Chromosomal Microarrays: Understanding Genetics of Neurodevelopmental Disorders and Congenital Anomalies

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J Pediatr Genet

Abstract

Chromosomal microarray (CMA) testing, used to identify DNA copy number variations (CNVs), has helped advance knowledge about genetics of human neurodevelopmental disease and congenital anomalies. It has aided in discovering new CNV syndromes and uncovering disease genes. It has discovered CNVs that are not fully penetrant and/or cause a spectrum of phenotypes, including intellectual disability, autism, schizophrenia, and dysmorphisms. Such CNVs can pose challenges to genetic counseling. They also have helped increase knowledge of genetic risk factors for neurodevelopmental disease and raised awareness of possible shared etiologies among these variable phenotypes. Advances in CMA technology allow CNV identification at increasingly finer scales, improving detection of pathogenic changes, although these sometimes are difficult to distinguish from normal population variation. This paper confronts some of the challenges uncovered by CMA testing while reviewing advances in genetics and the clinical use of this test that has replaced standard karyotyping in most genetic evaluations.

Keywords
- aCGH
- copy number variation
- microarray
- microdeletion
- microduplication
- molecular cytogenetics

Introduction

Throughout its history, various discoveries and techniques have revolutionized the field of human cytogenetics.[1,2] The use of hypotonic solutions allowed improved examination of chromosomes and the establishment of the human diploid chromosome number as 46 in 1956.[3] Banding techniques introduced in the 1960s and 1970s allowed identification of specific chromosomes and improved detection of chromosome abnormalities, although these traditional cytogenetic diagnoses rely on the frequently subjective practice of identifying altered banding patterns using light microscopy.[1,2] Detection of chromosome abnormalities expanded into the submicroscopic range as molecular cytogenetic techniques, such as fluorescence in situ hybridization (FISH), became more accessible and widespread.[1,2,4] While these molecular techniques provide an objective evaluation for chromosome abnormalities, such tests are targeted and require suspicion of a specific diagnosis to know which probes to use.[1,2,4] The completion of the Human Genome Project further revolutionized the field, opening the way for genome-wide molecular cytogenetic testing, including chromosomal microarrays (CMAs).[1,2] CMA testing has taken molecular cytogenetics to the next level: combining the objectivity and increased resolution of a molecular assay with a genome-wide approach that negates the pretest requirement for a suspected diagnosis.[1,2,4]

CMAs have facilitated the discovery of DNA copy number variations (CNVs) across the genome. CNVs are present in healthy control populations as well as individuals with

received
October 5, 2015
accepted after revision
April 23, 2016

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DOI http://dx.doi.org/10.1055/s-0036-1584306.
ISSN 2146-4596.

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disease, and a comparison of cases to controls is frequently required to understand the contribution of CNVs to disease.[5–7] Studies of individuals with a variety of conditions, including congenital anomalies,[8,9] intellectual disability/developmental delay (ID/DD),[10–14] autism spectrum disorders (ASDs),[12,13,15–18] epilepsy,[19,20] schizophrenia,[21–25] bipolar disease,[26,27] attention deficit hyperactivity disorder,[28,29] and cerebral palsy,[30] have all supported causative roles for CNVs in a subset of individuals with these conditions. For example, pathogenic CNVs have been detected in ~15% of >30,000 individuals undergoing clinical CMA testing, mostly with ID/DD and/or multiple congenital anomalies.[5,6] However, the connection between CNV and disease is not always clear, with some CNVs associated with variable abnormal and normal phenotypes. This review will explore this sometimes nebulous connection between CNVs and disease and lessons this has taught us about the genetics of human disease. It will also discuss the clinical use of CMA testing, where its diagnostic utility has made it a recommended first-tier test for many individuals presenting for genetic or neurologic evaluation.[11,14,31,32] Its increased clinical use has yielded evidence for clinical utility,[33–38] although some payers and specialists feel formal evidence is still lacking.[39–41]

Chromosomal Microarray Technology

The main goal of CMA testing is to identify CNVs: segments of DNA, ranging from hundreds to millions of basepairs in size, that are present in a different number of copies in an individual as compared with a reference genome. There are two types of CMAs: microarray-based comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP)-based microarrays. Both types of arrays use thousands to millions of segments of human DNA sequence (most commonly synthetic oligonucleotides) affixed to a solid support. With aCGH, DNA isolated from a test and a reference sample are labeled with different fluorescent dyes, mixed together in equal amounts, and hybridized to the array. Alterations in the ratio of the two fluorescent dyes indicate a different quantity of DNA in the test sample as compared with the control, and therefore these alterations correspond to locations of CNVs. SNP arrays use probes containing polymorphic nucleotides. A reference sample is not used in the experiment; computational algorithms translate signal intensity into information on copy number, as well as SNP genotype(s) present in the sample.[1,42,43] The resolution of any microarray is determined by its probes; probes derived from closely spaced genomic loci can detect smaller CNVs than probes from more distantly spaced loci. While some arrays use probes from equally spaced loci across the genome, most arrays used clinically have probes concentrated in clinically relevant genes and loci, with "backbone" (less dense) coverage throughout the rest of the genome. This allows for detection of smaller CNVs within disease-associated regions.[31]

Because SNP-based arrays provide data on genotypes as well as DNA copy number, they may be used to detect certain DNA copy number-neutral abnormalities. Stretches where there is absence of heterozygosity (AOH) can indicate consanguineous parents (with AOH spread throughout the genome) or segments of uniparental isodisomy, both of which may have implications for diagnosing genetic disease.[43,44]

Discovery of Microdeletion and Microduplication Syndromes

Prior to the advent of molecular cytogenetics, detection of a chromosome abnormality was limited to what could be seen under a microscope on a karyotype, which typically is at least 5–10 Mb in size. Rare abnormalities detectable on karyotype in patients with certain well-recognized syndromes, such as DiGeorge syndrome, or features of syndromes, such as Williams syndrome, helped to identify chromosomal causes of microdeletion syndromes; abnormal karyotypes in some patients led to the discovery of deletions too small to be seen by karyotype as the major cause of these syndromes.[45–47] These discoveries ultimately facilitated targeted testing for these microdeletions using methods such as FISH, which in turn began to uncover common underlying genotypes associated with a broader phenotypic spectrum. For example, 22q11.2 microdeletions were found to cause several related syndromes which had been given different names clinically, based on the major presenting features, including DiGeorge, velocardiofacial (or Shprintzen), and some cases of Opitz G/BBB syndromes.[48] Furthermore, testing of family members revealed intrafamilial variability among deletion carriers,[49] further broadening the associated phenotypic spectrum.

Increasing clinical and research use of CMAs greatly accelerated the pace of discoveries of microdeletion and microduplication syndromes. New, recurrent microdeletions and microduplications defined new syndromes, such as 17q21.31 microdeletions (Koolen-De Vries syndrome),[50,51] the reciprocal 17q21.31 microduplications,[52] 17q23.1q23.2 microdeletions,[53] and 3q13 microdeletions.[54] Some microdeletion and microduplication syndromes were not caused by recurrent CNVs, but instead individuals with overlapping deletions presented with similar phenotypes, which allows for the definition of smallest regions of overlap (SROs), or critical regions, for the syndrome, which likely contain the gene or genes responsible for the condition (►**Fig. 1**). Examples – just on the long arm of chromosome 1– include 1q43q44 microdeletions,[55,56] 1q41q42 microdeletions,[57–59] and 1q24q25 microdeletions.[60,61] Further insight into microdeletion/microduplication syndromes comes by limiting comparisons of CNVs to just those with a phenotype of interest. For example, with 1q43q44 microdeletions, microcephaly, agenesis of the corpus callosum, and seizures appear to be caused by different SROs/genes.[55]

Reduced Penetrance and Variable Expressivity

Some of the recurrent CNVs found by CMA seemed to defy the standard definition of syndromes. Similar to what had been observed earlier with 22q11.2 microdeletions, individuals who shared the same CNV did not have similar clinical features. Additionally, some of these CNVs were inherited

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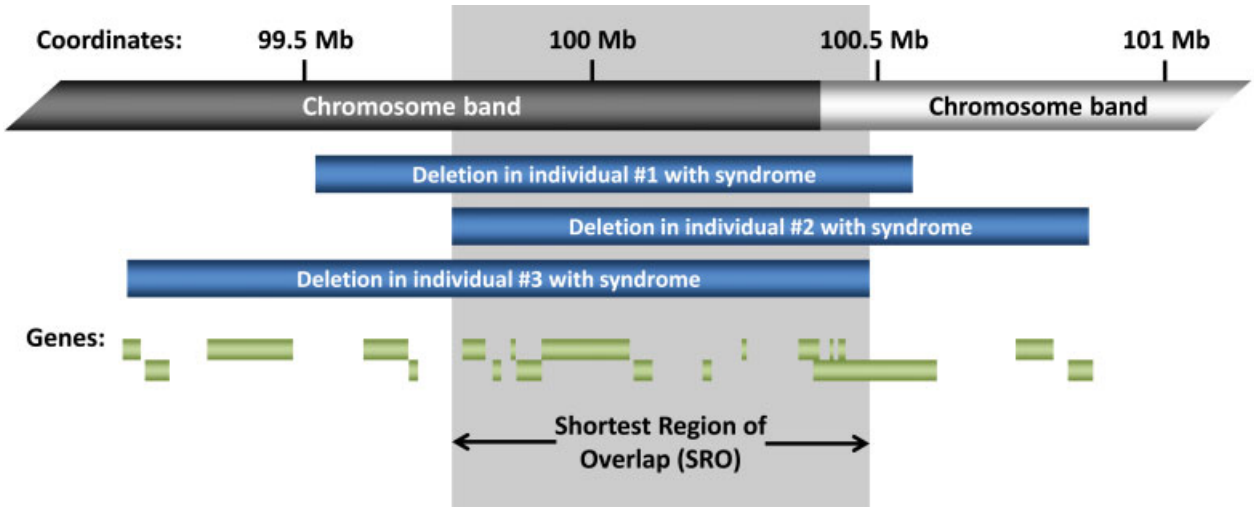

Fig. 1 Identification of overlapping copy number variations in individuals with a shared syndrome is used to identify a critical region for a microdeletion syndrome. The shortest region of overlap of the described deletions defines the minimally deleted region required for manifestation of that syndrome.

from apparently healthy parents, which, according to traditional cytogenetic interpretations, implied that they would likely be benign. However, as CMA testing was applied to increasingly larger cohorts of cases and controls, these CNVs were shown to be significantly increased in cases, providing strong evidence of some type of pathogenicity. A prime early example of such a CNV with reduced penetrance and variable expressivity was the distal 1q21.1 microdeletions and microduplications.[62,63] Larger case-control studies and collaboratively aggregated data from CMA laboratories have been able to build upon these early findings and provide evidence for a multitude of specific CNVs, both recurrent and nonrecurrent, as risk factors for the development of disease.[5–7]

Identification of a CNV risk factor associated with reduced penetrance and variable expressivity frequently poses challenges to clinical interpretation and genetic counseling. While the identification of such a risk factor in an affected individual is clinically significant (i.e., the CNV contributed to the development of an abnormal phenotype), there are likely additional factors that led to disease. In some more mildly affected individuals, the CNV may be the major risk factor, while in others, for example, with multiple congenital anomalies, additional factors may have more significantly contributed to the disease. These additional factors include genetic background (common and rare variation, including variation on the non-deleted alleles), epigenetics, and environmental factors.[42,64] There is empirical evidence for the need for additional genetic factors to interact with these reduced penetrance CNVs to cause more severe disease, as research has shown certain such CNVs, including 15q11.2 BP1-BP2 microdeletions, 16p11.2 proximal and distal microduplications, 16p12.1 (or 16p12.2 in hg19) microdeletions, 3q29 microduplications, 17p13.3 (*YWHAE*) microduplications, and 15q24 microdeletions, are more likely to co-occur with other large CNVs in a clinical population.[65] However, the additional genetic factors do not have to be additional CNVs, and identifying such genetic variation may be difficult. There are a few examples where one of these CNVs acts as a recessive allele for certain phenotypes, pairing with variants on the non-deleted chromosome to cause disease, for example with *RBM8A* and 1q21.1 proximal microdeletions in thrombocytopenia-absent radius syndrome[66] or *TBX6* and 16p11.2 proximal microdeletions in scoliosis,[67] but these seem to be rare, and additional genetic factors remain unknown in the majority of cases. It may therefore be challenging to determine if it would be useful to continue the diagnostic odyssey after CMA testing identifies a CNV risk factor, searching for additional contributing factors to disease.

Recurrence risk counseling for CNVs with reduced penetrance and variable expressivity can be particularly difficult. If a parent carries the CNV, there is a 50% chance of passing it on to each future offspring, but if the additional risk factors in the family are unknown, what is the likelihood of having another affected child? For at least some recurrent CNVs, there are estimates for penetrance, either for any phenotype significant enough to come to clinical attention[68,69] or for specific features such as schizophrenia.[41,69] Penetrance estimates show that not all CNVs confer equal risk; estimates for the frequency of carriers with significantly abnormal phenotypes range from ~10% for 15q11.2 BP1-BP2 microdeletions to ~60% for distal 16p11.2 microdeletions.[68] Unfortunately, it remains difficult to predict severity of possible outcomes, although some research suggests that there may be protective factors, such as being female.[70,71] Furthermore, it is important to note that "penetrance" is a relative term; there may still be negative effects of the CNV among so-called healthy parents or control populations. This is supported by recent studies of general populations that showed negative effects of such CNVs, including cognitive impairments, other neuropsychiatric features, alterations in body weight, and reduced fecundity.[72,73] Therefore, it is likely that most of these CNVs have some type of negative impact on an individual's development and neurologic function, although these impacts may not always be sufficient to bring the individual to clinical attention.

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Another notable feature of many recurrent CNVs is variable expressivity: the same CNV may be identified in populations of patients with intellectual disability, autism, and schizophrenia. Such effects may indicate that there are shared etiologies among neurodevelopmental disorders that are considered clinically distinct. Similar to considerations of penetrance, which feature manifests in any given individual also likely depends on genetic background.[42,74,75] Studies have demonstrated this concept through comparison of parental neurocognitive function to their children with de novo risk factor CNVs, showing a correlation between lower levels of parental functioning in specific domains and more significant impairments in those domains in their offspring, such as IQ and social responsiveness scores.[76,77] Therefore, for example, if an individual is prone to have a below average IQ, then an additional CNV risk factor may be more likely to manifest as intellectual disability than in a different individual with the same CNV who, based on genetic background, was prone to develop a higher IQ.

Genotype–Phenotype Correlations

CMA testing has facilitated improved understanding of genetic causes of many types of human disease. While some microdeletion and microduplication syndromes are contiguous gene syndromes, meaning that clinical effects result from deletion or duplication of several closely located genes, the phenotypes of other microdeletion and microduplication syndromes are driven mainly by deletion or duplication of a single gene. CMA testing has allowed for the definition of SROs or identification of single-gene deletions in individuals with the syndromic phenotype, thus establishing the critical gene(s) and providing insight into disease. Examples of critical single disease genes include *SATB2* in 2q33 microdeletions,[78] *MBD5* in 2q23.1 microdeletions and microduplications,[79–81] *MEF2C* in 5q14 microdeletions,[82,83] *SOX5* in 12p12 microdeletions,[84,85] *NFIA* in 1p31 microdeletions,[86] and *BHLHA9* duplications on 17p13.3 in split-hand/foot malformation with long-bone deficiency.[87] Detection of smaller or single-gene deletions has even provided insight into the etiology of well-established syndromes, like Prader-Willi syndrome.[88–91] In other microdeletion syndromes, the critical gene is identified when pathogenic point mutations are found in the gene, for example, *KANSL1* in 17q21.31 microdeletions[92,93] and *SETD5* in 3p25.3 microdeletions.[94] As newer genome-wide technologies such as exome and genome sequencing begin to gain broader clinical use, integration of data from CNV and sequencing studies are becoming another powerful tool to find novel human disease genes.[7]

As the density of array coverage over human disease genes increases with improving technologies, smaller CNVs in these genes are being discovered, and genotype–phenotype correlations are being further refined. The location of a CNV within a gene may influence the phenotype, likely due to differing impacts on the various isoforms of a gene and/or certain CNVs resulting in in-frame alterations. Predictions about how a CNV impacts gene function have long been understood to be important with genes such as *DMD*, where an in-frame versus out-of-frame CNV means the difference between Becker and Duchenne muscular dystrophy.[95] Similar genotype–phenotype correlations are beginning to be explored and have been proposed for genes including *NRXN1*,[96,97] *AUTS2*,[98] *MEF2C*,[99] and *CAMTA1*.[100] These correlations are mainly based on clinical observations, but model organism data[98] and examination of transcriptional products from CNV carriers[100] provide some additional support.

Clinical Use of Chromosomal Microarray Testing

CMA testing is now recommended as a first-tier test, replacing standard karyotype, for individuals with DD/ID, autism spectrum disorders (ASDs), or multiple congenital anomalies.[11,14,31,32] When considering replacing traditional karyotype, it is important to remember that CMA testing cannot detect balanced karyotypic abnormalities, such as reciprocal translocations, that could be of clinical significance if they disrupt a critical gene. One study estimated the frequency of such potentially pathogenic, balanced rearrangements to be ~1 in 400[14]; however, CMA's increase in detection of clinically significant CNVs too small to see on karyotype outweighs its loss of detection of balanced rearrangements, supporting the cost-effectiveness of starting with CMA testing.[11,14] Additionally, several studies have shown submicroscopic imbalances at the breakpoints of many apparently balanced chromosome rearrangements, and CMA testing would be able to identify many of those, thus detecting potentially pathogenic abnormalities that may appear balanced on karyotype.[101–103] This point illustrates the importance of further characterization of abnormalities found by CMA; follow-up experiments such as targeted FISH testing will be able to identify the cytogenetic mechanisms involved with some CNVs.[1,104] This is important to guide parental studies and recurrence risk counseling. Another example where cytogenetic characterization would be important is an unbalanced, intrachromosomal insertion, especially if its pathogenicity is due to disruption at the insertion point and not because of duplicated material. The gene content of such a duplication may not appear concerning on an array result, but it could be inserted in a critical gene, such as one report of an insertion disrupting *MECP2*.[105] Finally, follow-up testing should be performed for trisomies, with either a limited karyotype or metaphase FISH, as identification of familial Robertsonian translocations are critical for accurate genetic counseling.[1] For certain clinical indications where there is increased risk for a balanced chromosome rearrangement, such as recurrent pregnancy loss, standard chromosome analysis should remain a primary diagnostic test.[11]

The detection rate experienced clinically with CMA testing depends on two major factors: the phenotype of the patients being tested and the array being used. Many studies have found different CNV burdens among individuals with certain phenotypes; Cooper et al reported a greater CNV burden among individuals reporting cardiovascular or craniofacial features as compared with individuals with epilepsy or autism.[5] Frequently, individuals with combinations of features more commonly have pathogenic CNVs. For example, there is a higher detection for epilepsy comorbid with intellectual disability or congenital

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anomalies or for cerebral palsy (CP) with other nonmotor neurologic impairments than epilepsy or CP alone.[30,106,107] In a group with DD/ID, those with pathogenic CNVs were more likely to also have congenital anomalies (frequently heart defects), microcephaly, short stature, or low weight.[10] In individuals with ASDs, the co-occurrence of ID, major dysmorphic features, or congenital anomalies were more common in individuals with CNVs.[16,108] However, while such comorbidities may increase the likelihood of detecting CNVs in a given patient, there is still utility for testing patients with isolated findings such as ID/DD, ASD, or epilepsy, as the identification of a pathogenic CNV in such individuals can help guide medical management and counseling.[19] For example, testing an infant with a congenital heart defect may be able to identify a CNV that may also carry a risk of abnormal neurodevelopment, thus guiding appropriate management and counseling for that family.[8]

Detection rate also depends on the array type and design. As mentioned earlier, arrays using SNP technologies have the ability to detect copy-neutral AOH, which may help identify the presence of uniparental disomy, which can cause disease through imprinting or unmasking of recessive alleles, or consanguinity, in which case data from the array may help guide a search for a recessive gene causing the abnormal phenotype.[43] Additionally, probe number and probe placement impact detection rate. As more probes are used, smaller CNVs may be detected. As CNV size gets smaller, however, the likelihood of pathogenicity decreases; small CNVs are common in the general population. Therefore, more variants of uncertain significance are found with higher density arrays.[109,110] Because of this potential for uncertainty, some have proposed using size cutoffs for clinical reporting of CNVs.[11,110] However, as knowledge about human disease genes and clinical experience with CMA testing increases, the use of size cutoffs is becoming less popular. Thoughtful application of the technology will help to limit uncertainty. For example, several groups have developed arrays with exon-level coverage of known human disease genes, and such arrays found pathogenic CNVs affecting single exons, increasing the detection over more traditional clinical arrays (►**Fig. 2**).[109,111–115] As laboratories gain more experience with their array platforms, they learn

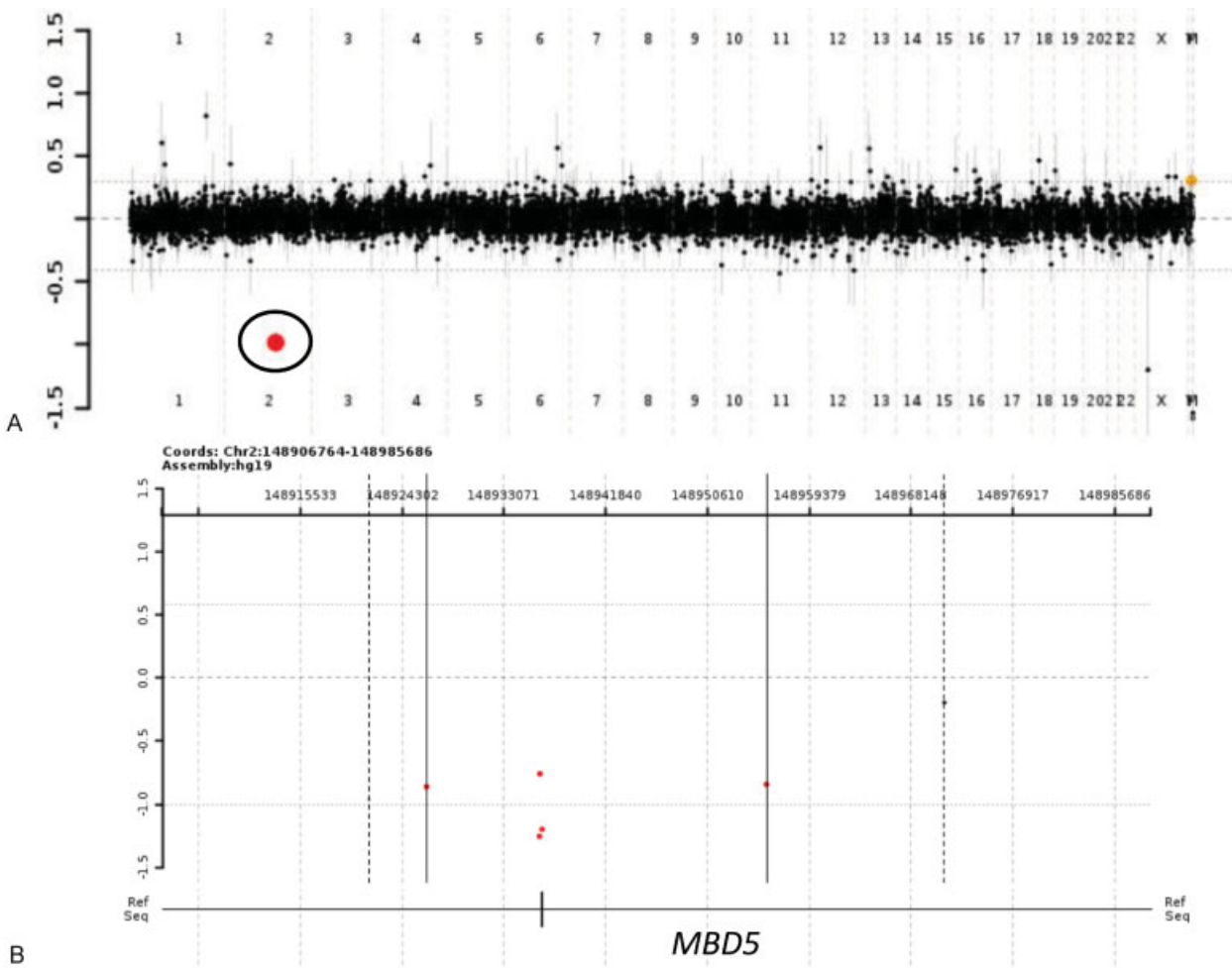

Fig. 2 Exon-targeted chromosomal microarray allows detection of clinically significant single-exon copy number variations. Genome-wide (**A**) and zoomed-in view (**B**) of aCGH results from a patient found to have a minimally sized 29kb loss in 2q23.1 within *MBD5*, affecting a single exon of the gene. Values along the y-axis represent the $\log_2$ ratio of patient:control signal intensity, with circled probes indicating a deletion. Values along the x-axis represent the genomic location of the probes, with the most proximal 2q23.1 probes to the left and the most distal 2q23.1 probes to the right (**B**). Solid vertical lines represent the minimal size of the deletion, and dashed vertical lines represent the maximal size of the deletion. Vertical line along the RefSeq gene line indicates the location of exon 3 of *MBD5*.

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more about common, likely benign variation, which will help reduce the likelihood of receiving uncertain results. However, like with other types of medical testing, both genetic and not, there is always a possibility of uncertain results, regardless of the testing platform. While parental testing in some cases may help with interpretation, such as finding the CNV in a similarly affected parent or finding that a CNV is de novo, it is important to remember that inheritance does not always correspond with interpretation. De novo CNVs can be benign, and CNVs inherited from healthy parents can be pathogenic.[6,42,116] Ultimately, close collaboration and sharing of information between the laboratory and the clinician is important to help maximize the usefulness of the interpretation of the array results.[32,117]

Identification of a pathogenic or likely pathogenic CNV on CMA testing offers benefits for the patient and family.[118] The CNV may be associated with a known syndrome, which may come along with information on prognosis, or it may include a known disease gene, allowing for appropriate counseling and monitoring for future complications. Even the detection of a risk factor CNV can allow for guidance of medical management, albeit with less certainty than with other CNVs.[11,13,42] Studies have estimated that at least 5 to 7% of individuals undergoing CMA testing, or approximately a third of those with a pathogenic finding, receive a result with specific implications for medical management.[33–35] Reviews of medical records demonstrate that clinicians are basing medical management decisions on outcomes of CMA,[36–38] thus supporting the clinical utility of the test. It is possible that these implications for medical management may be due to what is considered an "incidental" finding, or a finding that is unrelated to the reason for testing. For example, a large deletion may be causing developmental delay and/or congenital anomalies, but it may also include a gene that predisposes the individual to cancer or other late-onset diseases.[119] Alternatively, an individual may carry a small CNV of one of these genes, unrelated to the phenotype in question but having implications for medical management for the patient and potentially other family members who may also carry the CNV.[115] Identification of a pathogenic CNV can also guide appropriate parental testing to provide recurrence risk counseling. Interestingly, recent studies have shown that parental mosaicism for pathogenic CNVs may be more common than previously thought (4% in one study), suggesting in-depth parental analyses may be required for the most accurate counseling, although the relatively straightforward customized PCR testing on parental blood samples to detect low-level mosaicism is not yet a standard practice.[120] And, perhaps most importantly for some families, a diagnosis may be provided. The seemingly endless quest for a diagnosis can stop; some seek other families and support groups for their given diagnosis.[20] For rare individuals, the diagnosis may even indicate a specific, targeted treatment.[64,121,122]

Future Directions

Clinical use of CMAs has had a significant impact on our knowledge of the genetics of human disease. Aside from the discovery of specific disease genes, it revolutionized our knowledge of the contribution of inherited factors to the development of disease. Genetic "risk factors" may be similarly present in healthy parents and affected offspring and predispose to a variety of neurodevelopmental phenotypes. As newer genomic technologies enter the clinical realm, including exome and genome sequencing, it is important to remember the lessons learned from CMAs. These next-generation sequencing technologies are currently rapidly uncovering novel genetic causes of Mendelian disease,[123] but such straightforward explanations will likely not be present for all affected individuals. Like the risk factor CNVs, there will likely be sequence variants that predispose to a variety of abnormal phenotypes, and it will likely take large case-control studies to identify such factors. Discovery and interpretation of such factors will be one of the next big challenges for genome-wide clinical genetic testing.

CMA testing will most likely be displaced in the future by next-generation sequencing technologies. Extensive work is being done to improve bioinformatic methods for identifying CNVs from next-generation sequencing data. The CNVs detected using such techniques may be smaller than the resolution of most CMAs.[124] Even balanced chromosome rearrangements, which cannot be detected by CMA technology, can be identified from sequencing data.[125] While such CNV- and rearrangement-calling techniques are still being perfected, and CMA testing currently remains a mainstay of clinical diagnostic testing for many individuals with suspected genetic disorders, the future likely holds powerful genetic testing technologies to efficiently detect any of the variety of types of genetic variation in a single test. Like with CMA testing, this will generate vast amounts of data that will likely take years to study, providing continuing opportunities to increase our knowledge of human disease as the practice of medicine tries to keep up with the rapid pace of genetic discovery.

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