications are not associated with advanced maternal age (AMA) and, therefore, CMA should not be restricted to women older than 35 years of age.[3] This aligns with the ACOG statement in place since 2007, which states that all pregnant women should be offered the option of diagnostic testing regardless of maternal age.[4,5]

With the increasingly better performance of noninvasive screening for pregnancies with a common chromosomal abnormality (trisomies 21, 18, and 13, and sex chromosome abnormalities) the rates of invasive diagnostic procedures have declined. However, simultaneously, the introduction of CMA has made available diagnosis of an increased spectrum of cytogenetic disorders; many with phenotypes as severe as those of the common aneuploides.[6] Given the options now available to pregnant women, an understanding of the scope and accuracy of CMA becomes an important part of the broader picture. This article focuses on an overview of CMA, including common microdeletion and duplication syndromes, the different methodologies available, how it fits into prenatal care, and the critical counseling components.

CHROMOSOMAL MICROARRAY TECHNOLOGY

Historically, karyotype has been the primary approach to analysis on chorionic villus and amniocentesis samples. With a resolution of 7 to 10 Megabases (Mb) or million base pairs, it is able to detect whole chromosome aneuploidy and structural aberrations such as large deletions or duplications. However, the limitations of light microscopy prevent the diagnosis of submicroscopic changes such as microdeletions and duplications less than 7 to 10 Mb; some being as small as tens to hundreds of thousands of base pairs (kilobases). Identification of these requires testing using molecular cytogenomic techniques such as CMA. There are 2 main types of CMA performed currently: oligonucleotide and single nucleotide polymorphism (SNP) microarray.

Oligonucleotide Array Comparative Genomic Hybridization Versus Single Nucleotide Polymorphism Microarray

Array comparative genomic hybridization (aCGH) technology directly compares short DNA fragments from a patient sample to a reference sample to determine if there is a shortage (deletion) or excess (duplication) of patient DNA relative to reference DNA at specific loci (**Fig. 1**). The control element on the array is generally a synthetic short stretch (~25–35 base pairs) of DNA of known sequence and chromosomal location, called an oligonucleotide.