Copy Number Variation in Syndromic Forms of Psychiatric Illness: The Emerging Value of Clinical Genetic Testing in Psychiatry

Christian G. Bouwkamp, Ph.D., Anneke J.A. Kievit, M.D., Ph.D., Sander Markx, M.D., Joseph I. Friedman, M.D., Laura van Zutven, Ph.D., Rick van Minkelen, Ph.D., Terry Vrijenhoek, Ph.D., Bin Xu, Ph.D., Ineke Sterrenburg-van de Nieuwegiessen, M.D., Joris A. Veltman, Ph.D., Vincenzo Bonifati, M.D., Ph.D., Steven A. Kushner, M.D., Ph.D.

What is the likely probability that a parent with schizophrenia in whom the 16p11.2 microduplication syndrome is found will pass along that CNV to a particular offspring?

a. 1%, the population base rate of schizophrenia
b. 10%, the likelihood of parent to child transmission of schizophrenia
c. 50%, the likelihood of inheriting one of the parent's two chromosomes in meiosis
d. Depends upon whether an older offspring already has it

"Mr. A" is a 22-year-old man with a slim appearance who resides with his parents and works in their convenience store. For the past 2 years, he has been in a romantic relationship with a woman who lives independently nearby. Mr. A experienced his first psychotic episode at the age of 17, during which he was hospitalized for 6 weeks and treated with 5 mg/day of haloperidol, leading to a significant reduction in his psychotic symptoms. Mr. A was discharged with a diagnosis of psychotic disorder not otherwise specified, on maintenance treatment with haloperidol, and he began outpatient visits with a psychiatrist. During the first year after his discharge from the hospital, Mr. A's medication regimen was transitioned to 4 mg/day of risperidone because of extrapyramidal side effects on haloperidol, and his diagnosis was revised to schizophrenia. Since then, Mr. A has experienced several periods of increased psychotic symptoms. However, these were well controlled by transient increases of his risperidone dosage.

During outpatient family meetings with Mr. A and his parents, it became apparent that Mr. A's mother suffered from intermittent nonaffective psychotic episodes, which had never been formally evaluated or treated. The family agreed that Mr. A bore a close resemblance to his mother, both in psychiatric symptoms and in physical appearance. Mr. A's mother also reported having a younger sister whom she described as "a little odd." Throughout elementary school, Mr. A's performance was below average, and he was late in reaching developmental milestones. His elementary school teacher suggested to his parents that he may suffer from attention deficit hyperactivity disorder, but this was never formally evaluated. In secondary school, Mr. A continued to struggle academically and decided to stop attending school beyond the legal requirement at age 16. During the course of his outpatient treatment, neuropsychological testing revealed that Mr. A had substantial impairments in both attention and working memory. His full-scale IQ was determined to be 70, with a verbal IQ of 68 and a performance IQ of 72. Coincidentally, the family read an article in their local newspaper about genetic testing in patients with autism spectrum disorder, which prompted Mr. A to discuss genetic testing with his psychiatrist, who referred him for clinical genetic counseling.

During the physical examination by the clinical geneticist, Mr. A was noted to have dysmorphic facial features, including elongated face with low-set ears, elongated fingers and toes, and a flat nasal bridge. Oral examination revealed a high-arched palate. Genotyping of Mr. A and his parents revealed a maternally inherited *16p11.2* duplication. Brain MRI was notable for cavum septum pellucidum and enlargement of the third and fourth ventricles.

The psychiatric symptoms and dysmorphic features of Mr. A and his mother are consistent with the *16p11.2* microduplication syndrome (OMIM #614671). The genetic counselor discussed with Mr. A and his parents the findings and the implications for future offspring. Both Mr. A and his parents reported that they were comforted to learn that there was an identifiable cause of

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the familial psychiatric illness. However, Mr. A's mother also described experiencing some ambivalence about the outcome of the genetic testing, with feelings of guilt about her responsibility in "passing on" the pathogenic copy number variant to her son. His mother's concerns were discussed over several sessions with a clinical psychologist who is a member of the medical genetic counseling team. Mr. A is now aware that there is a 50% chance for each of his children to inherit the *16p11.2* microduplication. Mr. A and his partner have expressed a desire to have children and were specifically counseled about family planning. Additional family members potentially at risk for carrying the *16p11.2* microduplication by Mendelian inheritance were informed by Mr. A and his mother about the option to contact their clinical genetic counselor to discuss the possibility of having a genetic evaluation for themselves.

Despite extensive efforts and recent major successes (1, 2), the genetic architecture of psychiatric disorders has remained insufficiently understood to recommend genetic testing as part of the routine diagnostic evaluation in clinical psychiatry (3). With recent developments in advanced molecular genetic techniques and a considerable reduction in costs, there has been a dramatic improvement in our understanding of the genetic underpinnings of severe psychiatric disorders (1, 2, 4–6). The strong heritability of severe psychiatric disorders was initially suggested by high rates of concordance in studies of monozygotic twins as well as in adoption studies, especially in those involving monozygotic twins (7). Additionally, in large epidemiological studies, it has been repeatedly demonstrated that the risk of psychiatric illness is inversely proportional to the genetic distance from an affected relative (8).

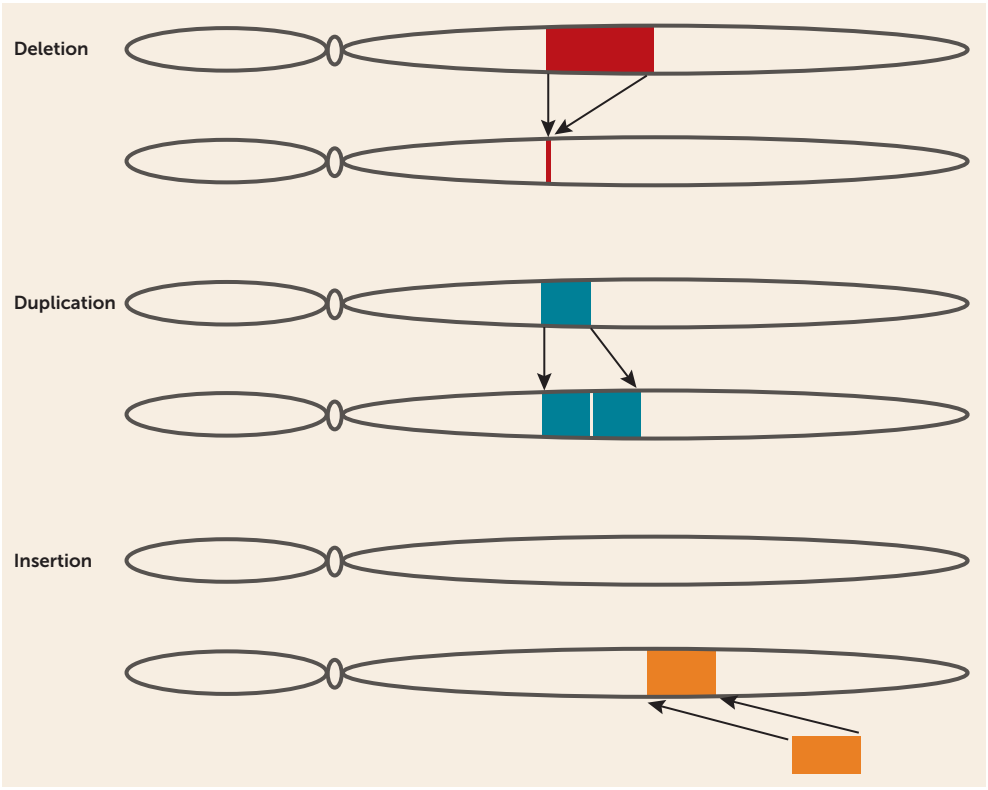
Large international consortia have undertaken highly successful efforts to unravel the genetic underpinnings for several of the major psychiatric disorders. For schizophrenia, a genome-wide association study (GWAS) was performed using >36,000 patients and >110,000 controls, which allowed for the identification of 108 loci reaching genome-wide significance (1). Using a polygenic risk score, these loci accounted for an estimated 3.4% of the variance in schizophrenia liability, which is generally considered insufficient for implementation as a routine clinical diagnostic measure (9). The largest effort to date for identifying rare coding variants was performed using roughly 2,500 cases and an equal number of controls, yielding no variants reaching genome-wide significance (4; but see also 10). Multiple genes have been reported to exhibit an increased burden of rare de novo mutations among patients with schizophrenia, which disproportionately involve genes coding for proteins that govern synaptic function (11–13). For bipolar disorder, the largest GWAS reported included a total of approximately 12,000 patients and 52,000 controls, in which genome-wide significant associations were observed for *CACNA1C* and *ODZ4* (14). For major depressive disorder, no genome-wide significant loci were identified in a 2013 GWAS mega-analysis comprising ~9,200 cases and ~9,500 controls in the discovery phase and ~6,800 cases and ~50,000 controls in the replication phase (15). However, consistent with the widely held assumption that the genomic architecture of many polygenic disorders will yield to analyses involving increasingly large cohort sizes, a recent GWAS of major depression involving a discovery cohort of ~75,000 cases and ~231,000 controls, and a replication phase with ~45,000 cases and ~106,000 controls, identified 15 genome-wide significant loci (16).

Genetic studies of autism spectrum disorder (ASD) have yielded notably strong associations with rare monogenic syndromes, including fragile X syndrome, tuberous sclerosis complex, and Angelman syndrome (17, 18). Investigations of idiopathic autism spectrum disorder have converged on de novo mutations as a frequent genetic determinant (19). The most recent large-scale study (2), involving 2,500 pedigrees, found that de novo coding mutations and copy number variants (CNVs) together explain approximately 30% of simplex ASD cases. The CNV results confirmed multiple previously identified susceptibility loci for ASD, including *1q21.1*, *3q29*, *7q11.23*, *16p11.2*, *15q11.2–13*, and *22q11.2* (20). Notably, de novo point mutations and CNVs were also recently demonstrated as the major cause of severe intellectual disability (21). Moreover, neurodevelopmental abnormalities, congenital heart disease, and extracardiac congenital anomalies appear to cosegregate among patients with de novo mutations (22), together providing further evidence of pathogenic rare genetic variation in syndromic forms of psychiatric illness that involve comorbidity between axis I psychiatric disorders, intellectual disability, congenital abnormalities, and dysmorphic features.

COPY NUMBER VARIANTS

CNVs are a common source of structural genomic variation involving gains (duplications or insertions), losses (deletions), or complex rearrangements of genomic sequence resulting in deviations from the diploid state (23, 24) (Figure 1). On average, each individual is estimated to have >1,000 CNVs, with similar rates of gains and losses, together involving ~10 Mb of genomic sequence (25). CNVs can include one or more genes, leading to disruptions of coding regions or alterations of gene dosage, although many CNVs involve exclusively intergenic sequence. A wide variety of CNVs have been shown to be important sources of pathogenic mutations, particularly those of large size (>100 kb), low frequency (<1% in the general population), and containing

FIGURE 1. Schematic of Major CNV Types[a]



[a] Segments of DNA can be deleted, duplicated, or inserted. The CNV duplication shown here is in an adjacent tandem alignment, but duplications can also be located on more distant parts of the same chromosome or on other chromosomes, thereby potentially disrupting other genes.

genes (5, 21, 25–27). With the advent of microarray technology, reliable detection of CNVs has been widely implemented for both research and clinical diagnostic use in a standardized and relatively low-cost workflow (25).

Rare CNVs have been well demonstrated as enriched in patients with a variety of severe psychiatric disorders (5, 28–30). The CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium and the Psychosis Endophenotypes International Consortium recently published a collaborative study (5) involving a large cohort of patients with schizophrenia (N=21,094) and unaffected controls (N=20,227). Overall, patients with schizophrenia were found to have a significantly increased burden of CNVs (>10 kb in size with a population frequency <1%). Eight loci reached genome-wide significance for their pathogenicity: deletions at *1q21.1*, *2p16.3* (*NRXN1*), *3q29*, *15q13.3*, *16p11.2* (distal), and *22q11.2*, as well as duplications at *7q11.23* and *16p11.2* (proximal). Remarkably, CNV deletions at the *22q11.2* locus were observed in 64 of 21,094 cases, compared to one of 20,227 controls ($p=5.7\times10^{-18}$; odds ratio=67.7, 95% CI=9.3–492.8). Carriers of these rare pathogenic CNVs have a significantly higher risk of developing psychosis and a range of other neuropsychiatric disorders, including mood and anxiety disorders, attention deficit hyperactivity disorder (ADHD) (31), ASD (32), and Parkinson's disease (33), as well as a variety of congenital malformations (31, 34, 35).

The eight CNVs found to be significantly associated with schizophrenia are collectively present in 1.4% of patients and together explain 0.85% of the variance of schizophrenia liability (5), while the 108 genome-wide significant loci of the latest schizophrenia GWAS explain 3.4% of the variance (1). Although the relatively low prevalence of highly penetrant CNVs among patients with nonsyndromic schizophrenia currently appears to limit the cost-effectiveness of CNV testing in the standard psychiatric diagnostic workup, with increasingly large data sets and continued reductions in cost, this remains a distinct possibility in the future.

Compared to patients with nonsyndromic forms of psychiatric illness, those with syndromic features have a significantly higher frequency of CNVs. In one of the first studies to examine CNVs in patients with syndromic psychiatric illness, deletion of *CNTNAP2* was found to be associated with comorbid schizophrenia and epilepsy (36). A subsequent study described patients with comorbid schizophrenia and epilepsy, in which 4% of the cases had a *15q11-q13* duplication while none were found in controls (37). Similarly, in a study investigating the relative frequency of CNVs in schizophrenia patients with or without intellectual disability, an excess of large (>1Mb) *15q11.2* duplications or deletions was found in patients with schizophrenia and comorbid intellectual disability (38). In an exemplary case, the *15q11.2* duplication carried by a proband was found to cosegregate in his family with schizophrenia and comorbid intellectual disability, hearing impairment, and ophthalmological problems.

THE CLINICAL GENETIC EXAMINATION AND CONSULTATION

Clinical geneticists provide a diagnostic service and counseling for individuals or families with, or at risk for, conditions that may have a discernible genetic etiology. Ideally, a clinical genetics consultation for patients with severe psychiatric disorders is an opportunity to assess etiology, prognosis, and risk for offspring through probability estimates based on empirical genetic findings (8, 39, 40). In certain instances, clinical, molecular, or metabolic diagnostics can provide

insight into the genetic cause of the disorder or syndrome (19, 22, 41). Client-centered psychiatric genetic counseling for patients and their families has already been implemented successfully in a few specialized centers, with demonstrable enhancement of patient empowerment and self-efficacy (39). Moreover, prenatal genetic counseling has also been demonstrated to be an important opportunity for discussing psychiatric illness risk, facilitating insight, and increasing etiological understanding in a therapeutic and collaborative manner (40).

When a patient is referred for genetic consultation, the proband, parents, and/or spouse are typically interviewed to learn about the motivation for their visit. In addition to the anamnesis, a detailed family history is obtained with a particular focus on pregnancy, delivery, and early developmental milestones. The clinical geneticist performs a physical examination of the proband, including dysmorphology assessment, in order to evaluate for the presence of syndromic features and/or minor physical anomalies (MPAs) that might be suggestive of genetic disease. MPAs are congenital anatomical defects (e.g., deformities of the head, eyes, ears, mouth, palate, hands, and feet) thought to be indicative of abnormal ectodermal development during the first and/or second trimester (42). Since the CNS is of ectodermal origin, MPAs are generally viewed as potential indicators of abnormal CNS development (43). A large number of studies have documented an increased prevalence of MPAs in patients with psychiatric disorders of a presumed neurodevelopmental etiology, such as schizophrenia and ASD (44).

In the present study, we specifically focused our investigation on patients with a syndromic form of psychiatric illness, defined as an axis I disorder in combination with multiple congenital abnormalities and/or dysmorphic features. A total of 50 patients with syndromic psychiatric illness, comprising two independent prospectively recruited consecutive case series, were screened for CNVs. In total, we identified pathogenic or likely pathogenic CNVs in 24.0% of patients (95% CI=12.2–35.8), with analogous findings in each independent cohort.

METHOD

Cohorts

Pilgrim Psychiatric Center cohort. Medical ethical approval was obtained from the institutional review board of Pilgrim Psychiatric Center in Brentwood, N.Y., and the Mt. Sinai School of Medicine in New York City. Patients, none of whom had previously undergone any genetic testing, were evaluated between February 2000 and June 2001. Informed consent was obtained from all patients. Patients with schizophrenia or schizoaffective disorder were diagnosed according to DSM-IV-TR criteria using the Comprehensive Assessment of Symptoms and History (45). Intelligence testing was performed using the Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) with the relevant classification terminology proposed by Groth-Marnat (46): average (full-scale IQ, 90–109), low average (full-scale IQ, 80–89), well below average (full-scale IQ, 70–79), and lower extreme (full-scale IQ, ≤69). Medical chart review, family history, dysmorphology assessment, and physical examination were performed by a qualified psychiatrist (J.I.F., S.M.).

Erasmus University Medical Center cohort. Medical ethical approval was obtained by the institutional review board of the Erasmus University Medical Center in Rotterdam, the Netherlands. Patients were referred by their treating psychiatrist to the Department of Clinical Genetics for diagnostic evaluations between January 2012 and July 2013. All patients were diagnosed according to DSM-IV-TR using the Structured Clinical Interview for DSM-IV Axis I Disorders. Medical chart review, family history, dysmorphology assessment, and physical examination were performed by a qualified medical geneticist (A.J.A.K.). The parents of the patients were invited to provide DNA samples, but participation was declined in all but one case.

Presentation and History

For the purposes of this study, we operationally defined a "syndromic" presentation as a DSM-IV-TR axis I psychiatric disorder in combination with at least two dysmorphic features and/or congenital abnormalities involving the head, hair, face, chin, eyes, ears, nose, mouth, lips, teeth, neck, thorax, abdomen, genitalia, skin, extremities, stature, or spine.

Family history of psychiatric illness was obtained by constructing a three-generation pedigree for each proband and systematically interviewing the proband and available family members regarding the psychiatric history of each person represented on the pedigree.

Genotyping

DNA was extracted from venous whole blood. Genotyping of the Pilgrim Psychiatric Center cohort was performed using the Affymetrix GeneChip Human Mapping 250K Nsp Assay, with the Affymetrix GeneChip Command Console (Affymetrix, Santa Clara, Calif.) for quality control analysis and variant calls. Genotyping of the Erasmus University Medical Center cohort was performed using the Illumina HumanCytoSNP-12v2.1 microarray, with the Illumina iScan Control and GenomeStudio software program, version 2.1, as well as the Nexus Copy Number Discovery software program, version 5.0 (BioDiscovery, Hawthorne, Calif.). Deletions were considered if they were supported by more than five sequential probes and larger than 150 kb. Duplications were considered if they were supported by more than seven sequential probes and larger than 200 kb. The results were filtered to remove common CNVs (population frequency >1%) present in the UCSC Genome Browser (hg18 build), the Database of Genomic Variants, and in-house databases. Copy-neutral regions of homozygosity were considered if they were larger than 5 Mb. Fragile X Syndrome testing was performed in the Erasmus University Medical Center cohort by Southern blot analysis of the FMR1 trinucleotide repeat length.

TABLE 1. Characteristics of Patient Cohorts Referred for Genetic Testing and Counseling

Center and Characteristic		
Pilgrim Psychiatric Center (N=19)	Mean	SD
Age (years)	38.4	10.0
	N	%
Male	9	47.4
Primary psychiatric diagnosis		
Schizophrenia	15	78.9
Schizoaffective disorder	4	21.1
WAIS IQ classification (N=18)		
Average (90–109)	1	5.6
Low average (80–89)	0	0.0
Well below average (70–79)	3	16.7
Lower extreme (≤69)	14	77.8
Erasmus Medical Center (N=31)	Mean	SD
Age (years)	34.6	11.7
	N	%
Male	20	64.5
WAIS IQ classification (N=29)		
Average (90–109)	0	0.0
Low average (80–89)	9	31.0
Well below average (70–79)	4	13.8
Lower extreme (≤69)	16	55.2
Primary psychiatric diagnosis		
Autism spectrum disorder	10	32.3
Schizophrenia	6	19.4
Psychotic disorder not otherwise specified	5	16.1
Schizoaffective disorder	4	12.9
Major depressive disorder	1	3.2
Dysthymic disorder	1	3.2
Bipolar disorder	1	3.2
Attention deficit hyperactivity disorder	1	3.2
Behavioral disorder not otherwise specified	1	3.2
Impulse control disorder	1	3.2
Family history of psychiatric illness	23	74.2

Pathogenicity Classification

CNV pathogenicity classification was implemented according to the guidelines of the American College of Medical Genetics (47) through consensus between a molecular geneticist and clinical psychologist (C.G.B.) and a medical geneticist (A.J.A.K). In rare instances of discordance regarding variant classification, a consensus decision was made through a collaborative discussion together with a qualified psychiatrist (S.A.K.). Variants were classified as pathogenic if there were at least two published articles in the literature describing the variant as being associated with the proband's phenotype. All other CNVs were classified as variants of uncertain significance (VUSs), with the specifier "likely pathogenic" assigned when there were at least two published fundamental neurobiological, functional genomic, and/or human genetic studies involving genes contained within a given CNV for which there was evidence for a causal influence on disease-relevant neurodevelopment, neural circuit function, or behavior.

Metabolic Studies

Erasmus University Medical Center patients were screened for metabolic abnormalities in blood plasma and urine. Blood plasma fraction was isolated according to standardized clinical protocols from venous whole blood collected using lithium heparin–coated blood tubes. Metabolic diagnostics included the following: acylcarnitines, amino acids, bile acids, creatine, guanidinoacetate, homocysteine, homogentisic acid, imidazole compounds, methylmalonic acid, mucopolysaccharides, oligosaccharides, organic acids, orotic acids, phenylalanine, tyrosine, phytanic and pristanic acid, purines and pyrimidines, sialic acid, sialotransferrins, sugars and sugar alcohols, sulfatides, tetraglucoside, and very long chain fatty acids.

RESULTS

Pilgrim Psychiatric Center

The basic demographic and clinical characteristics of the sample are summarized in Table 1. Axis I diagnoses were schizophrenia (78.9%) and schizoaffective disorder (21.1%). Nearly all patients (94.4%) had below average IQ, with a majority (77.8%) classified as lower extreme (full-scale IQ ≤69). Pathogenic or likely pathogenic CNVs were found in five of 19 patients (26.3%), and another five patients had VUSs (see the data supplement that accompanies the online edition of this article). The genomic coordinates of the identified CNVs are provided in Table 2, and detailed characteristics of these 10 patients regarding congenital abnormalities, dysmorphic features, intelligence testing, and psychiatric diagnoses are reported in Table 3.

Case Descriptions of Pilgrim Psychiatric Center Patients With Pathogenic CNVs

Patient PPC-3 was a 52-year-old man diagnosed with schizophrenia with an onset age of 14 years. His medical history was notable for hyperlipidemia and sideroblastic anemia. The patient exhibited dysmorphic features, including an elongated face with narrow orbital fissures, hypertelorism, flat nasal bridge, malar flatness, and retrognathia. He completed secondary school but was never employed and never married. His illness course was chronic and unremitting, with increasingly severe cognitive impairment and regressive behavior. WAIS-III testing at age 52 revealed a verbal IQ of 79, a performance IQ of 68, and a full-scale IQ of 77. CNV screening revealed a 2-Mb duplication of the long arm of chromosome 22 (*22q11.21*). *22q11.2* microduplications have been associated with both schizophrenia and ASD (OMIM #608363) (48). This variant was classified as a pathogenic variant. The patient was also noted to have a deletion involving *CNTNAP2*. However, it concerns a 159-kb intronic deletion in *CNTNAP2* that does not involve coding sequence and was therefore classified as a VUS. Lastly,

we identified a 423-kb duplication on the long arm of chromosome 8 (*8q24.22*) containing *KCNQ3, LRRC6*, and *TMEM71*. *KCNQ3* encodes the voltage-gated potassium channel, subfamily Q, member 3. Heterozygous missense mutations in this gene have been associated with seizures of the benign neonatal subtype, type 2 (49–51). The protein is mainly expressed in the brain. *LRRC6* is involved in autosomal recessive primary ciliary dyskinesia (52, 53). *TMEM71* has not been implicated with this phenotype. Based on the gene content, this variant was classified as a VUS, likely pathogenic, especially in relation to the seizure disorder. On the basis of the risk associated with this genetic diagnosis, the patient was evaluated for the possibility of a previously unrecognized and/or late-onset seizure disorder, which was identified and successfully treated.

Patient PPC-10 was a 27-year-old woman diagnosed with a severe, deteriorating course of schizophrenia (onset age unknown). She received special education and completed secondary school, and was never married and never employed. Her medical history included the surgical repair of a congenital cleft palate, velopharyngeal insufficiency with hypernasal voice, chronic middle ear infections, recurrent episodes of pneumonia, short stature, esotropia, aortic insufficiency, and tricuspid regurgitation. The patient had a seizure disorder with an abnormal background EEG showing bifrontal and bitemporal slowing. She exhibited prominent dysmorphic features, including narrow orbital fissures, telecanthus, square nasal root, bulbous/prominent nose, and retrognathia. WAIS-III testing revealed a verbal IQ of 66, a performance IQ of 59, and a full-scale IQ of 60. Microarray screening revealed a 2.6-Mb deletion on the long arm of chromosome 22 (*22q11.21*), a well-established CNV associated with the *22q11.2* deletion syndrome (OMIM #188400). *22q11.2* microdeletions are currently the most well established genetic risk factor for schizophrenia (5, 30). This variant was classified as pathogenic. In addition, we identified a 310-kb duplication on the long arm of chromosome 1 (*1q41*) containing *PROX1* and *SMYD2*. These genes have not been previously associated with the phenotype. This variant was classified as a VUS. On the basis of the risk associated with this genetic diagnosis, the patient was screened for the possibility of hypocalcemia, which was identified and successfully treated, resulting in a significant reduction in seizure frequency.

Patient PPC-12 was a 50-year-old woman diagnosed with schizophrenia, the symptoms of which first manifested at age 18. She attended high school until the 10th grade, and was never married and never employed. Her medical history was notable for seizure disorder, unilateral exotropia, and strabismus. WAIS-III testing revealed a verbal IQ of 66, a performance IQ of 65, and a full-scale IQ of 63. She was assessed by the Wide-Range Achievement Test–Revised reading subtest to estimate a premorbid verbal IQ and was found to have a premorbid full-scale IQ of 94, suggesting a trajectory of cognitive decline following the onset of schizophrenia. Her mother and both of her mother's siblings suffered from severe psychiatric illnesses that also required long-term hospitalization.

TABLE 2. Genomic Coordinates (hg18) of the Identified CNVs

Center and Patient	Variant	Genomic Coordinates (hg18)
Pilgrim Psychiatric Center		
PPC–2	Dup	Chr22:48,114,921–48,458,127
PPC–3	Del	Chr7:145,582,575–145,741,967
PPC–3	Dup	Chr8:133,398,572–133,821,537
PPC–3	Dup	Chr22:16,615,108–18,594,783
PPC–7	Dup	Chr15:58,705,395–58,764,487
PPC–9	Dup	Chr6:124,846,876–125,239,117
PPC–9	Dup	Chr7:149,198,031–149,883,752
PPC–9	Dup	Chr9:132,351,166–132,715,588
PPC–9	Dup	Chr10:128,282,537–129,138,470
PPC–10	Dup	Chr1:212,247,344–212,557,152
PPC–10	Del	Chr22:17,275,227–19,790,008
PPC–11	Dup	Chr16:18,028,700–20,139,336
PPC–12	Del	Chr7:146,360,344–147,928,119
PPC–15	Dup	Chr4:4,511,826–4,748,685
PPC–16	Dup	Chr6:162,807,280–163,306,684
PPC–18	Dup	Chr2:45,303,454–45,813,464
Erasmus University Medical Center		
EMC–1	Del	Chr5:37,423,970–37,662,323
EMC–4	Dup	Chr7:0–481,295
EMC–9	Del	Chr3:113,618,774–116,995,580
EMC–10	Del	Chr1:144,959,767–146,292,125
EMC–11	Dup	Chr11:107,153,898–107,489,611
EMC–11	Dup	ChrX:87,540,740–87,757,911
EMC–12	Dup	ChrY:0–2,736,035
EMC–12	Dup	ChrY:154,587,409–154,913,754
EMC–12	Dup	ChrY:0–27,198,031
EMC–14	Del	Chr16:29,528,999–30,171,562
EMC–16	Dup	Chr3:836,618–1,438,346
EMC–16	Dup	Chr11:50,080,786–50,675,483
EMC–21	Dup	Chr5:99,785,428–100,021,429
EMC–30	Del	Chr13:106,234,020–107,960,598
EMC–31	Del	Chr3:2,226,296–2,292,563
EMC–31	Dup	Chr3:2,341,695–2,571,325
EMC–31	Del	Chr8:82,798,696–83,515,397

At age 34, she experienced her only documented seizure, characterized as generalized tonic-clonic. EEG demonstrated slow dysrhythmia in theta with occasional delta waves, predominantly localized to the frontal lobes. Brain MRI demonstrated mild cerebral atrophy. As previously described, microarray screening identified a heterozygous 1.57-Mb deletion at the *7q35–7q36.1* locus, which includes *CUL1*, *EZH2*, *PDIA4*, and *CNTNAP2* (36). *CNTNAP2* encodes contactin-associated protein-like 2, which regulates neuronal-glial interactions and neural cell migration (54, 55). Both CNV deletions and exonic mutations of *CNTNAP2* have been previously associated with schizophrenia and ASD (OMIM #604569) (56, 57). This variant was classified as pathogenic. Knowledge of the genetic diagnosis promoted increased awareness of clinically significant prognostic risks, including late-onset language regression and cognitive deterioration.

Erasmus University Medical Center

The basic demographic and clinical characteristics of the sample are summarized in Table 1. Axis I disorders were predominantly ASD (32.3%) or a psychotic disorder (48.4%), and a majority of the sample (74.2%) had a positive family history for psychiatric illness. All patients who could be

TABLE 3. Characteristics of Patients in the Pilgrim Psychiatric Center Sample Who Had Positive Genetic Findings

Patient	Sex	Age (years)	Psychiatric Disorder	Full-Scale IQ	Performance IQ	Verbal IQ	Education Level	Somatic Symptoms
PPC-2	Male	32	Schizophrenia	75	79	75	11th grade	MRI findings, psychogenic polydipsia
PPC-3	Male	52	Schizophrenia	77	68	79	High school graduate	Hyperlipidemia, sideroblastic anemia, late-onset seizure disorder (at age 59)
PPC-7	Female	35	Schizoaffective disorder	54	51	64	Special education (12 years)	Seizure disorder, mitral valve prolapse and tricuspid insufficiency, strabismus, migraine headaches
PPC-9	Female	21	Schizoaffective disorder	59	58	65	Unknown	Pilonidal cyst
PPC-10	Female	27	Schizophrenia	60	59	66	Completed secondary school; special education	Cleft palate, seizure disorder, velopharyngeal insufficiency, chronic middle ear infections, recurrent episodes of pneumonia, esotropia, aortic insufficiency and tricuspid regurgitation
PPC-11	Male	40	Schizophrenia	64	65	68	Special education	None
PPC-12	Female	50	Schizophrenia	63	65	66	Dropped out of secondary school	Seizure disorder, unilateral exotropia, strabismus
PPC-15	Female	42	Schizophrenia	61	69	61	9th grade	Psychogenic polydipsia, hyponatremia, seizures secondary to hyponatremia, MRI findings
PPC-16	Male	48	Schizophrenia	N/A[b]			High school graduate	Mitral valve prolapse with mitral regurgitation, seizures after clozapine treatment
PPC-18	Male	36	Schizoaffective disorder	90	83	92	High school graduate	Hypothyroidism, psychogenic polydipsia, hyponatremia, chronic neutropenia, hiatal hernia, obesity

[a]VUS=variant of uncertain significance.
[b]IQ testing could not be performed.

assessed had below-average IQ, and a substantial proportion (55.2%) had a lower-extreme IQ. Pathogenic or likely pathogenic CNVs were found in seven of the 31 patients (22.6%). Another four patients had VUSs (see the online data supplement). The genomic coordinates of the identified CNVs are listed in Table 2. Detailed characteristics of these 11 patients regarding congenital abnormalities, dysmorphic features, intelligence testing, psychiatric diagnoses, and family history are provided in Table 4. Results of metabolic screening tests of blood plasma and urine, as well as fragile X testing, were normal for all patients.

Case Descriptions of Erasmus University Medical Center Patients With Pathogenic CNVs

Patient EMC-9 was a 53-year-old man with a diagnosis of dysthymic disorder and intellectual disability and a lower-extreme IQ of 55. His social-emotional development was estimated to be that of a 6-year-old. He exhibited an elongated face, ptosis, narrow palpebral fissures, a large, pear-shaped nose, and central obesity. We found a 3.38-Mb deletion on the long arm of chromosome 3 (*3q13.2-q13.31*) that included 25 genes. Molin et al. (58) and Lowther et al. (59) described several patients with *3q13.31* microdeletion syndrome. The *3q13.31* microdeletion syndrome is associated with developmental delay, muscular hypotonia, hypoplastic male genitalia, characteristic facial features, and obesity (OMIM #615433). This variant was classified as pathogenic. On the basis of the obesity risk associated with this genetic diagnosis, increased attention was given to avoiding medications associated with weight gain and metabolic side effects.

Patient EMC-10 was a 22-year-old man with a diagnosis of pervasive developmental disorder not otherwise specified,

Facial and Body Characteristics	Microarray Results	Diagnostic Classification[a]	Regions of Homozygosity
Elongated face, cleft palate, pectus excavatum	dup22q13.33 (343 kb)	VUS	None
Elongated face, narrow orbital fissures, hypertelorism, flat nasal bridge, malar flatness, retrognathia	del7q35 (159 kb), dup8q24.22 (423 kb), dup22q11.21 (2 Mb)	Pathogenic	None
Narrow orbital fissures, square nasal root with hypoplastic alae nasi, retrognathia	dup15q22 (580 kb)	VUS, likely pathogenic	None
Short stature	dup6q22.31 (392 kb), dup7q36.1 (686 kb), dup9q34.11–34.12 (364 kb), dup10q26.2 (856 kb)	VUS, likely pathogenic	None
Narrow orbital figures, telecanthus, square nasal root, retrognathia, prominent/bulbous nose, short stature	dup1q41 (310 kb), del22q11.2 (2.5 Mb)	Pathogenic	None
Sloping forehead, protruding supraorbital ridges, square nasal root, wide nasal tip, short philtrum, retrognathia, malar flatness, short and broad sternum, cleft palate	dup16p12.3 (2.11 Mb)	VUS	None
None	del7q35–36.1 (1.5 Mb)	Pathogenic	None
High nasal root protrusion, kyphosis	dup4p16.3–16.2 (237 kb)	VUS	None
Narrow orbital fissures, retrognathia, protruding supraorbital ridges, pectus excavatum	dup6q26 (499 kb)	VUS	None
High nasal root protrusion, flat alae nasi, diminished vermilion of the upper lip, clefted nasal tip, mild midline cleft lower lip, hypoplastic teeth, hypoplastic earlobes, slender tapered fingers, high-arched V-shaped steepled cleft palate	dup2p21 (510 kb)	VUS	None

intermittent explosive disorder, and intellectual disability (full-scale IQ of 69). His social-emotional development level was estimated as that of a 3-year-old. We identified a 1.33-Mb deletion on the long arm of chromosome 1 containing the critical region of the *1q21.1* deletion syndrome (OMIM #612474), a susceptibility locus associated with developmental delay, hypotonia, microcephaly, cardiac anomalies, hypermobility, seizures, and dysmorphology (60). This variant was classified as pathogenic. On the basis of the risks associated with this genetic diagnosis, a cardiac screening examination was performed and medications known to lower seizure threshold were avoided.

Patient EMC-12 was a 23-year-old man with a diagnosis of pervasive developmental disorder not otherwise specified, ADHD, oppositional defiant disorder, and substance abuse. He exhibited a high receding hairline, a region of hyperpigmentation on the left shoulder, an upturned nose, and a deeply grooved philtrum. Microarray screening revealed a gain for the entire Y chromosome, which was supported by gains in the pseudoautosomal regions located on X and Y. Karyotyping confirmed a single additional Y chromosome (47,XYY). Studies of patients with 47,XYY syndrome have identified an increased risk of ASD and ADHD, as well as a higher burden of externalizing symptoms (61). This variant was classified as pathogenic. Discussion of the genetic diagnosis helped to strengthen the therapeutic alliance with the mental health care team.

Patient EMC-14 was an 18-year-old man with a diagnosis of pervasive developmental disorder not otherwise specified and ADHD, and he was a convicted sex offender. He reported speech and language problems during childhood requiring special education. He exhibited broad and prominent eyebrows with synophrys, long palpebral fissures, full pouching lips, a high and flat philtrum, obesity, tapering fingers, and hyperextension of the proximal interphalangeal joint. His height was 2.5 standard deviations below the mean.

TABLE 4. Characteristics of Patients in the Erasmus University Medical Center Sample Who Had Positive Genetic Findings

Patient	Sex	Age (years)	Psychiatric Disorder[a]	IQ	Educational Level	Family History[a]	Somatic Symptoms	Facial Characteristics
EMC-1	Male	34	Bipolar II disorder	76	Lower-level secondary education	Mother with bipolar disorder	Diabetes, hypothyroidism, hypercholesterolemia, cryptorchidism, amblyopia, retractile testes	Upslanted palpebral fissures, epicanthus, downturned mouth corners, asymmetric prominent jaw, dental caries, flat philtrum, high skull
EMC-4	Male	37	PDD-NOS, psychotic disorder NOS, PTSD	69	Special education	Mother and siblings have learning disabilities	None	Receding hairline, hypertelorism, broad palpebral fissures, bushy eyebrows with synophrys, prominent nose tip, narrow upper lip, edentate upper jaw, dysplastic ear helices
EMC-9	Male	53	Dysthymic disorder	55	Special education	Alcohol abuse in father	Diabetes, hearing impairment (AD>AS), varices	Elongated face, flattened center of face, ptosis, narrow palpebral fissures, prominent pear-shaped nose
EMC-10	Male	22	PDD-NOS, intermittent explosive disorder	69	Special education	A sibling with intellectual disability	Ear infections, back problems	Hypoplastic alae nasi
EMC-11	Male	27	PDD-NOS, dysthymic disorder	85	Special education	No positive family history	None	Receding hairline
EMC-12	Male	23	PDD-NOS, ADHD, ADD, substance abuse	N/A[b]	Special education	Bipolar disorder and ASD	Inguinal hernia requiring surgery	High receding hairline, turned-up nose tip, deeply grooved philtrum
EMC-14	Male	18	PDD-NOS, ADHD	N/A[b]	Special education	Brother has ADHD	Chronic obstructive pulmonary disease, migraine, speech and language disorder	Broad and prominent eyebrows with synophrys, broad palpebral fissures, full pouching lips, high and flat philtrum
EMC-16	Male	43	Psychotic disorder NOS	80[c]	Primary education only	None; parents are consanguineous	Hypermetropia, syphilis	Flattened face, attached earlobes, hairy ears, prominent eyebrows
EMC-21	Male	55	Autistic disorder, depressive disorder NOS, OCD	82	Lower professional education	Father has schizophrenia, sibling has psychotic disorder	Obesity	Obesity, small palpebral fissures, hypoplastic alae nasi, high palate, long ears
EMC-30	Female	50	Psychotic disorder NOS	64	Special education	One brother with schizophrenia and one brother with intellectual disability	None	Long face, lipoma on the head, exophthalmos, full nose tip, hypotonic in the face
EMC-31	Female	36	Psychotic disorder, major depressive disorder	—[d]	Special education	One brother with intellectual disability	None	None

[a]ADD=attention deficit disorder; ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; NOS=not otherwise specified; OCD=obsessive-compulsive disorder; PDD=pervasive developmental disorder; PTSD=posttraumatic stress disorder; VUS=variant of uncertain significance.
[b]IQ testing could not be performed.
[c]Estimated IQ.
[d]IQ estimated as lower extreme (≤69).

Genotyping revealed a 643-kb deletion on the short arm of chromosome 16 (*16p11.2*) overlapping with the critical region of the *16p11.2* microdeletion syndrome (OMIM #611913) (31, 60, 62). Microdeletions of *16p11.2* confer high susceptibility to developmental delay, craniofacial dysmorphology, and ASD, as well as severe early-onset obesity, congenital cardiac abnormalities, seizures, and intellectual disability. This variant was classified as pathogenic. On the basis of the risks associated with this genetic diagnosis, a cardiac screening examination was performed and

Body Characteristics	SNP Array	Diagnostic Classification	Regions of Homozygosity	Metabolic Screen, Blood Plasma	Metabolic Screen, Urine	Fragile X Testing
Edema in the lower legs, panniculus	del5p13.2 (238 kb)	VUS	None	Normal	Normal	Normal
Increased lordosis and kyphosis, mild pectus excavatum, ugly scar formation, striae on the upper legs, Beighton score 2/9, normal tonus, slim posture, hypotrophic muscular system	dup7p22.3 (481 kb)	VUS	None	Normal	Normal	Normal
Height 1 SD below the mean, weight 2 SD above the mean, skull circumference 1 SD above the mean, central adiposity	del3q13.2q13.31 (3,377 kb)	Pathogenic	None	Normal	Slightly elevated lactate levels	Normal
None	del1q21.1 (1,332 kb)	Pathogenic	None	Normal	Normal	Normal
Clinodactyly in fifth finger, hemangioma, striae on arms and abdomen	dup 11q22.3 (336 kb) and dupXq21.31 (217 kb)	VUS, likely pathogenic	None	Normal	Normal	Normal
Hyperpigmentation on left shoulder	XYY	Pathogenic	None	Normal	Normal	Normal
Height 2.5 SDs below the mean, obese, tapering fingers, hyperextension of the proximal interphalangeal joint	del16p11.2 (643 kb)	Pathogenic	None	Normal	Normal	Normal
Increased thoracic kyphosis, hyperpigmentation, axial hypotonia, height 2.5 SDs below the mean, weight 2.5 SDs above the mean	dup3p26.3 (602 kb), dup11p11.12 (595 kb)	VUS, likely pathogenic	Multiple, parents consanguineous	High alanine and glutamine	Normal	Normal
Weight 2 SDs above the mean, hernia umbilicalis, panniculus, thoracic kyphosis, long hands and feet	dup5q21.1 (236 kb)	VUS	None	Normal	Normal	Normal
Height and skull circumference 0.5 SD below the mean, hallux valgus (right>left), increased thoracic kyphosis	del13q33.3 (1.7 Mb)	VUS	None	Not performed	Normal	Normal
None	del3p26.3 (66 kb) and dup3p26.3 (230 kb), del8q21.13 (717 kb)	VUS, likely pathogenic	None	Not performed	Normal	Normal

medications known to lower seizure threshold, induce weight gain, or promote metabolic syndrome were strictly avoided.

DISCUSSION

We performed comprehensive genetic analyses in two cohorts of patients with a syndromic presentation of psychiatric illness. In 12 patients (24%), we identified a pathogenic or likely pathogenic genetic variant. We found a similar percentage of pathogenic or likely pathogenic CNVs in each independent cohort (Pilgrim Psychiatric Center cohort: 5/19, or 26.3%; Erasmus University Medical Center cohort: 7/31, or 22.6%). Among the identified CNVs, many have been previously established as known genetic risk factors for psychiatric disorders (*22q11.2* microdeletion, *16p11.2* microdeletion, XYY syndrome) and developmental delay (*3q13.31* microdeletion, *1q21.1* microdeletion). Furthermore, we observed

likely pathogenic CNVs involving only a single gene that have been strongly linked to psychiatric illness (*CNTN4, CNTN6*).

Pathogenic CNVs associated with psychiatric phenotypes have a broad range of penetrance, varying from ~2%−33% for bipolar disorder, schizophrenia, or ASD, while the exposed attributable risk for pathogenic de novo CNVs varies between 79% and 87% (63). In particular, among individuals carrying a microdeletion at *22q11.2*, the lifetime prevalence of psychotic disorders is ~30% (64). Increasingly precise penetrance estimates will greatly facilitate discussions between patients, their families, and their health care providers regarding diagnosis, treatment, and prognosis (25).

Our findings are consistent with a recent study by Stobbe et al. (65), who reported clinical diagnostic findings in 24 consecutively evaluated adult patients with syndromic ASD, of whom 20.8% were found to have pathogenic or likely pathogenic CNVs. Furthermore, our observed rate of pathogenic CNVs (7/50, or 14.0%) is significantly higher than in the general-population schizophrenia cohort reported by Rees et al. (28) (171/6882, or 2.48%) (Fisher's exact test, $p=2.6\times10^{-4}$). Therefore, clinical genetic testing for CNVs may be particularly relevant in patients with syndromic forms of psychiatric illness.

Clinical genetic testing should be considered in the presence or absence of a significant family history. Although a positive family history suggests the presence of an inherited genetic variant, a negative family history can be indicative of a de novo variant. Notably, however, the absence of an identifiable inherited or de novo genetic variant does not rule out more complex genetic events due to somatic mosaicism that might not be detectable in DNA isolated from peripheral blood (66, 67). The considerable diagnostic importance of de novo mutations has been firmly established for intellectual disability (19, 21, 68). Accordingly, this might also be an important genetic mechanism underlying syndromic forms of psychiatric illness that should be evaluated in future studies. Moreover, future investigations with larger cohorts should be conducted to determine the relative contribution of the severity of intellectual disability, distinct congenital abnormalities, craniofacial dysmorphologies, and seizure disorders to the prior probability of CNVs in patients with psychiatric disorders.

Important clinical benefits have been shown to result from a genetic diagnosis. Multiple studies have reported a preference on the part of patients and their families to obtain an etiological genetic diagnosis, the benefits of which include improved knowledge of their disease and a feeling of empowerment to better advocate for themselves (39, 69). Patients who receive a genetic diagnosis experience a strengthening of the therapeutic alliance with their psychiatrist and mental health care providers (70). In addition, having an etiological genetic diagnosis facilitates access to medical benefits, educational opportunities, and social services for patients and their families (71, 72). Accordingly, formal genetic counseling is a critically important opportunity for patients and their families to understand the risks and opportunities for reproductive planning (39, 40).

Confirmation of a known genetic syndrome can also improve diagnosis, prognosis, treatment, and prevention. The knowledge of a genetic diagnosis provides a unique opportunity to consider future clinical course and prognosis on the basis of published information regarding patients with comparable genetic diagnoses. For example, CNVs involving *CNTNAP2* have been reported to increase the risk for adult-onset mutism (73) and epilepsy (36). Furthermore, pathogenic CNVs associated with neuropsychiatric symptoms frequently involve medical comorbidities for which diagnostic screening and preventive treatment are often available and of significant clinical consequence. For example, patients with *22q11.2* microdeletion exhibit high rates of immune deficiency, congenital heart disease, hypocalcemia, seizures (often provoked by episodes of hypocalcemia), scoliosis, obesity, hearing loss (sensorineural and/or conductive), thrombocytopenia, thyroid dysfunction, and renal anomalies (74). Additional examples include *16p11.2* microdeletion, which is associated with obesity, gastrointestinal symptoms (e.g., reflux, constipation, diarrhea), seizures, immune deficiency, scoliosis, and congenital heart disease (75, 76). *1q21.1* microduplication is associated with cardiac abnormalities (in particular tetralogy of Fallot), seizures, and macrocephaly (77).

Regarding treatment, there are important examples of CNV-associated risks of adverse effects or complications of psychopharmacological treatment, as well as emerging therapeutic opportunities. For example, patients with schizophrenia and *22q11.2* microdeletion appear to be at increased risk of adverse events from clozapine, including seizures, movement-related side effects (including myoclonus, tremor, unsteady gait, rigidity, and slurred speech), neutropenia, and myocarditis (78, 79). Clinicians should also be aware of the potential to exacerbate the predilection toward hypocalcemia in patients with *22q11.2* microdeletion through medication (e.g., anticonvulsants) or alcohol consumption, and the corresponding importance of vitamin D and calcium supplementation. Moreover, *16p11.2* microdeletion results in a strong predisposition to obesity, for which there should be concern regarding medications associated with weight gain and metabolic syndrome (75, 80). With the increasing success of psychiatric genetics, neuroscientists are gaining knowledge about the underlying neurobiological mechanisms of CNV-associated neurogenetic syndromes for which clinicians, patients, and their families should be aware of emerging clinical research studies. Notable recent examples of translational drug development studies include vigabatrin for *22q11.2* microdeletion syndrome (81) and oxytocin for *CNTNAP2* deletion (82).

Craniofacial abnormalities are known to be associated with alterations in brain development, consistent with the shared neurodevelopmental origin of the brain and the facial skeleton (83). However, the issue is complex, given that there is a generally broad phenotypic spectrum associated with carriership of pathogenic CNVs (84–86). In an Icelandic population-based study of more than 100,000

people without a history of schizophrenia or autism, ~1% were identified as carriers of pathogenic CNVs. Notably, although none of the people carrying these CNVs met traditional clinical diagnostic criteria for a neurodevelopmental or neuropsychiatric disorder, the majority exhibited a range of functionally significant cognitive and neuropsychological deficits (87).

For both schizophrenia (5) and autism (20, 88), case-control studies have shown a clear excess of CNVs. In contrast, the genome-wide burden of CNVs does not appear to be increased for bipolar disorder or recurrent major depression (89–91) (however, there is strong evidence for an association of bipolar disorder and recurrent depression with duplications at *16p11.2* [48, 89]). Notably, large (≥100 kb) CNVs—which we have focused on in the present study—generally appear to have larger effect sizes than small CNVs, but they are also significantly more rare. Accordingly, the contribution of smaller CNVs to phenotypic diversity in the general population remains less well studied, because of the requirement for increasingly large population-based cohort studies with detailed phenotypic data and higher-density genotyping (25). Future studies using high-resolution variant detection by whole genome sequencing are expected to greatly facilitate the identification of smaller pathogenic CNVs and indels.

The majority of the patients in our cohorts had intellectual disability in addition to axis I psychiatric disorders, for which the nature of the causality of the genetic effects remains an open question. Specifically, it remains unclear to what extent a given CNV might exert its effects directly through endogenous neurobiological mechanisms and indirectly through impairments in cognitive reserve (92) or social or emotional functioning. In this regard, it is notable that genome-wide CNV burden appears to be elevated in patients who have a psychiatric disorder and comorbid intellectual disability (2, 93, 94). This finding might therefore suggest that CNVs can exert their influence on psychiatric disease risk indirectly through reduced intellectual capacity (95). Conversely, the pattern of allelic pleiotropy observed for distinct CNVs and rare single-nucleotide variants suggests that the associated risk of psychiatric illness is likely to be independent of intellectual disability (48, 96, 97).

With regard to the classification of CNV pathogenicity, it is important to be aware that there remains a considerable degree of subjectivity when implementing the consensus guidelines (47). Classifications of pathogenic and benign are relatively higher confidence, given the stronger available evidence base required for these specifiers, while likely pathogenic variants and VUSs are dynamically evolving with the increasing availability of population-based genotyping data (e.g., the ExAC browser [98]) and clinical genetic information (e.g., ClinVar [99]), as well as the standardized implementation of genome-wide functional genomic, neuroimaging, and cognitive analyses (e.g., the ENIGMA consortium [100]).

Despite the substantial benefits for patients and their clinicians, genetic testing is not without clinically significant risks. Given that genetic testing currently leads to an etiological diagnosis in only a minority of cases, patients' expectations should be appropriately tempered. In the absence of identifiable pathogenic CNVs, there remains a distinct possibility that CNVs classified as VUSs and/or other types of genetic variants, such as rare protein-coding mutations or common polygenic risk, may be etiologically significant factors. Moreover, for patients who receive an inconclusive diagnosis (e.g., VUSs), the resulting uncertainty might increase their level of concern (69). Conversely, a confirmed pathogenic finding may induce anxiety regarding future prognosis and later-onset symptoms (70). Importantly, the decision of whether to perform genetic testing for diagnostic or predictive purposes should be made by the patient (or by a legal guardian, for those who are incapable of providing informed consent), and only after a comprehensive discussion with their psychiatrist and genetic counselor to weigh the risks and benefits of testing. Moreover, the outcome of genetic testing for a patient can have significant consequences for the entire family, for whom genetic counseling is strongly recommended to allow them a forum, either individually or as a group, regarding the implications for themselves and their children.

In summary, on the basis of the best available evidence, we propose that CNV screening should be considered for implementation within routine clinical practice for patients with syndromic forms of psychiatric illness. Although formal cost-effectiveness analyses are not yet complete, the current price of comparative genomic hybridization microarray testing is approximately $500–$1500 (101, 102), with a number needed to test of 4.35 based on the combination of our results and those of Stobbe et al. (65) (17 cases with pathogenic or likely pathogenic variants of a total of 74 screened). With the availability of exponentially larger data sets, an increasing proportion of the variants now considered likely pathogenic or VUSs on the basis of insufficient information are likely to be reclassified in the near future with even further improvements in the diagnostic yield for genetic testing of patients with syndromic forms of psychiatric illness.

SUMMARY AND CONCLUSIONS

Pathogenic or likely pathogenic CNVs are present in a substantial fraction of patients with syndromic forms of psychiatric illness. Currently, the diagnostic yield appears to be highest when genetic testing is implemented in patients with axis I psychiatric disorders in combination with multiple congenital abnormalities and/or dysmorphic features. Based on our case series and the published literature, intellectual disability is also a frequent comorbid symptom. Given that pathogenic variants associated with syndromic disorders are often de novo, genetic testing should be considered even if the family history is negative.

Below we summarize some important implications for clinical management following a genetic diagnosis in patients with syndromic forms of mental illness.

- Therapeutic alliance: Psychiatric genetic diagnoses generally lead to a strengthening of the therapeutic alliance, with patients and their families often reporting a resulting feeling of empowerment.
- Resources: Having an etiological genetic diagnosis facilitates access to medical benefits, educational opportunities, and social services for patients and their families. When available, genetic diagnosis–focused patient organizations are a valuable source of information, advocacy, and support.
- Genetic counseling: Formal genetic counseling is critically important for patients and their families to understand the risks and opportunities for reproductive planning.
- Prognosis: Genetic diagnostics provides the opportunity to consider a patient's future clinical course on the basis of published information regarding patients with comparable CNVs.
- Medical comorbidity: Pathogenic CNVs associated with neuropsychiatric symptoms frequently involve medical comorbidities for which diagnostic screening and preventive treatment might be available and of significant clinical consequence.
- Standard-of-care treatment: Clinicians should be aware of the CNV-associated risks of pharmacological treatment. Particularly notable are the risks of exacerbating underlying predilections toward obesity, metabolic syndrome, immune dysfunction, endocrine abnormalities, intellectual disability, and seizures.
- Emerging therapies: Clinical research and treatment studies of established genetic diagnoses are increasing in frequency and scope. Clinical trial registries, mostly notably ClinicalTrials.gov and EudraCT, as well as genetic diagnosis–focused patient organizations, are a valuable resource for identifying active studies.

C. If the CNV is on one of a parent's two chromosomes, then the likelihood that the CNV chromosome will be placed by meiosis into the sperm or egg that becomes an offspring is 50%. It is 50% for each of the offspring in that family, because each is the independent outcome of a different meiosis. The CNV may or may not lead to a psychiatric illness in a particular individual, and therefore whether or not a particular sibling will become ill is unknown.

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AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry and the Department of Clinical Genetics, Erasmus University Medical Center (Erasmus MC), Rotterdam, the Netherlands; the Department of Psychiatry and the Center for Precision Neuropsychiatry, Columbia University, New York; New York State Psychiatric Institute, New York; the Departments of Psychiatry, Neuroscience, and Human Genetics, Mount Sinai School of Medicine, New York; the Clinical Neuroscience Center, Pilgrim Psychiatric Center, West Brentwood, N.Y.; the Department of Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands; Delta Psychiatric Center, Portugaal, the Netherlands; the Department of Human Genetics, Donders Center for Neuroscience, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; and the Department of Clinical Genetics, School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands.

Address correspondence to Dr. Kushner (s.kushner@erasmusmc.nl).

The first four authors contributed equally to this article.

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