Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2010 November ; 49(11): 1091–1104. doi:10.1016/j.jaac.2010.08.009.

Genomic Copy Number Variation in Disorders of Cognitive Development

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Abstract

Objective—To highlight recent discoveries in the area of genomic copy number variation in neuropsychiatric disorders including intellectual disability, autism, and schizophrenia. To emphasize new principles emerging from this area, involving the genetic architecture of disease, pathophysiology, and diagnosis.

Method—Review of studies published in PubMed including classic studies of genomic disorders and microarray and copy number studies in normal controls, intellectual disability, autism, and schizophrenia.

Results—The advent of novel microarray technology has led to a revolution in the discovery of classic and novel copy number variants (CNVs) in various disorders affecting cognitive development. Across autism and schizophrenia, global CNV burden and de novo CNV burden are associated with disease. Also, specific recurrent CNVs may be associated with several *DSM* conditions. Each condition is also associated with heterogeneous and individually rare CNVs.

Conclusions—CNVs play an important role in the genetic architecture of the childhood neuropsychiatric disorders discussed. This discovery appears to suggest an important role for the strict regulation of gene dosage in the neurodevelopmental roots of these conditions. Microarrays have emerged as high-yield tests in the diagnosis and molecular subtyping of the childhood-onset disorders involving cognitive development. In summary, CNV studies in disorders of cognitive development have revealed interesting and important new insights and have opened an avenue of investigation that holds great promise for neuropsychiatric disease.

Keywords

microarray; copy number variation; intellectual disability; autism; schizophrenia

The advent of genomic microarray technology has allowed genomewide discovery of small deletions or duplications in the genome, known as copy number variants (CNVs). Although several such CNVs were previously known to be causative in genomic disorders affecting cognitive development, such as a deletion at 7q11.23 in Williams syndrome, microarrays have led to the discovery of numerous additional CNVs currently associated with intellectual disability (ID), autism, and schizophrenia.^{1,2} Many of these CNVs also appear to be shared across disorders.² Because of such shared CNVs and thus potentially some shared biologic underpinnings, these disorders are considered together in this review. In this review, recent and emerging discoveries in genomic copy number variation are proposed to

reveal important and previously underappreciated principles that are highly relevant to the concept of disease and to diagnosis in psychiatry. For one example, CNVs appear to indicate that strict regulation of gene dose in neurodevelopment may be a critical brain mechanism in susceptibility to disease.^{3,4} In this review, emerging principles of copy number variation in the human genome are discussed. The important role that CNVs play in ID, autism, and schizophrenia is reviewed. The following questions will be addressed: What have CNV studies taught us about the genetic architecture and underlying biological causes of autism and perhaps other neuropsychiatric disorders? What role may microarray studies play in clinical diagnosis?

CNVs and Advent of Microarrays

Microarray technology has been advancing at a rapid pace and has offered an opportunity to examine changes in “copy number” across the human genome. By way of background, the normal “diploid” male genome has 22 autosomes (non-sex chromosomes) and two sex chromosomes, an X and a Y. The female genome has 22 autosomes and two X chromosomes. One copy of 23 chromosomes is inherited from each parent and is thereby considered “diploid” or “copy number 2” for each chromosome (exceptions to this involve the sex chromosomes whereby males are “copy number 1” at the X and the Y chromosomes, and females “copy number 0” for the Y chromosome).

It has long been known from conventional microscopic examination of chromosomes, also known as karyotype analysis, that changes in chromosome numbers can cause abnormalities of cognitive development. The most commonly encountered condition in this realm is trisomy 21 (or Down syndrome), which results from an extra copy (“copy number 3”) of the entire chromosome 21 (or relevant portions of the chromosome; OMIM 190685). (In this review, genetic diseases will be referenced to their entry in the Online Mendelian Inheritance of Man [OMIM] database,⁵ which is an excellent reference for those interested in learning more about specific disease with known mutations.)

In addition to trisomy 21, various other “genomic disorders” have been studied by karyotype or fluorescent in situ hybridization (FISH), such as Williams syndrome due to a deletion at 7q11.23 (OMIM 194050) or Smith-Magenis syndrome due to a deletion of 17q11.2 (OMIM 182290). These classic “genomic” disorders are due to CNVs, and in most cases deletions as opposed to duplications of segments of chromosomal DNA (Table 1). CNVs range in size from 1,000 base pairs to millions of base pairs. They may involve a few genes, dozens of genes, or no genes at all (Figure 1). Microarray technology has revolutionized the field and many novel genomic disorders involving neuropsychiatric symptoms have been discovered in recent years using this technique.⁶ Microarray technology allows study of the human genome at the “submicroscopic” level. By using molecular techniques to visualize CNVs, losses (microdeletions, referred to as “copy number 1”) or gains (microduplications, referred to as “copy number 3”) of smaller fragments of genomic material may be discovered with ever increasing resolution, ease, and economy. Another critical advantage of microarray analysis is that it allows these investigations to be conducted in a “genomewide” fashion, examining every chromosome at submicroscopic resolution.

Although there are various distinct types of microarrays, the principles on which they work are similar. Segments of the human genome—most recently short oligonucleotide “probes” representing locations spaced across the entire genome—are arrayed or printed in fixed positions on tiny glass slides (approximately 1.5 × 1.5 cm). A subject's genomic DNA (prepared from a peripheral blood sample) is then labeled with a fluorescent dye and “hybridized” to the array. The goal in this type of analysis is to determine whether the individual carries microdeletions or microduplications anywhere on that individual's

chromosomes. Given the fixed position of the probes on the array, the fluorescent intensity for every given segment of the genome can be compared with a reference sample (assumed to be copy number 2). Gains or losses at each genomic segment may be scored based on an increase or decrease in fluorescence intensity compared with the reference sample(s). The probes may represent evenly spaced segments of DNA across the human genome and/or may cover “hot spots” for recurrent, disease-associated loci. The spacing between these given segments determines the resolution of the arrays. The widely used arrays in research currently have space for 1 to 2 million probes and provide a resolution of approximately 10 to 50 kb or higher across the 3 billion base pairs of the human genome. More “fine-tiling” arrays have also been developed for research and have revealed smaller and smaller CNVs across the genome.⁷

In 2004, the interpretation of copy number studies in disease was cast into a greater degree of complexity, when several laboratories concurrently demonstrated that genomic copy number variation is a part of normal human genetic variation.⁸⁻¹¹ Using various microarray technologies, these groups demonstrated many large genomic deletions and duplications existing in the human genome of typically developing people. That is, we all have CNVs peppered throughout our genome. Today the human genome is being studied, with increasing genomic resolution, and in increasing numbers of samples, to catalogue these CNVs.⁷ At present, there are known to be more than 55,000 CNVs that have been discovered in studies of the human genome, ranging in frequency from extremely rare (some unique within a single family) to more common and stereotyped CNVs (occurring in >1% of people), also known as copy number polymorphisms. Copy number changes are curated in various databases but perhaps the most widely used is the Database of Genomic Variants.¹²

Because CNVs occur in the genomes of “typically” developing people and those with disorders of cognitive development, discerning which CNVs increase susceptibility to disease has been an important challenge. CNVs may be de novo (occurring new in a child due to a germline change in a parent) or inherited. Frequently de novo CNVs herald an association with disease. Although subsequent studies of CNVs in the normal population have found the majority to be inherited, there is a de novo CNV rate in the normal population that is poorly characterized. CNVs may have a range of involvement in disease (Figure 2). Some CNVs such as those associated with genomic disorders are most frequently de novo and are highly penetrant, meaning they are almost always associated with disease; others may be inherited from a generally “healthy” parent and may increase susceptibility to disease but are incompletely penetrant; and others might be entirely benign whether de novo or inherited. A final note of great interest with regard to the biology of CNVs is that the rate of de novo CNVs from one generation to the next has been proposed to be higher than the rate of new base mutations (approximately 1.7×10^{-6} per locus per generation for CNVs compared with 1.8×10^{-8} for sequence variation¹³), and, therefore, CNVs represent one of the most dynamic forms of human genetic variation from one generation to the next. In addition to this high rate of de novo CNV change from generation to generation, CNVs have accumulated to perhaps more than 10% of the genome.^{7,14} In summary, CNVs, as one major class of genomic variation, need to be considered in detail by our field when considering the genetic contribution to disease, including those that may act in a Mendelian fashion or those that may contribute to disease by complex inheritance (i.e., interaction with other alleles and the environment).

There are various mechanisms by which CNVs arise but a sizable percentage of recurrent changes involve a mechanism known as nonallelic homologous recombination (NAHR) during meiosis or production of germ cells—incidentally the same mechanism by which most of the genomic disorders occur (Figure 3). It is thought that NAHR leads to one of the resulting germ cells harboring a deletion of the genomic segment and the other, a reciprocal

duplication of the same segment. In general, deletions result in more severe clinical symptoms and duplications milder symptoms that may go undiagnosed. The mechanism of NAHR is strongly supported by the existence of segmental duplications (segments of genome with near identical sequence that are prone to misalign and recombine) surrounding the region in the genome.

Early CNV Studies in Neuropsychiatric Illness

Even before microarray technology arrived, a number of “genomic disorders” (characterized by stereotypical losses or gains of genomic segments) had been identified, many of which involve abnormalities of cognitive development (Table 1) and various specific “syndromic features.”^{6,14} In addition to Williams syndrome and Smith-Magenis syndrome as stated above, velo-cardiofacial syndrome (VCFS) is due to a stereotyped deletion of 1.5 to 3 million base pairs on the long-arm of chromosome 22 (22q11.2 deletion; OMIM 193430). This deletion removes up to 45 genes, many of which play various roles in neurodevelopment and neurotransmission.¹⁵ Somatic consequences of VCFS include cleft palate and cardiac anomalies and a range of cognitive symptoms, which might include ID, autism, learning disability, attention-deficit/hyperactivity disorder, and/or psychosis. Nearly 30% of patients with VCFS develop a psychotic disorder and/or major affective disorders as adults.¹⁶⁻¹⁸ The 22q11.2 deletion is known to have widely variable expressivity (i.e., the same deletion can cause a range of severity of somatic and psychiatric symptoms) and highly variable penetrance (i.e., some carriers of the deletion will not exhibit a clinical phenotype). Indeed, this deletion was reported early in a cohort of subjects ascertained for childhood-onset schizophrenia (COS).¹⁹

Well before the advent of microarrays, clinicians who suspected a 22q11.2 deletion would conduct FISH, a molecular test somewhat more cumbersome and now replaced by microarrays in many circumstances. In 1995, an adult psychiatrist and genetics researcher, Maria Karayiorgou, and her colleagues demonstrated the occurrence of 22q11.2 deletions in subjects ascertained for idiopathic schizophrenia without known VCFS symptoms in 1% to 2% of cases.²⁰ This represented among the first associations of a CNV with an idiopathic psychiatric condition and that genetic susceptibility loci may be shared across diagnoses. Although idiopathic autism^{21,22} and schizophrenia^{19,20,23} (without full somatic symptoms of VCFS) were reported to be caused by 22q11.2 deletions, FISH testing had not widely entered clinical practice for these disorders.

Other genomic disorders (accompanied by distinctive syndromic features) include deletions of 15q11-q13 that cause Prader-Willi syndrome (OMIM 176270) or Angelman syndrome (OMIM 105830). This particularly interesting deletion was discovered to be associated with Prader-Willi syndrome by medical geneticist David Ledbetter et al.²⁴ Notably, this region of the genome is subject to parental imprinting (i.e., certain genes are exclusively expressed from the paternal and not maternal chromosome and vice versa). Hence, distinct disorders appear depending on the parent from which the deletion is inherited, such that Prader-Willi syndrome results from the paternal-derived deletion and Angelman syndrome from the maternal-derived chromosome.

Before the advent of microarray technology, the duplication of regions at 15q11-q13 (OMIM 608636; which represents the same region as or region related to that deleted in Prader-Willi syndrome and Angelman syndrome) was associated with autism²⁵⁻²⁹ and in some situations was specifically found in nonsyndromic forms of autism spectrum disorder (ASD).²⁶ With respect to this duplication, child psychiatrist Edwin Cook and others were among the first to show that this duplication may be associated with autism when maternally inherited but not paternally inherited.^{26,30} Genomic duplications at 15q11-q13 represent an

important discovery. Not only did this discovery demonstrate the importance of CNVs as a mechanism of genetic susceptibility in autism, but also this specific genetic event has been estimated to occur in 1% to 3% of ASD (OMIM 608636). For this reason, 15q11-q13 FISH was among the first genetic tests for ASD diagnostic subtyping.

CNVs, Genomic Disorders, and ID

Genomic disorders are those that are associated with a known, recurrent deletion or duplication. Numerous such genomic disorders are known and these conditions are most frequently “syndromic” such that they are associated with specific medical conditions, which in the past had raised suspicion and led to FISH testing. In addition, genomic disorders are frequently associated with abnormalities in cognitive development (Table 1). Of particular interest to neuropsychiatry, many of these genomic conditions appear to demonstrate genotype-phenotype correlations with regard to neurobehavioral symptoms and with respect to the medical condition. For example, Williams syndrome is frequently described as being associated with mild to moderate ID with uneven cognitive profiles, relatively intact language and facial processing skills, and decreases in visuospatial abilities.³¹ Williams syndrome personality traits have been described as hypersociable and it has been noted that music ability may be exceptional.^{32,33} Or, as described above, 22q11.2 deletions (the VCFS locus) are frequently associated with a range of neurocognitive symptoms including up to 30% displaying psychotic features.

In terms of ID, in addition to trisomy 21, structural chromosomal rearrangements have long since been associated with a wide variety of disorders of developmental conditions including syndromic and nonsyndromic ID. Karyotype analysis (allowing detection of rearrangements of 5 to 10 million base pairs in size and balanced translocations) and molecular testing for fragile $\times$ syndrome have long since been recommended in the diagnostic work-up for ID, and microarrays are rapidly moving into this realm of diagnostic studies. ID occurs in approximately 2% of the population worldwide³⁴ and is among the most costly causes of lifelong morbidity in the United States.³⁵ Karyotype analysis has yielded relevant findings in approximately 5% of newborns with ID,³⁶ and microarray studies appear to contribute an additional 10% to 20% (depending on the prescreening process).³⁷

The study of CNVs in ID has been reviewed recently,³⁸⁻⁴¹ yet several points should be emphasized in the specific context of neuropsychiatric disease. First, most CNVs and related structural anomalies are widely heterogeneous, occurring all over the genome with many, many “private” mutations, that is, changes (deletions, duplications or translocations) that are unique to individual patients. Such “private” changes make interpretation of causality difficult, but clinical geneticists have relied on three criteria to aid in this regard: size of the CNV, de novo status, and rarity of the finding, that is, has the change been previously reported in a control population. In addition to numerous, heterogeneous, and individually rare CNVs, many recurrent CNVs have emerged that appear to be associated with disease, in these cases, based on occurrence in disease compared with control populations. Here, too, many of these CNVs have appeared all over the genome (i.e., are widely heterogeneous) and are individually rare (although apparently recurrent at low frequency), occurring between segmental duplications and likely arising due to NAHR. Such recurrent CNVs include genomic segments involving 1q21.1, 1q41-42, 2p15-q16.1, 3q29, 7q11.23, 9q22.3, 12q14, 14q11.2, 15q13.3, 15q24, 16p11.2, 16p11.2-12.2, 16p13.1, 17p11.2, 17q21.31, 19q13.11, 22q11.2, and Xq28 (Table 1). These CNVs may be associated with specific syndromic features, although in most cases features are generally quite variable and hard to discern given the rarity of the syndromes and the nonspecific nature of some symptoms. Indeed, moving forward, one of the most important areas of study is collaboration across groups with the aim of increasing numbers of subjects with each genomic finding for genotype-

phenotype studies and thus characterizing whether these are novel microdeletion/microduplication syndromes; however, unlike some of the genomic disorders described above, an increasing number of these recurrent CNVs (although apparently associated with disease) do appear to be inherited and/or incompletely penetrant. As will be described below, most of these recurrent CNVs that are emerging in ID have also been recently discovered in CNV studies of idiopathic autism and/or schizophrenia (Table 1).

CNVs and ASDs

As in ID, numerous studies have presented widely heterogeneous, individually rare, cytogenetic anomalies associated with autistic symptoms.⁴² Given the association of 15q11-q13 duplications in particular with autism, some hypothesized early that a subset of autism was associated with additional, rare recurrent CNVs. However, testing this hypothesis awaited the advent of dense, genomewide microarray technology. Also, given the occurrence of CNVs in the normal population, testing this hypothesis awaited the application of genomewide arrays to large-enough samples of patients and controls. Indeed, in 2007, a strong association of autism and de novo CNVs was clearly demonstrated.⁴³⁻⁴⁵ In these studies, such de novo CNVs were more strongly associated with simplex autism (i.e., sporadic or cases in which only one child is affected in the family) compared with multiplex pedigrees (in which many are affected). This critical observation not only implicates CNVs in the pathobiology of autism, but also that spontaneous genetic change might play a large role in genetic susceptibility, a possibility that may be consistent with decreased fecundity (i.e., negative evolutionary selective advantage) particularly for those with patients with lower adaptive function. At present, there are several stereotyped, recurrent CNVs that may be associated with autism or autistic features that have been discovered using modern microarray technology¹ (Table 1). Many of these are frequently discovered to be de novo in patients, but they may also be inherited (Figure 2). Although occasionally these changes may be found in typically developing people, population study suggests these CNVs significantly increase susceptibility to disease. Given incomplete penetrance, demonstration of the association of these CNVs with the disorder is based on large population-wide studies of frequency in cases compared with controls (Figure 4). These case-control studies are quite challenging given the possibility of systematic difference in CNV frequencies between subpopulations due to different geographic ancestries, a problem defined as population stratification. These studies therefore rely on careful matching of case and control populations for differences in geographic ancestry, and the studies rely on large, sufficiently powered sample size.

In some situations, such as for the neurexin-1 gene (*NRXN1*), CNVs may occur recurrently in the same gene; however, the specific CNV is not stereotyped but variable.⁴⁶⁻⁴⁹ In the case of these *NRXN1* CNVs, CNVs are found in disease in an inherited and a de novo fashion; however, when case-control studies are done in large samples, these CNVs appear more frequently in disease than in cases,⁴⁸ indicating that these CNVs may increase susceptibility to disease on a population-wide basis, but do not appear to act in a Mendelian fashion in contrast to most classic genomic disorders.

Even the most common of these recurrent CNVs are individually rare, each accounting for 2% of autism or less; however, additively these CNVs may play a role in 7% or more of ASD cases.^{43,44} In addition, as is the case with 22q11.2 deletions, most CNVs are not specifically associated with autism but are also found in other disorders of cognitive development. At present, studies of phenotype-genotype associations have been underpowered, and thus, these studies have not indicated that specific phenotypic features are associated with given CNVs, and early data suggest that, although there may be correlations in some cases with somatic symptoms, the neurobehavioral symptoms may be

more widely variable. How many more recurrent CNVs will be discovered in autism is uncertain. There may be many more that are below the resolution of current arrays in size and/or are sufficiently rare that they are not yet seen as recurrent given the current size of study samples. The genomewide arrays have also led to the discovery of a multitude of “private” CNVs, that is, CNVs thus far unique to individual families. Although many intriguing CNVs have emerged, the association of these CNVs to disease remains uncertain.

CNVs and Schizophrenia

In 2008, a series of critical studies concurrently demonstrated a strong association of numerous, individually rare CNVs with schizophrenia. Studies by Walsh et al.,⁵⁰ the International Schizophrenia Consortium (ISC),⁵¹ and Stefansson et al.⁵² demonstrated an increase in burden of rare, large CNVs over controls. Stefansson et al. and the ISC identified overlapping recurrent CNVs, including 22q11.2 deletions, but also deletions at 1q21.1 and 15q13.3. Each of these deletions has also been associated in other studies with ID,⁵³ autistic symptoms,⁵³⁻⁵⁵ and the latter with idiopathic generalized epilepsy.⁵³ Each of these CNVs contains several genes; however, the 15q13.3 CNV is particularly interesting for the involvement of the α_7 nicotinic acid receptor, which had been previously implicated in schizophrenia⁵⁶ and seems to be a target protein that may be readily amenable to pharmaceutical agents. Stefansson et al. also identified a recurrent CNV with greater frequency on 15q11.2 in patients compared with controls. This region is in the neighboring region involved in Angelman syndrome, Prader-Willi syndrome, and autism; however, it is involved in a minority of these conditions and contains an interesting gene, *CYFIP1*, which encodes a protein that interacts with the fragile X mental retardation protein (FMRP). In addition to the discovery of associated recurrent CNVs, the study by Walsh et al.⁵⁰ and the ISC study⁵¹ demonstrated that there is an increase in the overall burden of large, rare CNVs in schizophrenia, and these CNVs are more likely to be associated with genes and may more frequently have roles in neurodevelopment. These results have been replicated in additional studies.^{53,57,58}

Published concurrently with the studies described above, Karayiorgou et al. reported a strong association of CNVs with schizophrenia.⁵⁹ Their results extended the observations by demonstrating a high association of de novo, rare CNVs in sporadic cases of schizophrenia compared with “familial schizophrenia” (i.e., multiplex pedigrees) and controls. Naturally, this result is strongly similar to that reported by Sebat et al. for autism in which increased de novo variant burden in simplex pedigrees is shown.⁴³ In a follow-up study, Xu et al. demonstrated an increase in inherited, rare variants in familial cases compared with controls, suggesting that these variants may represent recent mutation (i.e., not strictly de novo but not generally common across the population).⁶⁰ As in most prior studies, these studies have reported widely heterogeneous, individually rare loci across the genome.

Several important questions emerge from these CNV studies in schizophrenia. The first relates to just how much of the phenotype may be attributable to rare CNVs. Indeed, the frequency of these (generally large) CNVs across the genome is highly variable from study to study. The ISC, among the largest of the studies to date regarding CNVs in schizophrenia (with 3,391 cases), has reported a frequency of such rare variants as approximately 1.15 large CNVs per case compared with approximately 0.99 in controls.⁵¹ Overall, approximately 13.1% of cases of schizophrenia possessed unique deletions or duplications compared with 10.4% in controls. Of interest, recurrent CNVs in the ISC study and the Icelandic study⁵² accounted only for a fraction of a percent of the schizophrenia population. For example, in the Icelandic study, the 15q11.2 deletion was found in 0.55% of cases, the 15q13.3 was found in 0.17% of cases, and the 1q21.1 was found in 0.23% of cases. In the ISC study, 22q11.2 deletions were found to be among the strongest risk factors for

schizophrenia (odds ratio for having schizophrenia = 21.6); however, it was found in approximately only 0.3% of cases. In contrast, in autism the most common recurrent CNVs (such as the 16p11.2 deletions or duplications) may occur as commonly as 1% to 2% and may have an odds ratio as high as 50 to 100.⁶¹

Each of these measurements of burden will be highly dependent on study size and on the nature of ascertainment of subjects; however, the notion that there may be an increased burden attributable to CNVs in autism or ID compared with schizophrenia may be consistent with the earlier onset of the disease and relative greater impairment with regard to cognitive symptoms. The study by Walsh et al. in this regard demonstrated an increase in burden of rare CNVs in subjects with schizophrenia with earlier onset (20% compared with 15% with adult-onset schizophrenia).⁵⁰ Their patient sample included subjects from the well-known longitudinal studies involving COS.⁶² In this regard, subjects with COS had been described previously as having overlapping symptoms with pervasive developmental disorder, in that approximately 25% of subjects with COS exhibited pervasive developmental disorder symptoms before the onset of psychosis.⁶³ A particularly notable recent study in this regard has demonstrated a strong association of the 16p11.2 duplications (but not deletions) with schizophrenia.⁶⁴ The 16p11.2 deletions and duplications had been associated with autism initially^{44,61,65} and subsequently with a range of conditions including ID and obesity.⁶⁶⁻⁶⁹ Additional loci shared across autism and schizophrenia include CNVs in the *NRXN1* locus, which have been associated with schizophrenia,^{70,71} autism,⁴⁴⁻⁴⁶ and ID.⁷²

All CNV studies seem to support the notion that rare CNV burden is correlated to susceptibility to disease, and this may be shared across autism and schizophrenia, and many loci are shared across conditions. Although these findings support the notion that there may be some shared molecular mechanisms across conditions, these findings alone do not call for throwing away our clinical nosology—there are truly distinct ages of onset and distinct profiles in cognitive function. One criticism of the schizophrenia CNV studies has been the level of description of cognitive status before the onset of psychotic symptoms. Clinicians will be well aware of a group of patients with psychosis who have premorbid abnormalities in cognitive development or even mild ID, such as described by Doody et al., the so-called *Pfropfschizophrenie*.⁷³ Although there certainly may be a few situations in these studies where a subject ascertained for schizophrenia had premorbid, mild ID, the likelihood that this accounts for all cases described seems low and subsequent studies have had a greater level of detail with regard to premorbid symptoms, further decreasing the possibility of this interpretation for the data.⁵⁸ Yet the shared role of CNVs in these three conditions does emphasize the similarities across conditions that may have shared biologic roots. Indeed, the history of autism—previously referred to in a confusing manner as “infantile schizophrenia” or the reference to autistic symptoms in schizophrenia by Bleuler⁷⁵—further reminds us of possible shared elements. These elements include at the biologic level in a very general way a shared role for neurodevelopment (vast majority of autism and ID and a significant subset of schizophrenia). At the clinical level, clearly another shared element of disease is the central role of cognitive symptoms. Because of these shared attributes and the shared biologic role for CNVs, these conditions—ID, autism, and schizophrenia, or syndromes that may represent atypical forms thereof—have repeatedly been referred to in this review, in the general way, as disorders of cognitive development.

CNVs and Diagnostic Subtyping

Microarray testing has entered the clinical arena, such that clinicians are sending patient DNA for microarray testing in the setting of a new diagnosis of idiopathic ID and/or autism. It is now widely believed by clinical geneticists that the yield of this testing is high (particularly in the setting of ID and dysmorphology).^{74,76} The test is also reimbursed by

insurance in many centers. That said, the interpretation of these tests in a diagnostic context is not always certain and relies heavily on comparisons with control populations. In general, findings from these microarray tests are categorized by approximately one of three labels: “pathogenic” or “disease-associated,” “benign,” or “variant of uncertain clinical significance.” These distinctions relate to the incomplete penetrance and variable expressivity of these genomic CNVs. For example, on the side of “pathogenic,” the 15q11-13 duplication may be found in idiopathic autism in approximately 1%, and this deletion is rarely incompletely penetrant. In cases of CNVs in patients, testing of the parents may shed further light on interpretation; that being said, de novo status does not immediately mean pathogenic nor does inherited status from a parent immediately mean nonpathogenic. In the case of 1q21.1 deletions (OMIM 612474), there are multiple examples of inheritance from seemingly unaffected parents; however, due to the population-wide association of this CNV to disorders ranging from ID to schizophrenia, this CNV is generally considered disease-associated.⁵³ An example of a benign variant might include a CNV that is found commonly in the population without association to a given phenotype (i.e., a copy number polymorphism). An example of a variant of uncertain significance might be one that is novel (inherited or de novo), but previously not seen. In this case, patients might be told that data will be collected from larger populations in the future, so the significance of such CNVs may be better understood.

This discussion might seem confusing enough that readers might be discouraged from pursuing microarray testing in the clinical setting. Alternatively, one might ask, “What good are these tests. Does it change my clinical management?” At present, in addition to ruling out a host of genomic conditions, there are only a few ways in which CNV diagnoses navigate treatment. These include, for example, serum calcium monitoring in the case of 22q11.2 deletion,⁷⁷ potentially more aggressive monitoring of proneness to obesity in 16p11.2 deletions,⁷⁸ and caution in the use of γ -aminobutyric acid-A receptor agonists in the setting of 15q11-q13 duplications.⁷⁹ However, moving forward, “genotype-phenotype” studies or correlating clinical treatment and outcome with a given CNV are active areas of research and hold great promise for further individualized biological treatments. Also, the discovery of a “likely pathogenic” or a “disease-associated” genetic finding does give the patient and the family a specific medical diagnosis. Their condition becomes converted from idiopathic autism to “autism associated with 15q duplication.” Given the extent of stigma and blame unfortunately associated with neuropsychiatric conditions, and given the extent to which caregivers may seek cures not grounded in a biologic causation (due to the lack of biological explanation), the potential benefits of a molecular diagnosis should not be underestimated. Approximating recurrence risk in families may be informed by CNV findings, particularly in the case of highly penetrant CNVs such as 22q11.2 deletions and 15q11-q13 duplications.

Thus far, use of microarrays for genetic subtyping of schizophrenia has not become widespread. The emerging CNV studies in schizophrenia and the notion of molecular diagnosis have initially been met by the field with a greater degree of controversy compared with that in the autism field. In part, this may be simply due to the likely lower frequency of recurrent CNVs in schizophrenia compared with autism, and this issue may be addressed further as frequency data improve with increases in sample sizes.

Discussion

What have CNV studies taught us about the biology of psychiatric disorders? Indeed, these CNV studies may yield fundamental insights into the genetic architecture and genetic causation of psychiatric disorders. Since the adoption studies of Ingraham and Kety⁸⁰ and even before, psychiatric disorders have been known to be highly heritable. However, the

genetic architecture or the specific mechanism whereby a patient's DNA contributes to an expression of any given disorder has remained elusive. With increasing clarity in psychiatric genetics, CNVs have emerged as strong susceptibility factors in autism and schizophrenia in addition to ID; but as noted above, even the most common recurrent CNVs are individually rare. These studies reveal fundamental principles about the genetic architecture of disease: a significant subset of ASD and ID in particular is associated with myriad individually rare, distinct genetic susceptibilities. Naturally, common variants with individual minor effect but with cumulative effect also appear to make important contributions to genetic architecture particularly in schizophrenia.⁸¹⁻⁸⁵ Yet the CNV studies across diseases have provided resounding support for rare variation with a degree of clarity that has been unusual for psychiatric genetics.

The recent genetic findings described in this review have resulted in a change in terminology. Researchers, such as Geschwind and Levitt,⁸⁶ have coined the term “the autisms,” for example, to emphasize the heterogeneity inherent in the diagnosis. The resulting concept is that one *DSM-IV* “diagnosis,” namely “autistic disorder,” may itself have myriad distinct pathophysiologies. The *DSM* diagnoses may represent a final common pathway or neurobehavioral expression of distinct genetic causes. This notion, that one clinical entity may be the result of various distinct biological causations is, of course, not new to brain disease, because ID and epilepsy—commonly comorbid with autism—fit well under this model (i.e., with a multitude of distinct genetic and environmental susceptibilities). In contrast, another important concept that has emerged is that one genetic locus can have multiple clinical outcomes, likely explained by interactions with other genetic entities, environmental factors, or stochastic aspects of brain development.

What is the biologic significance in terms of disease mechanism of any given CNV, whether a deletion or a duplication? One straightforward interpretation is that the “dosage” of gene expression is tightly controlled during neurodevelopment and that abnormalities of levels of gene expression, too much or too little transcription of a given gene, can perturb brain development and lead to cognitive disorders. Initial data supporting this hypothesis arise from one recent study in which several autism loci implicated genes whose expression was shown to change in response to neuronal activity, a marker of genes involved in synaptic changes that underlie learning.⁴ A tantalizing possibility around the topic of gene dose is the possibility that genomic duplications may play a special role in neuropsychiatric disorders compared with deletions that may appear most relevant to ID. For example, 15q11-13 duplications and 16p11.2 duplications appear to be associated with the milder disorder, autism and schizophrenia, respectively, compared with the deletions associated with these loci, namely ID syndromes (Prader-Willi or Angelman syndrome) in the case of 15q11-13 deletions or ID or autism in the case of 16p11.2 deletions. This possibility, which clearly needs to be further established with larger studies, might suggest that, although disorders may emerge from too little or too much gene expression, increases in gene dosage may be less deleterious than decreases. Certainly these observations appear to be borne out for X-linked methyl CpG binding protein 2 mutations wherein loss of function mutations are lethal in males and cause the severe neurologic disorder of Rett syndrome, yet duplications of the methyl CpG binding protein 2 are consistent with life in males, albeit associated with encephalopathy, mental retardation, or autism.⁸⁷

Another critical question relates to which genes in any given CNV may be playing the central role or no role at all in the disease mechanism. Clearly any gene that may act in a dosage-sensitive fashion at the level of protein function may play a role. Studies of the 22q11.2 deletion (perhaps with the largest record of functional study in chromosome-engineered transgenic mice) seem to point to the notion that multiple genes may be involved and even that single genes may have multiple different effects on distinct roles of brain

development.^{88,89} Arguments against multiple acting genes within CNVs come from the discovery of mutations in the UBE3a gene in the Angelman syndrome deletion, which have implicated this gene as likely the major player in Angelman syndrome due to 15q11-13 deletions.⁹⁰ Therefore, a clear sense of which genes may be involved may come from resequencing or association studies; however, even with such data, it is unlikely that the possibility of interacting effects of genes within loci can be excluded. Therefore, the notion of CNV diseases (sometimes called “contiguous gene” disorders) such as oligogenic or multigenic diseases of gene dosage may be central to our understanding of disease mechanism.

In conclusion, the introduction of microarray technology and its application to CNV studies in disease and in normal populations have heralded a new era in the genetics of psychiatric disorders. Concepts that have emerged for disorders that involve cognitive development (namely ID, autism, and schizophrenia) include the notion that a notable subset of patients with these disorders may harbor genetic susceptibilities in the form of individually rare CNVs. In addition, one CNV locus may be associated with various disorders according to the current diagnostic criteria of the *DSM-IV*. Perhaps even more pertinent, microarrays have entered the realm of diagnostic subtyping for ID and autism and this may soon occur for other disorders. Although interpretation of these clinical tests may not always be straightforward, there are many specific results that convert idiopathic diagnoses based on descriptive psychopathology to diagnoses based on associated biological susceptibilities. CNVs have also suggested biologic mechanisms involving the function of interacting dosage-sensitive genes in brain development. In a world where idiopathic neuropsychiatric disorders may be met with stigma and blame, molecular explanations and diagnosis such as brought on by this field of CNVs may be important for families.

Acknowledgments

The author acknowledges research support from the National Institute of Mental Health (1K23MH080954-01) and the Charles H. Hood Child Health Research Foundation and holds a Career Award for Medical Scientists from the Burroughs Wellcome Fund.

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Figure 1.

Copy number variants. Note: Typical loci are copy number 2 because one maternal copy and one paternal copy are inherited. Certain loci may undergo duplications or deletions and may vary in size, involving none to dozens of genes, represented by boxes. These copy number variable regions of genome are frequently flanked by low copy repeats or segmental duplications, represented by arrows.

Figure 2.

Copy number (CN) variants may be de novo or inherited, associated with disease (highly penetrant or incompletely penetrant), benign, or of unknown significance. Note: The pedigree on the left represents a highly penetrant de novo variant (not present in parents' somatic cells, but here occurring spontaneously in the paternal germline). Pedigree on the right represents an inherited copy number variant that may be associated with disease with incomplete penetrance. BAP = broader autism phenotype.

Figure 3.

Nonallelic homologous recombination represents one mechanism that gives rise to copy number variants and is schematized by recombination within neighboring but nonallelic segmental duplications, represented by arrows.

Figure 4.

Schematic of case-control studies for rare copy number variants where cases are represented by people on left and controls by people on the right. Note: Genders are noted by boxes (male) and circles (female). Darkening represents carriers of copy number variants of interest. A larger number of copy number variant cases over controls suggests association with susceptibility to disease.

Table 1
Representative Recurrent Copy Number Variants (CNV)

CNV Locus	Size (kb)	Del/Dup	Classic Genomic Disorder?	ID	Autism Symptoms	Schizophrenia	Epilepsy	OMIM Number ^a
1q21.1	1,350	del		Mild to moderate	Yes	Yes	Yes	612474
	1,350	dup		Mild to moderate	Yes	ND	ND	612475
3q29	1,500	del		Mild to moderate	ND	Yes	ND	609425
	453-1,760	dup		Mild to moderate	Yes	ND	ND	611936
7q11.23	2,284	del	Williams-Beuren syndrome	Mild to severe	No	ND	ND	194050
	2,284	dup		Mild to severe	Yes	ND	Yes	609757
15q11-q13	4,770-8,147	del-maternal	Prader-Willi syndrome	Mild to severe	No	ND	Yes	176270
	4,700-8,147	del-paternal	Angelman syndrome	Mild to severe	Yes	ND	Yes	105830
15q13.3	1,930	del		Mild to severe	Yes	ND	Yes	608636
	1,930	dup		Mild to severe	Yes	Yes	Yes	612001
16p11.2	700	del		Mild to moderate	Yes	Yes	No	
	700	dup		Mild to moderate	Yes	ND	Yes	611913
17p11.2	3,775	del	Smith-Magenis syndrome	Moderate to severe	No	No	Yes	182290
	3,775	dup	Potocki-Lupski syndrome	Mild to moderate	Yes	ND	ND	610883
22q11.2	1,500-3,000	del	Velocardiofacial syndrome	Mild to severe	Yes	Yes	Yes	188400
	1,500-3,000	dup		None to mild	Yes	ND	ND	608363
Xq28		del		Moderate to severe	Yes	No	Yes	300260
	215-640	dup	MECP2 duplication	Moderate to severe	Yes	No	Yes	300815

Note: Representative recurrent CNVs occur at heterogeneous loci across the genome. Some reflect previously known "classic genomic" disorders, yet others are novel. These CNVs may vary in size, although certain CNVs (those arising by nonallelic homologous recombination due to segmental duplications) are frequently stereotyped in size. Some CNVs are shared across all disorders discussed—intellectual disability (ID), autism, and schizophrenia; however some loci are more commonly deletions in a given disorder and duplications in a second disorder. Also, some CNVs have yet to be found in given disorders. For example, the 7q11.23 deletion is associated with Williams syndrome, whereas the duplication may be associated with an autism-like syndrome, and this CNV has yet to be reported in schizophrenia. Del = deletion; dup = duplication; MECP2 = methyl CpG binding protein 2; ND = not determined.

^aNumbers from Online Mendelian Inheritance in Man database (OMIM).⁵