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Copy Number Variants: A New Molecular Frontier in Clinical Psychiatry

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Abstract

Molecular genetic research, building on genetic epidemiology, has provided the field of psychiatry with a host of exciting advances. It is now clear beyond any reasonable doubt that genetic inheritance influences liability to develop almost every major psychiatric disorder. Rapid progress in identifying genes contributing to psychiatric liability, recently accelerated by the advent of approaches such as genome-wide association studies and chromosomal microarray analysis, raises a critical question for psychiatric practice and training: how will molecular genetics alter the practice of psychiatry for front-line clinicians? The premise of the present review is that our growing knowledge regarding the roles of copy number variants in behavioral disorders will soon require revision of standards of evaluation and care for psychiatric patients.

Keywords

DNA copy number variants; Schizophrenia; Autism spectrum disorders; Segmental duplications

Introduction

Copy number variants (CNVs) are variations in the number of copies of large stretches of DNA sequence in the human genome (>1,000 bp, although that definition is arbitrary) [1]. Cytogeneticists have known for many decades that de novo or inherited alterations in chromosomal structure can lead to human neurodevelopmental disorders. However, only with the recent advent of specific molecular approaches for examining the whole genome has the full extent of the importance of CNVs in human behavioral disorders become apparent. Among the key technologies supporting our growing understanding of CNVs in psychiatric disorders are high-throughput single nucleotide polymorphism (SNP) genotyping; chromosomal microarray analysis (CMA); and, most recently, whole-genome sequencing. As the cost of those approaches continues to decline, the breathtaking pace of discoveries involving CNVs in psychiatric illness is likely to accelerate. We focus on CNVs in this article because unlike small-scale variation such as SNPs, CNVs are already emerging as potentially important in the diagnosis and management of individual patients.

Why are CNVs, as opposed to SNPs, rapidly emerging as useful tools in the clinical evaluation and treatment of psychiatric patients? The answer to that question requires consideration of several factors. First, CNVs, especially those large enough to affect multiple genes, exert much larger effects on phenotypes and clinical outcomes than SNPs. For example, deletions at 22q11.2, which are typically about 1.5 or 3.0 megabases (Mb) in size, increase the risk of schizophrenia by 20- to 30-fold over that in the general population [2]. Such magnitudes of effect are simply unheard of for SNPs in any complex disorder. Second, in addition to their impact on behavioral outcomes, CNVs can lead to medical complications that can impact clinical decision making in patients whose primary presentation is behavioral. Examples of such clinical utility are reviewed below. Finally, diagnostic procedures for identifying CNVs are already in routine use in clinical settings, whereas SNP variation is in most cases detected in research settings. Thus, CMA is already in wide use in clinical genetics laboratories across the United States, and some have advocated its application as a standard of care in the evaluation of childhood behavioral disorders [3•].

Recurrent CNVs constitute a particularly important class of CNV—one that occurs in specific locations in the genome in which low-copy repeat sequences (LCRs) occur. LCRs are large (>10,000 bp) stretches of DNA that are identical or nearly identical in sequence. When LCRs are aligned in the same direction near one another on the same chromosome, they can be improperly aligned during meiosis, leading to the duplication of the intervening sequence in one allele and the deletion of this same region in the other, a process known as *nonallelic homologous recombination*. Nonallelic homologous recombination in regions containing LCRs generates the de novo production of recurrent CNVs in the human population.

Perhaps paradoxically, studies designed to examine the role of SNPs in major mental illness have largely established that CNVs account for a small but epidemiologically and clinically important proportion of patients with schizophrenia, autism spectrum disorders (ASDs), and other psychiatric disorders. SNP-based genome-wide association studies (GWAS) have consistently detected recurrent CNVs and rare large sporadic CNVs in a greater proportion of cases than controls [4-11], with some evidence suggesting that the elevated CNV burden relative to healthy controls occurs in schizophrenia but not in bipolar disorder [8]. Table 1 summarizes the recurrent CNVs associated with psychiatric disorders. Although specific pathogenic CNVs are rare, their cumulative frequency is nontrivial.

For example, in a recent review, the cumulative rate of just recurrent CNVs in schizophrenia was about 2.5% [12]. That rate, which agrees well with the 2% estimate from another recent review [13•], does not include the rare large (and therefore likely to be pathogenic) CNVs that also have been found in every sizeable GWAS of schizophrenia. Thus, studies that ascertained cases solely on the basis of research diagnostic criteria for schizophrenia and schizoaffective disorder consistently found clinically important rates ($\geq 2.5\%$) of previously undiagnosed pathogenic CNVs. The 2.5% figure, however, almost certainly underestimates rates of CNVs in clinically diagnosed schizophrenia spectrum disorders for at least two reasons. First, agreement between research and clinical diagnoses of schizophrenic psychoses is modest at best, with K values commonly less than or equal to 0.5 [14, 15], and in studies not reporting K, agreement rates of about 40% to 80% [16, 17], with the agreement rate climbing as the research definition broadens toward a “spectrum” of disorders [18]. Thus, at a minimum, the cases in current research sample repositories are unlikely to be fully representative of clinically diagnosed patients with schizophrenia spectrum psychoses. Second, schizophrenia genetic studies often exclude patients at greatest risk of CNVs, such as those with intellectual disability (ID) or epilepsy. The ascertainment

strategies underlying modern GWAS studies of major mental illnesses therefore have been consistently biased against including patients with CNVs.

Bassett and colleagues [19] recently evaluated a community sample of 234 consecutive cases meeting the *DSM-IV* criteria for schizophrenia or schizoaffective disorder from a mental health center serving a catchment area of about 150,000 people. They found that 2.5% of those cases carried a CNV detectable by karyotyping plus fluorescent in situ hybridization (FISH) for 22q11 deletion syndrome (22q11DS). However, that study also probably underestimated the rate of CNV for at least two reasons. First, the investigators conducted cytogenetic and molecular analysis only on the 27 cases (13% of the total) meeting additional phenotypic criteria (hypernasal speech, physical birth defects, ID, dysmorphic facies, or short stature) and thus would have missed CNVs in patients in whom psychosis was the only clinically apparent manifestation. Second, except for 22q11 deletions, their methods were incapable of detecting submicroscopic CNVs, including every other known schizophrenia-associated CNV [13•]. The study also could have missed atypical 22q11 deletions not detectable by the FISH probe used by the investigators, which targets the gene *TUPLE1* but would miss smaller deletions not affecting the locus. The International Schizophrenia Consortium study detected two such deletions in 13 22q11DS cases [5].

From the data just reviewed, we hypothesize that the rate of pathogenic CNVs in clinical schizophrenia populations approaches or exceeds 5%. If the rate of pathogenic CNVs in the schizophrenic population is between 2% and 5%, then there are 0.02 to 0.05×2.8 million (<http://www.nimh.nih.gov>), or 56,000 to 146,000 patients with schizophrenia in the United States carrying potentially health-threatening CNVs, most of whom remain undiagnosed. Those numbers have potentially huge implications for research, public health policy, and clinical care.

The remainder of this review summarizes current knowledge of the role of specific recurrent CNVs in psychiatric disorders, with an emphasis on those that have been involved in schizophrenia and ASDs, because these disorders have been most thoroughly studied with regard to CNVs. Although most of the following sections follow the order of the chromosomes on which specific CNVs occur, we begin with a discussion of 22q11DS because this CNV disorder has been known for almost two decades to be involved in psychiatric disorders. In many ways, it serves as a prototype for all CNV disorders in that variable expressivity (ie, individual differences in phenotypic features) and variable penetrance (ie, individual differences in the probability of a particular phenotypic feature) are hallmarks of the disorder.

22q11.2 Deletion Syndrome: The Prototypic Copy Number Variant Disorder

Behavioral manifestations in 22q11DS vary widely [20] but are common in children and adults. Behavioral difficulties in children with the syndrome had been described as early as 1985 [21], and psychosis in adolescents with the disorder was reported in 1992 [22]. Pulver and colleagues [23] confirmed that schizophrenia was common in patients with 22q11DS. Karayiorgou and colleagues [24] found several previously undiagnosed cases of 22q11DS in a series of patients with schizophrenia diagnosed solely on the basis of clinical presentation. The latter study was a landmark because it raised the prospect that a small but clinically and epidemiologically significant proportion of the schizophrenic patient population carried undiagnosed 22q11 deletions. It is now clear that 22q11DS occurs at a low but nontrivial rate (~0.75%, about 30-fold more frequently than in the population at large) in clinically diagnosed schizophrenia patients [25]. Selecting specific phenotypic characteristics prior to molecular testing (eg, facial dysmorphism, conotruncal heart defects, high arched palate or

cleft palate, ID) can substantially increase the diagnostic yield for the deletion in cohorts of patients with schizophrenia [2].

A variety of other psychiatric disorders have been associated with 22q11DS, including attention-deficit/hyper-activity disorder and ASDs [20, 26]. Table 2 summarizes candidate genes residing within the 22q11DS region for which there is some evidence (usually mixed positive and negative results) supporting associations with risk of psychiatric disorders.

A recent study comparing symptom profiles among ASD patients with 22q11DS, those with Klinefelter's syndrome (karyotype 47 XXY), and ASD patients with no specifically defined genetic syndrome suggested that the ranges of overall ASD symptoms in both 22q11DS and Klinefelter's syndrome were narrower than in the idiopathic group and differed from each other [27]. Discriminant function analysis of symptom scores (derived from the Autism Diagnostic Interview, Revised) showed clear distinctions in the profiles of each group. Although the study can be criticized for several methodologic difficulties (eg, the patient samples were ascertained separately, thus introducing the possibility of selection bias), it is an important step forward because the results suggest that specific aspects of the broad ASD phenotype may associate specifically with definable genetic differences among patients. If true, such associations could form the basis for dissection of genetically regulated developmental pathways leading to specific "points" in the "phenotypic space" of ASDs, and may also provide a basis for comparing pathways leading to ASDs versus schizophrenia.

22q11DS also serves as an important prototype for demonstrating the clinical importance of diagnosing specific CNV disorders in patients whose clinical presentation is entirely or predominantly behavioral. For example, 22q11DS associates with hypocalcemia that in its most severe form could lead to fatal status epilepticus. Hypocalcemia in 22q11DS results from the variable degree of parathyroid hypoplasia that occurs in those afflicted, and can vary over an individual patient's lifetime. The condition usually can be corrected by dietary supplementation with vitamin D and calcium, but to establish the diagnosis, clinicians must test ionized serum calcium levels rather than rely on the total calcium levels available in standard metabolic panels. The failure to test specifically for ionized calcium in patients with 22q11DS can lead to poor clinical outcomes. For example, schizophrenia patients are almost always treated with antipsychotic medications. As a class, those agents tend to lower the seizure threshold. Clozapine is among the worst offenders in terms of its effect on seizure threshold but remains a uniquely effective treatment in patients whose psychotic symptoms do not respond well to other antipsychotic medications [28]. Patients with schizophrenia, 22q11DS, and untreated hypocalcemia who are given clozapine will be at extremely high risk of seizures, owing to the synergistic effects of low calcium and the medication. Clinicians unaware of the patient's 22q11DS diagnosis almost certainly would discontinue clozapine when the patient has a seizure after starting clozapine. In that scenario, prophylactic administration of vitamin D and calcium, rather than discontinuation of clozapine, would have been an unexplored therapeutic alternative. Failure to diagnose 22q11DS in the approximately 0.75% of schizophrenia patients who carry such deletions can thereby deprive them of potentially effective treatments. Such cases have been documented, so this matter is of more than theoretical interest [29]. As we learn more about the large variety of clinical management issues associated with each CNV disorder, moving from phenomenologic diagnosis to molecular diagnosis of psychiatric disorders promises to become increasingly valuable for patient care.

1q21 Deletions

Recurrent deletions of 1q21, spanning about 1.35 Mb, were originally identified in a large cohort of patients with schizophrenia [4]. The 1q21 deletion was detected in 11 of 4,718 cases with schizophrenia (0.23%), compared with 8 of 41,199 controls (0.02%), providing compelling evidence of the association of this CNV and schizophrenia. Almost simultaneously, the identical CNV was identified in patients referred for clinical testing with a wide array of phenotypic features, which include isolated heart defects, cataracts, müllerian aplasia, and microcephaly [30]. It is noteworthy that patients with the reciprocal 1q21 duplication have macrocephaly, pointing toward a dosage-sensitive gene involved in head growth. Additionally, several of these patients had a behavioral phenotype manifesting as an ASD [30, 31]. Differing from other well-known microdeletion syndromes, such as Angelman's and Prader-Willi (15q11.q13 deletions), but similar to 22q11DS, deletions in 1q21 lead to wide phenotypic variability and are sometimes found in apparently unaffected parents of affected individuals. However, a thorough phenotypic assessment in these apparently unaffected parents frequently reveals a subclinical neurocognitive or behavioral phenotype [32].

There are at least seven genes in the 1q21 deleted interval, although the one responsible for the behavioral phenotype of patients with this CNV has not been identified. *GJA5* and *GJA8* are both part of the connexin family of genes and play an important role in membrane junctions. Mutations in *GJA5* are known to cause atrial fibrillation, whereas mutations in *GJA8* give rise to cataracts. Interestingly, *GJA8* has been previously associated with schizophrenia [33]. However, the gene responsible for the neurobehavioral phenotype of these patients remains unknown.

3q29 Deletions

Microdeletions of 3q29 have been associated with a variable array of phenotypes, including mild to moderate mental retardation, slightly dysmorphic facial features, gate ataxia, and long tapering fingers [34]. Also mediated by segmental duplications, this recurrent deletion is 1.6 Mb in size and contains 21 genes, several of which are interesting candidates for psychiatric disorders. *DLG1* and *PAK2* are interesting candidates, as they are both autosomal homologs of well-described X-linked ID genes *DLG3* and *PAK3*. *DLG1*, also known as synapse-associated protein 97 (*SAP97*), also interacts directly with *PTEN* to inhibit axonal stimulation of myelination. This molecular brake is important in maintaining proper myelin thickness. When removed, it produces myelin outfoldings and demyelination. In fact, this brake ceases to function in peripheral neuropathies such as Charcot-Marie-Tooth [35]. Additionally, and perhaps most importantly, *DLG1* interacts directly with α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate receptors, both key components of the glutamatergic synapse [36], which is in line with recent research showing the role of glutamatergic dysfunction in schizophrenia [37]. *PAK2* also appears as an interesting candidate, as it regulates cytoskeleton dynamics, consequently regulating the morphology of the synapse and glutamate receptor complexes in the process [38].

15q13.2-13.3 Deletions

The proximal region of the long arm of chromosome 15 contains a series of five highly similar LCRs that predispose this region of the genome to a variety of rearrangements [39]. The most well-known of such rearrangements consist of deletions between the two most proximal LCRs, giving rise to the imprinted disorders Prader-Willi syndrome or Angelman's syndrome, depending on whether the deletion is paternally or maternally inherited, respectively. More distal deletions on chromosome 15, involving loss of DNA between the

third and fifth or fourth and fifth LCRs, give rise to 15q13.2-13.3 deletion syndrome. Such deletions have been identified consistently in GWAS of ASD [40, 41] and schizophrenia [4, 5]. ID is common in 15q13.2-13.3 deletion syndrome, as are difficulties with aggressive behavior and rage outbursts [11, 40, 42]. Seizure disorders are also common in 15q13 deletion syndrome, with one study estimating this single set of CNVs to account for about 1% of idiopathic cases of epilepsy [43].

Among the loci deleted in 15q13 deletion syndrome is *CHRNA7*, encoding the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR). This observation is of great interest for at least two reasons. First, linkage and association studies have implicated *CHRNA7* as an important genetic modifier of a schizophrenia-related physiologic phenotype known as *gating of the P50 auditory evoked potential* (P50-AEP). The P50-AEP is a positive deflection on electroencephalogram that occurs about 50 ms after a brief auditory stimulus. Gating of the P50-AEP refers to the phenomenon in which an auditory stimulus shortly before the index stimulus attenuates the P50-AEP. Such gating is often impaired in individuals with schizophrenia, as well as in their unaffected relatives. Freedman and colleagues [44] reported linkage between markers on 15q13 and P50-AEP gating in families segregating schizophrenia, and subsequent association studies suggested that variation at *CHRNA7* accounts for this linkage [45]. Together with the foregoing results, the association of 15q13 deletion syndrome with ASDs and schizophrenia suggests *CHRNA7* as a prime candidate gene relevant to altered development and function of the brain in psychiatric disorders.

The second reason for specific interest in *CHRNA7* is that the pharmacology of the $\alpha 7$ nAChR is well-developed, with many compounds available for use in animal models and in some cases humans, which could be used as probes with which to examine the role of the receptor in development, and possibly even for therapeutics. We recently described an adult male patient with 15q13 deletion syndrome, schizophrenia, rage outbursts, and epilepsy whose aggressive behavior was substantially attenuated by treatment with an acetylcholinesterase-inhibiting positive allosteric regulator of the $\alpha 7$ nAChR, galantamine. The case provides at least a single example in which diagnosis of a CNV disorder led directly to altered pharmacotherapy in a clinical situation [46].

16p11.2 Duplications

Weiss and colleagues [47] performed a genome-wide search for recurrent CNVs associated with ASDs, using data from SNP genotyping arrays from several large GWAS of ASDs. They noted significant associations of both deletions and duplications in an approximately 590-kb region flanked by LCRs located on chromosome 16p11.2. The finding was even more noteworthy because macrocephaly (enlarged head circumference), an endophenotype observed in a substantial minority of children with ASDs, was also associated with the deletion at 16p11.2.

Simultaneously with the report of the Weiss et al. [47] group, two other research teams reported associations between ASDs and CNVs at 16p11.2 [48, 49]. Importantly, one of those studies confirmed an association between 16p11.2 deletions and ASDs using an independent molecular approach: array comparative hybridization [49]. Although those investigators also found a single case of 16p11.2 duplication in their sample, they observed the duplication in two of their controls and therefore did not conclude that the duplication was associated with ASDs. However, other studies have confirmed both the deletion and duplication as clearly associated with ASDs [48, 50] despite the variable expressivity highlighted by observations of apparently unaffected individuals occasionally carrying the duplication. Detailed examination of ASD probands carrying CNVs at 16p11.2 revealed that the heterogeneous phenotypic spectra associated with these genomic variants include ID and

variable facial dysmorphology [50]. That study also found evidence suggesting that 16p11.2 deletions may be more penetrant with regard to ASDs than are duplications. Another study confirmed the phenotypic heterogeneity associated with CNVs at 16p11.2, adding epilepsy and motor delay to the manifestations associated with the deletion or duplication, and attention-deficit/hyperactivity disorder to those associated with the duplication [51]. Interestingly, that same study found macrocephaly to associate with the deletion, and microcephaly (diminished head circumference) with the duplication.

McCarthy and colleagues [6] reported that schizophrenia is also associated with duplications (but not deletions) at 16p11.2. Interestingly, consistent with earlier results in ASDs, this group also observed an association of the 16p11.2 duplication with head circumference in the schizophrenia sample, suggesting that this endophenotype may not be specific to ASDs, but rather associated with the duplication and a broader risk of neurodevelopmental disorders. If the “specificity” of the association between schizophrenia and only the duplication at 16p11.2 withstands more extensive study in additional cohorts of patients, such an observation could help distinguish genes within the CNV region that may more specifically predispose to ASDs (when haploinsufficient) rather than schizophrenia (when present in excess). However, more data are necessary before it is clear that only the duplication associates with schizophrenia.

16p13.11 Deletions and Duplications

The short arm of chromosome 16 is particularly rich in LCRs [52], with the result that nonhomologous recombination events in the region are common. Thus, another set of recurrent CNVs distal to the 16p11.2 region just discussed occurs on 16p13.11. These CNVs vary somewhat in length due to the complexity of the region, but most are about 1.4 to 1.65 Mb in length. Both duplications and deletions were originally described as associated with ASDs and ID [53, 54], although apparently unaffected carriers of the duplications were identified in several families with affected members. However, a study that screened a large cohort of patients with ID or multiple congenital anomalies, as well as two cohorts of European ancestry adults with no known evidence of behavioral disorders (but who were not specifically evaluated) found only the deletions to occur significantly more frequently in patients than in controls. Those observations led the authors of that study to suggest that duplications at 16p13.1-13.2 may be nonpathogenic variants. A more recent study of more than 4,300 patients with schizophrenia and more than 35,000 controls ascertained in several European countries and evaluated using SNP genotyping arrays found an overall association between duplications at 16p13.1 and schizophrenia, with an approximately threefold excess observed in the patient group. When the investigators classified the duplications according to their positions across three subregions of 16p13.1, they found a stronger association with duplications residing in the proximal two subregions (with respective ORs increasing from 3.27 to 7.27). The authors of the latter study, while acknowledging the difficulty of declaring duplications at 16p13.1 to be pathogenic (given heterogeneity in duplication size and the prior inconclusive results with regard to ID and multiple congenital anomalies), argue that additional factors add to evidence that such duplications are pathogenic. They point out that the subregion analysis just summarized, in addition to strengthening the statistical association, also identifies a strong candidate locus, *NDE1*. That gene encodes a protein that interacts with *DISC1*, which itself is the product of a strongly supported “schizophrenia gene.” Another binding partner of *NDE1* is the gene product of *LIS1*, which is strongly associated with the severe neurodevelopmental disorder lissencephaly.

17q12 Deletions

Although previously described in association with a medical syndrome including renal cysts and maturity-onset diabetes mellitus, until recently, there was no evidence that a central nervous system phenotype was associated with 17q12 deletion syndrome. However, recent studies have shown that ID, ranging from mild to moderate, is common in patients with 17q12 deletion syndrome. More interestingly, behavioral anomalies have been identified in small cohorts of these patients, particularly involving problems in social interactions reminiscent of ASDs. A recent report found that six of nine patients with 17q12 deletion syndrome met *DSM-IV-TR* criteria for ASDs [55•]. This finding was then confirmed in larger cohorts of patients with ASDs [55•]. Additionally, given the clinical and genetic overlap between ASDs and schizophrenia, large cohorts of patients with schizophrenia were investigated to assess the frequency of the deletion. A strong association was identified between 17q12 deletion syndrome and schizophrenia. This CNV was absent from a very large sample of control individuals (52,448), which could be interpreted as a strong impact of this CNV over the phenotype of affected individuals, albeit variable expressivity [55•].

Interestingly, the 17q12 region overlaps with a replicated linkage and association peak found in families with ASDs [56-60]. It is tempting to hypothesize that one of the genes within this region is responsible for that linkage signal. However, the frequency of the deletion across different populations is 1 in 900 on average, and the frequency of yet-undiscovered mutations in one of the genes, which would account for a similar phenotype, is very likely rare as well and may not fully explain the linkage signal.

The 17q12 deletion syndrome region harbors 15 genes, with haploinsufficiency in one or more of these likely accounting for the neurocognitive phenotypes observed in these patients. *HNF1B* is responsible for the core features of the renal cysts and diabetes syndrome referred to earlier [61]; however, patients with point mutations or single gene deletions do not appear to have a behavioral phenotype, which would mean that one of the other genes within the region may be responsible for the central nervous system findings. *LHX1* is a transcription factor involved in brain development and axonal guidance and appears as an interesting candidate [62]. Knockout mice lack proper patterning of the midbrain–hindbrain barrier [63]. Nevertheless, no mutations in humans have been documented, so the pathogenic role of haploinsufficiency cannot be clearly established. More studies are needed to clarify this issue.

Conclusions

In just a few years, genome-wide studies have revealed that many CNV disorders can present as psychiatric syndromes, most notably ASDs and schizophrenia. Furthermore, as summarized in Table 1, the same CNVs often associate with more than one behavioral disorder. In clinical practice, these observations suggest we should be including CNV disorders in the differential diagnosis of behavioral disorders, especially when clinical evidence of a syndromic presentation occurs. Thus, patients presenting at any age with ID or seizures in combination with psychosis, ASDs, attention deficits, or mood disorders are candidates for testing for an underlying CNV. Similarly, psychiatric disorders in the presence of multiple medical problems or congenital abnormalities should prompt consideration of clinical genetic evaluation. As already noted, more than a decade ago, Bassett and Chow [2] suggested clinical criteria for referral for 22q11DS testing by FISH. Those criteria now suggest testing by CMA, as patients with syndromic behavioral presentations clearly are at risk of multiple CNV disorders.

At least for 22q11DS and possibly for 15q13.3 deletion patients, differences in approach to clinical management are likely to be indicated even today. As experience and research with CNV disorders progresses, it seems likely that every psychiatrist will need to begin considering testing for such disorders with a widening variety of their patients. The era of molecular psychiatry is truly upon us.

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Table 1

Recurrent copy number variants associated with psychiatric disorders

Location	Type	Associated psychiatric disorders	Common medical complications	References
22q11.2	Deletion	SCZs, SDs, ID, ASDs, MDs, ADHD, BPD	CHDs, IDEF, HPTH, CLP, VPI, FD, MCAs, MC, CTs	Stefansson et al. [4], Bassett et al. [64], Botto et al. [65], Rockers et al. [66]
17q12	Deletion	SCZs, SDs, ID, ASDs, ADHD	RCs, DM (MODY5), PA, GMs	Stefansson et al. [4], Consortium [5], Loirat et al. [10]
16p13.11	Duplication and deletion	SCZs, SDs, ID, ASDs	MCAs	Kirov et al. [8], Heinzen et al. [67], Hannes et al. [68]
16p11.2	Duplication	SCZs, SDs, ID, ASDs	CAKUTs, OB	McCarthy et al. [6], Kirov et al. [8], Bachmann-Gagescu et al. [69], Sampson et al. [70]
15q13.3	Deletion	SDs, ID, ASDs	CRCAs, CHDs, FD	Ben-Shachar et al. [11], Middeldorp et al. [71], van Bon et al. [72]
3q29	Deletion	SCZs, ID, ASDs, BPD	FD, CLP, MCAs, AG, VPI, MC	Willatt et al. [34], Mulle et al. [73], Ballif et al. [74]
1q21	Deletion	SCZs, ID, ASDs	TAR, CHDs, CTs	Stefansson et al. [4], Consortium [5], Kirov et al. [8], Velinov and Dolzhanskaya [75]

ADHD attention-deficit/hyperactivity disorder, *AG* ataxic gait, *ASD* autism spectrum disorder, *BPD* bipolar disorder, *CAKUT* congenital anomaly of kidneys and urinary tract, *CHD* congenital heart defect, *CLP* cleft palate, *CRCA* colorectal carcinoma, *CT* cataract, *DM* diabetes mellitus, *FD* facial dysmorphology, *GM* genital malformation, *HPTH* hypoparathyroidism, *ID* intellectual disability, *IDEF* immune deficiency, *MC* microcephaly, *MCA* multiple congenital anomaly, *MD* mood disorder, *MODY5* maturity-onset *DM* of the young, type 5, *OB* obesity, *PA* pancreatic atrophy, *RC* renal cyst, *SCZ* schizophrenia spectrum disorder, *SD* seizure disorder, *TAR* thrombocytopenia absent radius, *VPI* velopalatal insufficiency

Table 2

Candidate genes in the 22q11 deletion region associated with risk of psychiatric disorders

Locus	Gene product and function	References
COMT	Catechol- <i>O</i> -methyltransferase: catalyzes catabolism of neurotransmitters dopamine and norepinephrine.	Abdolmaleky et al. [76], Bassett et al. [77], Lachman et al. [78], Munafo et al. [79], Shifman et al. [80]
PRODH	Proline dehydrogenase: participates in synthetic pathway for excitatory neurotransmitter, glutamate.	Gogoa et al. [81], Jacquet et al. [82], Meechan et al. [83]
ZDHHC8	Zinc finger, <i>DHHC</i> -type containing 8: likely a transmembrane palmitoyl transferase that post-translationally modifies proteins involved in intracellular trafficking and synaptic function; variants associated with abnormal SPEMs in schizophrenia	Shin et al. [84]
RANBP1	Variants associated with abnormal SPEMs: may be due to linkage disequilibrium with <i>ZDHHC8</i>	Cheong et al. [85]
RTN4R	No Go-66 receptor: a key protein in axonal pathfinding during development	Sinibaldi et al. [86]

SPEM smooth-pursuit eye movement