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The Utility of Chromosomal Microarray Analysis in Developmental and Behavioral Pediatrics

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Abstract

Chromosomal microarray analysis (CMA) has emerged as a powerful new tool to identify genomic abnormalities associated with a wide range of developmental disabilities including congenital malformations, cognitive impairment, and behavioral abnormalities. CMA includes array comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays, both of which are useful for detection of genomic copy number variants (CNV) such as microdeletions and microduplications. The frequency of disease-causing CNVs is highest (20%–25%) in children with moderate to severe intellectual disability accompanied by malformations or dysmorphic features. Disease-causing CNVs are found in 5%–10% of cases of autism, being more frequent in severe phenotypes. CMA has replaced Giemsa-banded karyotype as the first-tier test for genetic evaluation of children with developmental and behavioral disabilities.

The ability to identify genetic abnormalities as the cause of developmental and behavioral disorders has changed dramatically over the last 5 years primarily related to the introduction of chromosomal microarray analysis (CMA; Miller et al., 2010; Schaaf, Wiszniewska, & Beaudet, 2011). There is evidence that the new diagnostic information changes management for children with disabilities (Coulter et al., 2011). Advances in clinical genetic testing are a direct reflection of the ability to examine the human genome at increased resolution, allowing for the identification of relatively smaller imbalances of chromosome material. For decades, chromosomal analysis in the form of a Giemsa-banded karyotype had been the mainstay of identifying genetic abnormalities causing developmental disabilities (Moeschler & Shevell, 2006; Yunis & Chandler, 1978). In more recent years, fluorescence in situ hybridization (FISH) greatly expanded the ability to diagnose specific deletion syndromes, such as DiGeorge syndrome (deletion 22q11.2 or deletion 10q13-q14), Williams syndrome (deletion 7q11.23), Prader-Willi syndrome (paternal deletion 15q11-q13), Angelman syndrome (maternal deletion 15q11-q13), Smith-Magenis syndrome (deletion 17p11.2), deletion 1p36 syndrome, and many others (Jalal et al., 2003; Roberts, Cox, Kimonis, Lamb, & Irons, 2004). FISH has routinely been performed using metaphase chromosomes (Figure 1a), which is adequate for detection of deletions, but fails to detect duplications because two copies at adjacent sites in the genome result in overlapping fluorescent signals. Two signals can be distinguished in interphase FISH (Figure 1b) providing increased resolution of adjacent sites. Although biochemical testing and sequencing of specific genes can identify additional, causative genetic abnormalities in children with developmental disabilities, cytogenetic studies, more recently including telomere FISH using probes for all gene-containing telomeres (ends of chromosomes), have produced a much higher diagnostic yield,

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Conflict of interest: The author is Professor and Chair of the Department of Molecular and Human Genetics at Baylor College of Medicine (BCM); the Department offers extensive genetic laboratory testing and derives revenue from this activity.

when used as a screening test in children with developmental disabilities (Jalal et al., 2003; Roberts et al., 2004).

The new molecular cytogenetic technologies depend primarily on the use of arrays to determine copy number across the entire genome. Two array platforms have been used widely: array comparative genomic hybridization (array CGH) and single nucleotide polymorphism (SNP) arrays (Conlin et al., 2010; Rosenberg et al., 2006; Schaaf et al., 2011). These two approaches have much in common, but there are important differences between the two as described in the following two paragraphs. The terms CMA and array genomic hybridization have been used to describe the general use of both of these approaches.

Array CGH uses a DNA sample from the child with the identified disorder and a DNA sample from a normal control. The DNA from the patient is labeled with one color of fluorescent dye (red or green), and the control DNA is labeled with the other color. The labeled DNA samples are then mixed and hybridized to DNA fragments on glass slides. Initially, this strategy employed bacterial artificial chromosomes (BAC) arrays that were large DNA fragments of more than 10 kilobases (kb). More recently, most array CGH is performed with oligonucleotides of 50–70 base pairs (bp) on the array (Neill, Torchia, Bejjani, Shaffer, & Ballif, 2010; Ou et al., 2008). Upon laser scanning of the slides, regions of the genome with equal copy number in the child with the disorder and the control will yield a yellowish color from equally balanced contribution of red and green dyes for each oligonucleotide or BAC clone. If the child with a disorder has a deletion, the color will be shifted in favor of the control DNA, while the color will be shifted in the direction of the child's DNA if the child has a duplication. An example of array CGH for a deletion involving the neurofibromatosis 1 gene (NF1) and 11 other genes is shown in Figure 2. This figure shows the copy number across the entire genome (all chromosomes), across chromosome 17, and an expanded view of the deleted region. The outstanding signal to noise distinguishing regions of normal copy number from deleted regions and the precise delineation of deletion boundaries are noteworthy in Figure 2.

SNP arrays were designed initially to detect genotypes for thousands to hundreds of thousands of SNPs across the entire genome with the focus on genome-wide association studies. To do this, the arrays utilize two oligonucleotides, one matching each of the two variant alleles. The genotype is then determined by a single-base extension reaction (Illumina methodology) or by differential hybridization to oligonucleotides that distinguish a perfect match from a single-base mismatch (Affymetrix methodology). It became clear that SNP arrays also detect copy number changes, although that was not the initial intent. Examples of an Illumina SNP array for detection of a deletion or duplication are shown in Figure 3.

Some of the key differences in the two methodologies are listed in Table 1. In array CGH, each oligonucleotide has a single sequence and the size ranges from 50 to 70 bp. For SNP arrays, the oligonucleotides are typically about 20 bp for the mismatch hybridization method and can be similar or longer for the single-base extension method. Two DNAs, the child and the control, are labeled with different dyes and hybridized to a single slide for array CGH. For SNP arrays, only the child's DNA is hybridized. Array CGH can provide resolution down to the size of the oligonucleotides, and typically has better signal to background characteristics (compare copy number data in Figures 2 and 3) than SNP arrays. The resolution of SNP arrays is limited, in part, by the distribution of SNPs across the genome, but even if nonpolymorphic oligonucleotides are utilized, the signal to background is typically less optimal for SNP arrays than for arrays using longer oligonucleotides as is typical in array CGH. As practiced until recently, array CGH did not provide any detection

of SNP genotypes so that uniparental parental disomy and consanguinity were not detectable. In contrast, the SNP arrays provide substantial, but not complete, detection of uniparental disomy and detection of consanguinity. The commercial platforms for array CGH have been manufactured primarily by Agilent Technologies (Santa Clara, CA) and Nimblegen (Roche Nimble-Gen Inc., Madison, WI). SNP arrays have been manufactured primarily by Illumina (San Diego, CA) and by Affymetrix (Santa Clara, CA). More recently, Agilent Technologies is offering array CGH with inclusion of SNP detection that is adequate for detection of blocks of absence of heterozygosity associated with uniparental disomy or consanguinity, but is not suitable for a specific genotyping.

An example of the extremely robust signal to background achieved with array CGH that allows for optimal detection of deletions and duplications is shown in Figure 2. There is virtually no overlap for the signal from oligonucleotides within the deleted region as compared to the normal flanking regions. The robust signal to background for array CGH allows detection of deletions or duplications covered by as few as 3–6 oligonucleotides. This can allow detection of deletions or duplications of one or a few exons (Boone et al., 2010). In contrast, SNP arrays have the ability to detect uniparental disomy and consanguinity that was undetected by the usual array CGH platforms until the recent Agilent modification. SNP arrays will detect all cases of uniparental disomy arising through monosomy rescue and will detect some, but not all, cases of uniparental disomy arising to trisomy rescue. An example of a SNP array from a case of Prader-Willi syndrome caused by maternal uniparental disomy is shown in Figure 4 with segments of both isodisomy and heterodisomy. Angelman syndrome caused by uniparental disomy through monosomy rescue would show isodisomy for the entire chromosome. A substantial minority of Prader-Willi syndrome cases caused by uniparental disomy arising via trisomy rescue show heterodisomy for all of chromosome 15 and are not detected by SNP arrays or by array CGH.

By 2004 and 2005, it was increasingly apparent that many children with developmental disabilities and birth defects had underlying genetic abnormalities that could be identified by array CGH or SNP arrays (Shaw-Smith et al., 2004; Veltman et al., 2002). These platforms essentially provided the equivalent of performing hundreds or thousands of FISH tests simultaneously with relatively equivalent ability to detect both deletions and duplications in contrast with metaphase FISH that detected only deletions. It was clear relatively soon that chromosomal microarrays were far more effective than a karyotype in detecting disease-causing genetic abnormalities as exemplified by deletion 1p36 (Yu et al., 2003). Not surprisingly, the yield of abnormalities among samples obtained in the neonatal period is among the highest reported, and one study found disease-causing copy number variants (CNVs) in 20% of neonates tested (Lu et al., 2008). Children with more severe phenotypes were found to have deletion CNVs more frequently than duplications, and typically these represented de novo events in the probands. The identification of multiple children with similar phenotypes caused by similar de novo deletions strengthened the interpretation that particular CNVs were causing the clinically recognizable phenotypes with very high or complete penetrance (i.e., everyone with the CNV has an abnormal phenotype). Another early observation was that duplication syndromes could be quite common, although they were not detected by metaphase FISH in the past. Duplications of the critical region for Williams syndrome (Berg et al., 2007; Somerville et al., 2005; Van der Aa et al., 2009), and duplications of a cluster of genes, including the *MECP2* gene (del Gaudio et al., 2006; Van Esch et al., 2005) were recognized as common causes of intellectual disability as soon as arrays were in widespread use. Loss of function mutations in *MECP2* typically cause Rett syndrome in females, and the same mutations in males usually cause prenatal lethality and are rarely observed as live births. In contrast, duplication of this region in males is associated with a much more severe phenotype than classical Rett syndrome in females. The severe phenotype in males is inherited in an X-linked fashion with heterozygous females

having a normal or near-normal phenotype (Ramocki et al., 2009). Numerous novel deletion and duplication syndromes have been reported using array-based detection over the last 6–7 years, and more detailed reviews are available (Visser, de Vries, & Veltman, 2010; Weiss, 2009).

It is also noteworthy that benign CNVs are extremely common in the human genome. The magnitude of this variation was unexpected. One of the most in-depth studies found an average of 1,098 validated CNVs, and a cumulative CNV locus length of 24 Mb (0.78% of the genome) when comparing two genomes by CGH (Conrad et al., 2010).

Intellectual Disability

Most of the early work on the use of arrays to identify causative deletions and duplications focused on children with moderate to severe intellectual disability often in combination with birth defects and dysmorphism. The earliest articles appeared in 2002–2004 (Shaw-Smith et al., 2004; Veltman et al., 2002) and were soon followed by reports of larger numbers of cases coming from routine clinical labs (Ballif et al., 2007; Lu et al., 2007). In general, the more severe the cognitive impairment and associated findings, the greater the likelihood of identifying a causative CNV. Reviews suggest that karyotype analysis alone identifies underlying abnormalities in 3%–5% of children with moderate to severe intellectual disability excluding Down syndrome (Stankiewicz & Beaudet, 2007). Combination of karyotype with selected FISH, including perhaps telomere FISH, increases the level of detection to approximately 8%–10%. Arrays with the highest resolution of coverage are thought to detect abnormalities in 15%–20% of children with more severe disabilities (Miller et al., 2010), particularly if associated with dysmorphic features, birth defects, or epilepsy. Criteria for assessing whether a CNV in a child is disease causing or benign is available elsewhere (Miller et al., 2010), but some CNVs cannot be interpreted conclusively and are of uncertain significance.

Clinicians frequently wish to know what percent of children with particular phenotypes or developmental disabilities will have causative genetic abnormalities detected by an array analysis. The answer to this question depends on many variables, and thus there is no simple answer. First, the more severe the disabilities and the more these are accompanied by birth defects, epilepsy, and dysmorphism, the higher the likelihood of finding a causative abnormality (Miller et al., 2010). Thus, the phenotypes of the individuals included in any sample play a major role in determining the rate for detection of causative abnormalities. Second, there will be a significant number of children with novel CNVs of uncertain significance. To some extent, the larger the CNV and the greater the gene content, the more likely it will be disease causing (Miller et al., 2010). Of course, even a very small CNV may be disease causing if it inactivates a dosage-sensitive gene. In general, but not uniformly, deletions will be more likely than duplications to cause a phenotype (Miller et al., 2010). Again generally, but with many exceptions, de novo CNVs are more likely to be associated with disease phenotypes, assuming that the children being tested are selected for the presence of clinical abnormalities. In contrast, CNVs inherited from a phenotypically normal parent are less likely to be the cause of clinical symptoms present in the child than a de novo CNV. However, large CNVs can occasionally be benign (Knight, Yong, Tan, & Ng, 1995), and CNVs inherited from unaffected parents may be associated with incomplete penetrance or variable expressivity, such that the CNV is indeed benign in the parent, but disease causing in the child (Ben-Shachar et al., 2009). Thus, there is no way to determine with absolute certainty in every single case whether a CNV is disease causing or not. In addition, many series reported in the literature do not have data available for both parents of all children tested. In general, most groups report a 20%–25% detection rate of causative CNVs in children with moderate or severe intellectual disability. Many large clinical laboratories

report the frequency of disease-causing abnormalities in large series of samples submitted for widely varying phenotypic findings (e.g., Cooper et al., 2011). Typically, the detection rate for abnormalities has been increasing as arrays have provided higher and higher resolution, and even exon-by-exon coverage for hundreds or thousands of genes, but this trend is counterbalanced in unselected series as physicians are submitting samples on children with milder and milder phenotypes. In earlier years, the majority of samples came from children with moderate to severe intellectual disability with or without additional findings. More recently, samples frequently come from children with mild intellectual disability, mild autism-related phenotypes, idiopathic epilepsy, and attention deficit hyperactivity disorder (ADHD; personal observations). The frequency of causative abnormalities among these is still significant, but certainly substantially less as compared to the more severe phenotypes.

Conceptually, it is useful to consider three groups of phenotypic abnormalities associated with CNVs. The first would be the most severe abnormalities where the phenotype almost always prevents reproduction. All or almost all of such cases will represent de novo mutations. Examples of this group would include deletions of 17p11.2 causing Smith-Magenis syndrome, deletions of 15q11-q13 causing Angelman syndrome, and deletions of 22qter covering the *SHANK3* gene, referred to as the Phelan-McDermid syndrome. A second group includes CNVs where affected individuals frequently reproduce and where the penetrance may be anywhere from 50% to 100%. Both symptomatic (penetrant) and asymptomatic (nonpenetrant) individuals may have offspring. With this group of CNVs, a substantial fraction of cases will be de novo, but a substantial fraction will also be inherited. A parent transmitting the CNV may have a normal phenotype or may have disabilities themselves. Examples of this group include duplications of the Williams syndrome critical region, and deletions of chromosome 15q13.3. The third group of CNVs is the one that has relatively weak associations with phenotypic effects. These CNVs are almost always inherited, and there is frequently difficulty in determining whether they have a true phenotypic effect or whether they may be entirely benign. The frequency for these CNVs in the general population may be relatively high, as there is no or little evolutionary selection pressure to eliminate them. Examples of this final group include deletions and duplications of chromosome 15q11.2 (the breakpoint 1 to breakpoint 2 region of Prader-Willi/Angelman domain) and a particularly common, small duplication of the *CHRNA7* neuronal nicotinic acetylcholine receptor (Szafranski et al., 2010).

Chromosomal karyotype and FISH still have utility in certain circumstances. In the case of a gain of copy number, the location of the added material is uncertain, and if the gain is relatively large, FISH can be used to determine whether the duplication is interstitial or is associated with some other rearrangement. Karyotype can distinguish trisomy 21 from translocation Down syndrome, while CMA does not. Therefore, a karyotype is the most appropriate test for a child with a clinical diagnosis of Down syndrome. CMA will not detect truly balanced translocations, but it frequently demonstrates that translocations that are apparently balanced by karyotype, frequently involve genomic gain or loss when studied by CMA (Schluth-Bolard et al., 2009). Truly balanced, de novo translocations in a child with disability are not detected by CMA, but they are rare, and it is difficult to determine if they are the cause of a phenotype. One consensus statement suggests that karyotype and FISH are not cost-effective in a child with intellectual disability after a normal array study (Miller et al., 2010). Karyotype and FISH are useful in determining if the parents and other relatives of a child with an unbalanced translocation have a balanced translocation.

Autism

The different extremes of the autism spectrum are quite instructive relative to the likelihood of identifying underlying causes of CNVs. Some children with autism have relatively severe intellectual disability and many dysmorphic features, and some reports identify causative CNVs in 25%–30% of these cases (Jacquemont et al., 2006). Miles, in an excellent review, distinguishes “complex” and “essential” autism, and defines complex autism as distinguished by the presence of generalized dysmorphism or microcephaly (Miles, 2011). Using this definition, 20%–30% of children ascertained on the basis of an autism diagnosis are in the complex group; the male:female ratio is higher in essential compared to complex autism (6.5:1 vs. 3.2:1), whereas the overall sex ratio in autism is 4:1. There are some curious and complex aspects of the relationships of sex with penetrance of CNVs. Two groups studying the Simons Simplex Collection of families found *de novo* CNVs in 6%–7% of male probands versus 8%–12% of female probands, but because the overall M:F sex ratio was 6.5:1, there were more autistic males than females with *de novo* CNVs (Levy et al., 2011; Sanders et al., 2011). Assuming that the frequency of occurrence of these CNVs is equal in the two sexes as other evidence supports, the penetrance of *de novo* CNVs for autism is sex-limited and higher in males. The “missing” females may have neurobehavioral disabilities, but be less likely to meet criteria for autism, or some may have a normal phenotype. Children with essential or nondysmorphic autism have a much lower frequency of *de novo* CNVs, although the severity of intellectual disability varies widely. This group can have a sex ratio as high as 8:1 (male:female; Kalra, Seth, & Sapra, 2005; Scott, Baron-Cohen, Bolton, & Brayne, 2002), and the etiology remains largely unknown. The experience with array analysis for children with severe complex autism may suggest, based on general genetic principles, that there would be many similar children with autism with point mutations involving specific genes that would currently be undetected by array analysis. There are many examples where most children with a particular diagnosis have point mutations with a normal CMA result, but occasional children have a larger mutation detected by an array; examples of such diagnoses include Rubinstein Taybi syndrome, Cornelia de Lange syndrome, or CHARGE syndrome. The likelihood that many children with severe phenotypes have *de novo* point mutations suggests that whole genome sequencing in these children would identify an underlying causative *de novo* mutation in the majority and even up to perhaps 90% of such individuals. The rationale is that *de novo* point mutations or very small CNVs are both common and can easily inactivate a dosage-sensitive gene, that these events are undetected by current methods, and that they represent the most likely cause of phenotypes such as this in the absence of other risk factors. They might also explain advanced paternal age as a risk factor for disability phenotypes (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2010; Saha et al., 2009).

Array analysis and a limited amount of candidate gene sequencing have now identified many genotypic abnormalities underlying autism (Betancur, 2011; O’Roak et al., 2011). Some of the best documented cytogenetic and single-gene abnormalities are summarized in Tables 2 and 3. Some of the most common CNVs detected in autism are deletions of 16p11.2, maternal duplications of the Prader-Willi/Angelman region, and duplications of the Williams syndrome critical region.

The diagnostic laboratory at Baylor College of Medicine has emphasized the potential advantages of exon-by-exon coverage for many candidate genes that may contribute to neurobehavioral phenotypic abnormalities. Using an array with exon-by-exon coverage for 1,700 genes, a significant number of smaller exon deletions that would be undetected by most array platforms were detected (Boone et al., 2010).

Schizophrenia

Although the prevalence of schizophrenia in adults is about 1.3% (Narrow, Rae, Robins, & Regier, 2002), it is much lower among children under age 13 (less than 1 in 10,000 children; Remschmidt & Theisen, 2005), but the great majority of CNV data are from adults. Schizophrenia is of particular interest because numerous CNVs that have been seen in association with intellectual disability, autism, and epilepsy are also seen in schizophrenia and perhaps bipolar disorder (Sebat, Levy, & McCarthy, 2009). This is particularly true for deletions of chromosome 1q21.1, 15q13.3, and 22q11.2. In the case of chromosome 16q11.2, deletions are particularly common in association with autism, whereas the reciprocal duplication predisposes to different neuropsychiatric phenotypes, particularly schizophrenia (McCarthy et al., 2009). The frequency of identifying underlying causative CNVs in schizophrenia is clearly lower than for the more severe childhood phenotypes, although it may be in the order of 1%–3% of unselected schizophrenia populations (Malhotra & Sebat, 2012). Stewart, Hall, Kang, Shaw, and Beaudet (2011) have unpublished evidence that causative CNVs are more common in patients with both schizophrenia and idiopathic epilepsy than in unselected epilepsy. It is important to note that a single CNV can be associated with widely divergent phenotypes and that a single phenotype can be caused by many different mutations, both CNVs and point mutations (Sebat et al., 2009).

Attention Deficit Hyperactivity Disorder

There are many fewer publications using copy number array analysis to study the ADHD population in comparison to the number of studies of intellectual disability and autism. Like autism, the heritability estimates for ADHD are substantial and range from 30% to 80% (Boomsma et al., 2010; Freitag, Rohde, Lempp, & Romanos, 2010). However, the phenotype is milder than for intellectual disability and severe autism, and association with birth defects, epilepsy, and dysmorphisms is less common. In addition, although reliable statistics on ADHD reproductive fitness are not available (Williams & Taylor, 2006), it is obvious that the impairment of fitness is much less than for severe autism or intellectual disability. On the basis of the experience with intellectual disability and autism, we might predict that the frequency of single CNVs as causative factors might be less, and that those observed might be more often inherited than de novo. Cytogenetic abnormalities can be found in children with ADHD and normal intelligence, but the frequency is far lower than for intellectual disability (Stephen & Kindley, 2006). One recent study of ADHD found four families with deletions in the gene encoding for tyrosine phosphatase (PTPRD) and one family with four affected members with a deletion in the glutamate receptor gene (*GRM5*; Elia et al., 2010). One study found de novo CNVs in 3 of 173 (1.7%) ADHD cases and rare inherited CNVs in 19 of 248 (7.7%) ADHD probands (Lionel et al., 2011). The clinical utility of array-based copy number analysis in children with ADHD remains to be determined. Causative abnormalities probably occur (Williams et al., 2010), but they may be much less frequent than for intellectual disability.

Tourette Syndrome

As with ADHD, the heritability of Tourette syndrome is thought to be substantial, but there are few reports of analysis of genomic copy number in such children. In one study, deletions were found in four genes in 9 of 111 families; *NRXN1*, *CTNNA3*, and *FSCB* in 2 families each, and *AADAC* in 3 families (Sundaram, Huq, Wilson, & Chugani, 2010). All 9 of these children had ADHD in addition to Tourette syndrome. Another study found not a CNV, but a nonsense mutation interpreted to be disease causing in the L-histidine decarboxylase gene (*HDC*) in nine affected cases in a two-generation family with Tourette syndrome (Ercan-Sencicek et al., 2010). An excellent review of the genetics of Tourette syndrome including

extensive discussion of the role of HDC and histaminergic neurotransmission in the mechanism and modulation of Tourette syndrome and tics is available (State, 2010).

Learning Disability

There is some evidence for heritability of learning disabilities (Oliver & Plomin, 2007), reading difficulties (Astrom, Wadsworth, & DeFries, 2007; Wadsworth & DeFries, 2005), and language impairment or delay (Bishop & Hayiou-Thomas, 2008; DeThorne, Petrill, Hayiou-Thomas, & Plomin, 2005; Hayiou-Thomas, Oliver, & Plomin, 2005). However, there are almost no data yet regarding whether causative CNVs might occur in this population.

Mood Disorders and Aggressive Behaviors

There is very little information about the role of CNVs in the etiology of bipolar disorder in children, but such studies should be forthcoming soon. Aggressive behaviors can be seen with many microdeletion and microduplication syndromes. Aggressive behaviors may be particularly common or severe in deletions 15q13.3. One report described a male child with “five admissions to psychiatric facilities because of aggressive behavior and rage” (Helbig et al., 2009), and antisocial behaviors were reported in unavailable biological parents of children removed from the home of parents who might themselves have had the deletion (Ben-Shachar et al., 2009).

Epilepsy

Idiopathic epilepsy frequently accompanies developmental disabilities, especially with more severe phenotypes. Deletion 15q13.3 has been found in ~1% of cases of idiopathic epilepsy (Helbig et al., 2009). Other CNVs are also found relatively frequently with idiopathic epilepsy (de Kovel et al., 2010; Mefford et al., 2010). It seems prudent at this time to perform CMA in cases of idiopathic epilepsy whether accompanied by developmental disabilities or not.

Ethical, Legal, and Social Issues

Clinicians evaluating children with disabilities have a responsibility to make a maximal attempt to establish a genetic etiology and provide access to genetic counseling regarding recurrence risk whether a genetic abnormality is identified or not. Approximately one fourth of the most severe developmental disabilities (Miller et al., 2010), particularly when associated with congenital malformations, could now be detected by invasive prenatal diagnosis using copy number arrays (Van den Veyver et al., 2009). Some suggest that such testing should be offered to all families (American College of Obstetricians & Gynecologists, 2007), although many will choose not to have such testing. Arrays with SNPs can also detect a significant fraction of uniparental disomy, especially that for Angelman syndrome, a very severe disability. Studies of cost–benefit have suggested that offering of invasive prenatal diagnosis to all women was cost effective even before the availability of arrays (Harris, Washington, Nease, & Kuppermann, 2004). Given that arrays are now the first-line test for postnatal studies of developmental disorders, perhaps they should be the first-line test for prenatal studies as well, given that the same genotypes are involved, although there is some concern regarding detection of CNVs of uncertain significance. Reviews discussing the potential prenatal use of CMA are available (Fruhman & Van den Veyver, 2010; Park et al., 2010), and an NIH-funded study in the United States comparing karyotype and array has enrolled over 3,000 participants, and the results of the study are in press.

Arrays that include SNP coverage detect blocks of absence of heterozygosity. If a child is the product of a father–daughter, mother–son, or brother–sister relationship, approximately one fourth of the genome will be identical by descent, and this will identify the unanticipated fact that a child is the product of an incestuous relationship. No parental samples are needed to indicate the presence of incest, although such samples are needed to identify the biological parents. Social service units ready to deal with legal implications, child protection, and social needs similar to those commonly available for child abuse may be useful in such cases. The frequency of incest-related births is not well known, but this will be increasingly recognized by use of arrays. The occurrence of childhood disabilities is high in children born from incestuous relationships (Jancar & Johnston, 1990).

Conclusions, Opinions, Recommendations

It is widely accepted that all or almost all children with intellectual disability should be studied by CMA (Miller et al., 2010). Even in the presence of prematurity or perinatal hypoxia, there is the possibility that an underlying genetic abnormality predisposed to the seemingly nongenetic etiology, and there is potential for genetic counseling if an abnormality is found. It has been suggested that CMA be the first-tier clinical diagnostic test for individuals with developmental disabilities (Miller et al., 2010). The more severe and complex the phenotype, the greater the likelihood of identifying a causative genotype. It is desirable that the array be the highest resolution available at reasonable cost, and it is preferable that it include SNP coverage sufficient to detect uniparental disomy and consanguinity. In the case of definitive abnormalities where a parent may have the same genotype (e.g., DiGeorge syndrome), parental studies should be performed for purposes of genetic counseling. Parental studies are generally not performed if the genotype has 100% penetrance (e.g., Smith-Magenis syndrome or nontranslocation trisomy 21) such that a clinically unaffected parent cannot reasonably be expected to have the same genotype. Parental studies are often very helpful for the interpretation of the potential causative significance of a rare CNV in addition to the value for genetic counseling. A Giemsa-banded karyotype is not indicated in a child with an intellectual disability phenotype if array analysis is normal unless there is clinical evidence of an obvious chromosomal disorder such as Down syndrome or a family history of chromosomal rearrangement (Miller et al., 2010). Similarly, CMA is indicated in children with autism, especially when accompanied by intellectual disability, epilepsy, birth defects, or dysmorphic features. One study of an autism cohort in which only 12% of cases had intellectual disability, still found likely causative CNVs in 7% of children and concluded that CMA should be considered as part of the initial diagnostic evaluation of children with autism spectrum disorders (Shen et al., 2010). There is still room for debate and need for more data regarding whether CMA should be performed routinely for cases of ADHD or learning disability.

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Figure 1.

Comparison of metaphase and interphase FISH. Panel a shows metaphase FISH for a deletion detected by the presence of a red signal on the normal chromosome and not the deleted chromosome. Panel b shows interphase FISH with duplication on the chromosome with two red signals and one red signal on the normal chromosome. (See the online version of this article for Figure 1 in color.) Provided by Ankita Patel and Sau Wai Cheung; used by permission of Baylor College of Medicine.

Figure 2.

Array CGH showing a deletion on chromosome 17 encompassing the neurofibromatosis 1 (NF1) gene and 11 other genes. The study was performed using the Agilent platform. Each dot in the “All chromosomes” view represents a bin of oligonucleotides, while each dot in the other views represents a single oligonucleotide. Black ovals indicate the deleted region. Red ovals indicate the nondeleted oligonucleotides nearest the deletion. The black square at the Y chromosome indicates a benign copy number variation. (See the online version of this article for Figure 2 in color.) Provided by Ankita Patel and Sau Wai Cheung; used by permission of Baylor College of Medicine.

Figure 3.

Single nucleotide polymorphism arrays showing a deletion of chromosome 1 (top) and a duplication of chromosome 22 (bottom) using the Illumina 610 Quad platform. For the deletion in the upper panel, the absence of AB genotype in the B allele data is shown by the upper black oval. The decreased copy number is shown by the lower black oval. For the duplication in the lower panel, the region with AAB and ABB genotypes is shown by the upper black oval and the gain in copy number by the lower black oval. Provided by Joanna Wiszniewska; used by permission of Baylor College of Medicine.

Figure 4.

Single nucleotide polymorphism (SNP) array for a case of Prader-Willi syndrome caused by maternal uniparental disomy for chromosome 15. Analysis was performed on the illumina SNP array platform. The B allele ratio is shown above with AA, AB, and BB genotypes indicated. The copy number is shown below and is normal. There are two regions of isodisomy of 39.5 and 6.4 megabases (Mb), and the intervening segment shows heterodisomy. Provided by Joanna Wiszniewska; used by permission of Baylor College of Medicine.

Table 1

Comparison of Array CGH and SNP Arrays

aCGH	SNP
Single sequence oligos of ~60 bp	Two oligos 20–60 bp of different sequence
Two labeled DNAs (patient and control) Per hybridization	Only patient DNA labeled and hybridized
Resolution down to size of oligonucleotides; exon by exon	Resolution limited by SNP distribution and signal to background
No detection of uniparental disomy or consanguinity	Able to detect consanguinity and Most uniparental disomy
Limited SNP addition possible recently	Detection of most known clinically relevant CNVs, but not exon by exon

Table 2

Multigene Chromosomal Abnormalities Most Often Associated With Autism

Deletions	Duplications
15q13.3	Prader-Willi/Angelman region 15q11–13
16p11.2	Williams region 7q11.23
22q13.3	DiGeorge region 22q11.2
Many others	XXX, XXY, XYY

Table 3

Individual Genes Often Mutated in Autism

SHANK3	PTEN
<i>NRXN1</i>	<i>MECP2</i> /Rett
<i>CNTNAP2</i>	<i>FMR1</i> /Fragile X syndrome
<i>IL1RAPL1</i>	<i>TSC1</i> and <i>TSC2</i> /Tuberous sclerosis
<i>NLGN4</i>	Many others