REVIEW

Clinical applications of schizophrenia genetics: genetic diagnosis, risk, and counseling in the molecular era

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Abstract: Schizophrenia is a complex neuropsychiatric disease with documented clinical and genetic heterogeneity, and evidence for neurodevelopmental origins. Driven by new genetic technologies and advances in molecular medicine, there has recently been concrete progress in understanding some of the specific genetic causes of this serious psychiatric illness. In particular, several large rare structural variants have been convincingly associated with schizophrenia, in targeted studies over two decades with respect to 22q11.2 microdeletions, and more recently in large-scale, genome-wide case-control studies. These advances promise to help many families afflicted with this disease. In this review, we critically appraise recent developments in the field of schizophrenia genetics through the lens of immediate clinical applicability. Much work remains in translating the recent surge of genetic research discoveries into the clinic. The epidemiology and basic genetic parameters (such as penetrance and expression) of most genomic disorders associated with schizophrenia are not yet well characterized. To date, 22q11.2 deletion syndrome is the only established genetic subtype of schizophrenia of proven clinical relevance. We use this well-established association as a model to chart the pathway for translating emerging genetic discoveries into clinical practice. We also propose new directions for research involving general genetic risk prediction and counseling in schizophrenia.

Keywords: schizophrenia, genetics, 22q11 deletion syndrome, copy number variation, genetic counseling, genetic predisposition to disease

Introduction

Schizophrenia is arguably one of humankind's most severe diseases.[1,2] Driven by new genetic technologies and advances in molecular medicine, recently there has been concrete progress in understanding some of the specific genetic origins of this complex psychiatric illness, summarized in several recent reviews.[2–8] There has, however, been little focus on how we might practically apply the findings.[9–11] In this review, we critically appraise recent developments in terms of immediate clinical utility. We use the well-established association of schizophrenia with microdeletion 22q11.2 as a model to chart the pathway for translating emerging genetic discoveries into clinical practice. We also propose new directions for research involving general genetic risk prediction and counseling in schizophrenia.

Clinical features of schizophrenia[9,12]

Schizophrenia is a common psychiatric illness that typically involves lifelong but treatable changes in thinking, behavior, and emotions. It has a lifetime morbid

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risk of approximately 1%. The principal symptoms are psychotic in nature: delusions (false beliefs), hallucinations (false perceptions), and thought disorder (disorganization of thought processes). In addition to these "positive" symptoms, there are also "negative" symptoms of blunted affect (reduced emotional expression), poverty of speech, anhedonia (reduced ability to feel pleasure), and amotivation, as well as disorganization of behavior and emotions. Depression, anxiety, irritability, agitation, sleep disturbance, and cognitive impairments, including changes in attention, memory, insight, and judgment, are also common. Onset of schizophrenia occurs most commonly in early adulthood from 17 to 30 years of age, but can arise in childhood (in <1% of cases) through to the elderly age range. The diagnosis of schizophrenia is a clinical diagnosis, based on course of illness as well as cross-sectional symptoms. Diagnostic reliability is high when standard diagnostic criteria are combined with a direct examination and thorough history, including information from the patient, relatives, and others, to differentiate schizophrenia from other psychotic disorders. As with most neuropsychiatric disorders, there are no characteristic neuropathological findings (Table 1), which, coupled with the absence of any diagnostic tests and substantial clinical heterogeneity (variable signs and symptoms), emphasizes the importance of detailed expert phenotyping (cf "shallow phenotyping").[13]

Genetic epidemiology of schizophrenia

Psychiatric genetics has historically focused in large part on the study of schizophrenia and its epidemiology.[14] It is well-established that the heritability of schizophrenia is >80%,[15–17] amongst the highest known for complex genetic disorders.[18] Consistent evidence from family, twin, and adoption studies over the past century strongly indicates that predisposition is largely genetically determined (MIM #181500).[19–24] Non-genetic factors, for example, marijuana use and hypoxia-mediated factors like birth complications or childhood head injury, increase risk for schizophrenia only modestly.[9,25–32] Studies of schizophrenia in twins[33,34] support reduced penetrance (genetic variants that do not express in every carrier as disease) and variable expression (variants that express as different diseases in different carriers),[35,36] which is common to most human genetic diseases. As for most diseases, there is also substantial evidence for genetic heterogeneity and probably allelic heterogeneity.[18,36] Gene–gene interaction (epistasis) is likely in schizophrenia[37,38] and indeed is ubiquitous in nature.[39] Molecular evidence for early predictions of spontaneous (de novo) mutations in schizophrenia,[40,41]

Table 1 Schizophrenia within the context of other common complex neuropsychiatric diseases (as of 2011)

	Schizophrenia	ASD	Epilepsy	Parkinson disease	Alzheimer disease
Clinical features					
Approximate lifetime risk	~1%	~1%	~0.5%	~1.6%[a]	~10%[a]
Typical onset	Young adulthood	Early childhood	Childhood	Mid to late adulthood	Mid to late adulthood
Clinical heterogeneity	Yes	Yes	Yes	Yes	Yes
Clinical diagnostic imaging/biomarker(s)/test(s)	No	No	Yes	No	No
Definitive neuropathological diagnosis	No	No	No	Yes	Yes
Primary mode of neuropathogenesis	Developmental	Developmental	Developmental	Degenerative	Degenerative
Genetic features					
Heritability	>80%	~90%	~45%[b]	~30%	~70%
Genetic heterogeneity	Yes	Yes	Yes	Yes	Yes
Major common variant(s)	No	No	No	No	Yes
Rare sequence mutation subtype(s)	No	Yes	Yes	Yes	Yes
Rare chromosomal anomaly/structural mutation subtype(s)	Yes	Yes	Yes	No	Yes
Genetic diagnosis changes medical management[c]	Yes	No	Yes	No	No
Pharmacogenetics as standard of care	No	No	No	No	No
Routine use of genome-wide scans[d]	No	Yes	No	No	No
Family history as predominant recurrence risk factor	Yes	Yes	Yes	Yes	Yes
Sources (reference numbers)	See text[9]	61, 190, 233, 234	235–239	240–243	244–247

Notes: [a]Estimated based on risk after age 55–65 years, and therefore highly dependent on the mean life expectancy of the population; [b]no consensus estimate, with a wide range of reports in the literature;[235,239] [c]management changed for the associated neuropsychiatric disease; this does not include more informed genetic counseling, the precipitation of other referrals or investigations,[248] or the potential for earlier/more aggressive treatment as a result of early clinical diagnosis because of an increased index of suspicion; [d]without accompanying developmental delay/mental retardation, ASD, or multiple congenital anomalies.
Abbreviation: ASD, autism spectrum disorder.

recently reframed as the "common disease – rare alleles" model,[42] adds to the complex genetic picture. Thus, it is not surprising, in hindsight, that classic Mendelian inheritance patterns are very rarely observed in schizophrenia, and that elucidation of causal genetic factors has been so challenging. Researchers have remained undeterred, because of the myriad possible benefits for patients, families, and clinicians that could result from an improved understanding of the genetic etiology of schizophrenia (Table 2).

22q11.2 deletion syndrome

To date, 22q11.2 deletion syndrome (22q11.2DS; previously DiGeorge syndrome and velocardiofacial syndrome) is the only established genetic subtype of schizophrenia of proven clinical relevance.[3,43] The association of 22q11.2DS with schizophrenia followed soon after the discovery in the early 1990s that the 22q11.2 deletion was the underlying molecular anomaly unifying several, seemingly distinct, clinical syndromes first described in the 1960s and 1970s.[44,45] Many of the features suggested above with respect to the genetic epidemiology of schizophrenia, including spontaneous mutations, reduced penetrance, and variable expressivity, are found in 22q11.2DS.

Molecular origins and epidemiology

22q11.2DS is associated with a hemizygous microdeletion on chromosome 22q11.2 of variable length (typically 3 Mb) and, in some cases, variable position within this region.[9,46] There is no apparent critical region at this locus for any major phenotype, including schizophrenia.[47–50] Most deletions are flanked by segmental duplications[51] and occur as de novo mutations mediated by nonallelic homologous recombination.[46,52] Only 5%–10% of cases have been found to be inherited from transmitting parents,[53–56] most frequently mothers with mild neuropsychiatric phenotypes.[57] Nevertheless, 22q11.2DS is the most common genomic disorder[58] in humans, with an oft-cited estimated prevalence in the general population of 1 in 3000–4000 live births that is likely to be an underestimate.[59,60] Fluorescence in situ hybridization using a standard 22q11.2 probe (D22S75 or

Table 2 Potential future roles for molecular genetics in the clinical management of schizophrenia

Area of benefit	Details and examples
Medical (of primary benefit to the clinician and patient)	
Prediction and prevention	• Personalized genetic (ie, inborn) lifetime risk for psychosis*
	• Narrowing of window for age at onset in high risk cases
	• Personalized neurocognitive and/or neuroimaging precursors of psychosis
	• Opportunity to limit important deleterious gene by environment interactions
	• Anticipation of potential extra-psychiatric features*
	• Tailored early interventions to delay or prevent onset, or attenuate course
Diagnosis	• At first onset of psychosis, higher index of suspicion for schizophrenia (as a result of improvements in prediction)*
Management	• Coordinated multisystem management and anticipatory care for possible extra-psychiatric manifestations of causal genetic variant(s)*
Treatment	• Earlier/more aggressive treatment (as a result of improvements in prediction and diagnosis)*
	• Preference for or avoidance of particular antipsychotic medications
	• Tailored dosing (eg, via knowledge of fast and slow metabolizers; pharmacogenomics)
	• Less potential confusion of medication side effects with extra-psychiatric manifestations of causal genetic variant(s) (eg, metabolic syndrome, parkinsonism, seizures)*
	• Novel personalized therapeutic targets
Prognosis	• Improved course (as a result of improvements in prediction/prevention, diagnosis, treatment, and management)*
	• Personalized data on natural history and longevity*
Psychosocial (of primary benefit to the patient and family)	
Understanding	• Partial answer to the question, "Why me?"*
	• Explanation for potential premorbid developmental signs and symptoms (eg, learning difficulties)*
	• Extra reassurance that parenting or personal life choices did not play a major role in causing the illness*
Counseling	• Personalized recurrence risks for family members*
	• Better informed reproductive decision making and possibility for prenatal detection*
Hope	• Proof of progress in understanding the illness*
	• Prospect of continued improvements in treatment and management, as above*

Note: *Already possible for 22q11.2 deletion syndrome (22q11.2DS) subtype of schizophrenia (see text for details).

TUPLE1) has been used since 1992 to detect most deletions in this region,[9] but is now being superseded by clinical microarrays that should increase diagnostic yield.[46,61,62] Several lines of evidence support the generally pathogenic nature of 22q11.2 deletions and the high penetrance of observable phenotypes,[3,63,64] so that no distinction is typically made between individuals with 22q11.2 deletions and individuals with 22q11.2DS.

Association with schizophrenia

Several studies have confirmed that 22q11.2DS accounts for approximately 1% of all cases of schizophrenia (see Bassett et al[65] and references therein). Conversely, an estimated 22.5% of adults with 22q11.2DS develop schizophrenia[66] or a related psychotic disorder.[67] In other words, a 22q11.2 deletion is a variant of large effect, associated with a greater than 20-fold increase in risk for schizophrenia.[9] The clinical expression of the schizophrenic illness is essentially indistinguishable from that found in the general population with respect to prodrome, age at onset, presentation, cognitive profile (except for lower mean IQ), and, according to limited data available, response to treatment.[43,66–71] Thus 22q11.2DS represents the best available specific genetic model of schizophrenia, with minimized genetic heterogeneity and substantial evidence this is a representative form of this illness.[2] Empirical evidence for a strong negative selective pressure[57] and high rate of recombination at the 22q11.2 locus[72] is consistent with the common disease – rare variant model for schizophrenia.[42]

Clinical relevance

For patients with schizophrenia, a clinician today should be armed with a high index of suspicion for 22q11.2DS and/or consistently use established clinical screening criteria to detect features suggesting this genetic diagnosis, such as dysmorphic facies, a nasal voice, congenital anomalies, and/or learning difficulties.[65,73] This would prompt a comprehensive diagnostic assessment, including developmental, medical, and family history, and a physical examination by a clinician experienced in genetic syndromes and dysmorphology.[9] Genetic testing would follow if sufficient features were present to support a clinical diagnosis of 22q11.2DS[73] and should proceed in all patients with comorbid mental retardation and/or multiple congenital anomalies.[3,61]

In a patient with schizophrenia, detection of a 22q11.2 deletion is clinically relevant.[9] Consensus clinical practice guidelines[46] now exist that detail opportunities for anticipatory care and optimizing medical management of associated features, and for genetic counseling that can be informed by extensive (and rapidly expanding) knowledge of pathogenesis, recurrence risk, and lifelong expression, natural history, and clinical outcomes.[54,56,57,63,66,67,70,74–88] Careful attention to the commonly accompanying endocrine and neurological features in particular may be helpful in the psychiatric management of patients with 22q11.2DS.[9,63] As is common in patients with schizophrenia, the psychiatrist may be the only physician the patient sees regularly and may therefore be expected to provide primary care for accompanying medical conditions, and/or have the responsibility for arranging appropriate investigations and follow-up.

For patients already diagnosed with 22q11.2DS, what are the potential implications of knowing about the risk for schizophrenia prior to first onset of psychosis? As for schizophrenia in the general population,[29] there is little evidence for any additional environmental factor(s) affecting risk of psychosis in 22q11.2DS.[9,89] Avoiding substance use, particularly early marijuana use, and lifelong general health measures such as good nutrition, and physical and mental exercise, may decrease risk to some extent.[9] Common genetic modifiers of some effect may exist,[90,91] as for the congenital cardiac phenotype,[92,93] but have not been convincingly demonstrated[67,94–96] (see Philip and Bassett[48] for more details), and additional copy number variation/variants (CNV) do not seem to play a major role in expression of schizophrenia.[53] Prospective[97–99] and retrospective[68,70,100] research is ongoing to identify specific neurocognitive and neuroimaging predictors of future psychotic symptoms, as none are yet known. The greatest potential benefit of early diagnosis of a 22q11.2 deletion would likely be to facilitate the recognition of the early stages of schizophrenia or another psychiatric illness, and promptly seeking expert help in diagnosis and effective treatment.[9,78] Limiting the duration of untreated psychiatric illness is associated with better prognosis.[101] Psychosis in an adolescent or young adult with 22q11.2DS should also be easier to diagnostically classify as schizophrenia in its early stages because of the significant association between these two elements,[102] despite the potential additional diagnostic complexities that could be posed by comorbid mental retardation.[103]

Schizophrenia in the molecular age

Foreshadowed by the association with 22q11.2 deletions, there is further emerging evidence that multiple rare variants contribute significantly to the genetic vulnerability for schizophrenia. Other select genomic disorders caused by rare, recurring CNV represent emerging genetic subtypes of schizophrenia of growing clinical importance (Table 3).

Table 3 The current established and emerging genetic subtypes of schizophrenia are characterized by large, rare, recurring copy number variation and variable expressivity

Genetic subtype of schizophrenia	Established	Emerging				
Genotype						
Locus	22q11.2	1q21.1	3q29	15q11-q13	15q13.3	16p11.2
Copy number change	Loss	Loss	Loss	Gain[a]	Loss	Gain
Typical size	3.0 Mb	1.4 Mb	1.6 Mb	6.0 Mb	1.5 Mb	0.6 Mb
Phenotype[b]						
MIM number	188400/192430	612474	609425	608636	612001	611913
Schizophrenia	Yes	Yes	Yes	Yes	Yes	Yes
Other psychiatric illnesses[c]	Yes	Yes	Yes[d]	Yes[d]	Yes	Yes
ASDs	Yes	Yes[d]	Yes	Yes	Yes	Yes
Developmental delay/mental retardation	Yes	Yes	Yes	Yes	Yes	Yes
Seizures/epilepsy	Yes	Yes	No[e]	Yes	Yes	Yes
Congenital anomalies[f]	Yes	Yes	Yes	No[e]	Yes	Yes
References	See text[46]	64, 159, 163, 164, 166, 168, 170, 172, 173, 175, 249–254	64, 161, 162, 166, 255–261	64, 127, 157, 159, 160, 180, 262–268	64, 159–161, 164, 166, 173, 253, 254, 269–278	64, 161, 164, 166, 173, 182, 253, 279–288

Notes: [a]Originating on maternally derived chromosome; [b]there are no pathognomonic signs or symptoms, and the penetrance of each microdeletion or microduplication with respect to each component phenotype is incomplete; [c]major depressive disorder, bipolar disorder, attention-deficit hyperactivity disorder/hyperactivity (unspecified), generalized anxiety disorder/anxiety (unspecified), aggression/temper outbursts, and/or major behavior problems (unspecified); [d]rare reports only; [e]no compelling data as yet, but there remain few detailed reports of the phenotype in individuals with this structural variant; [f]cardiac anomalies, palatal anomalies (such as velopharyngeal insufficiency), skeletal abnormalities, and/or other major birth defects.
Abbreviations: ASDs, autism spectrum disorders; Mb, mega base pairs; MIM, Mendelian Inheritance in Man.

This encouraging progress comes after several decades of genome-wide and targeted molecular studies, representing essential, though largely unfruitful, tests of standard genetic hypotheses usually involving common variants at the level of nucleotide sequence (eg, single nucleotide polymorphisms [SNPs]) and DNA structure (eg, copy number polymorphisms [CNPs]). In retrospect, these studies were driven by genetically naïve expectations for schizophrenia. These included that there would exist (1) a single major locus, (2) common genetic variants of large effect, and (3) variants specific to schizophrenia (ie, not frequently associated with other conditions).

Genome-wide linkage and association studies

Associations with schizophrenia

Initially, several genome-wide linkage studies of multiply affected families identified regions where candidate genes for schizophrenia are likely to be. Some of these loci have been replicated and/or supported by meta-analyses,[9,18,104–108] including 1q21-q23, 6p22, 8p21, and 13q32-q34.[109–118] As expected,[119] however, there are also negative studies of all loci.[18,120–122] Despite a few highly significant findings that have led, for example, to identification of functional SNPs in candidate genes,[123] one of the most important collective contributions of these studies has been the confirmation that

there is no unifying single gene mutation for familial forms of schizophrenia.

In addition, there have now been several large-scale, case-control genome-wide association studies (GWAS) of schizophrenia using SNP-based microarray technology. Overall, this strategy, based on studying common SNPs, has proven to be relatively ineffective for the study of complex neuropsychiatric diseases, compared with the relative successes for auto immune diseases like diabetes and inflammatory bowel disease.[124] Some of these GWAS failed to find significant evidence of association and/or have not replicated weak associations.[125–129] Others have reported common sequence variants of very small effect, including several in the human leukocyte antigen (HLA) region (6p).[130–137] The latter findings recall early studies of protein-based HLA polymorphisms.[138,139] Meta-analysis using GWAS data from thousands of individuals with schizophrenia has revealed a few weak-effect associations, in the *ZNF804A* gene.[140–143] GWAS of common structural variants such as CNPs, while fewer in number, have yielded comparable findings of nominal effect.[127,144]

GWAS using common SNPs and data on drug dosages and treatment response in schizophrenia (ie, pharmacogenomics studies) are reviewed elsewhere.[145,146] These show modest results similar to those for diagnosis of schizophrenia, and broad clinical applications still represent more a dream than a

reality; the family history with respect to treatment response remains arguably the best predictor of treatment efficacy and side effects.[147] Findings from thousands of targeted candidate gene association studies of schizophrenia using individual SNPs (and, occasionally, specific rare sequence variants), catalogued online in the SzGene database[148] (www.szgene.org) and the database of Genotypes and Phenotypes (www.ncbi.nlm.nih.gov/gap), are either negative altogether or sporadically positive without replication and/or positive but with modest effect size. None are associated with a relative risk for schizophrenia anything approaching that of the ε4 variant of the APOE gene relative risk for Alzheimer disease (Table 1).[9] Taken together, the GWAS and targeted association study results conclusively indicate there are no common genetic variants of large effect for schizophrenia.

Clinical relevance

Although linkage approaches and GWAS of common variants have yielded a collection of several dozen candidate genes, the individual effect sizes of associated variants are modest. Mutation testing in these genes has no role in the clinic at this time. Larger and larger sample sizes have ensured that variants of smaller and smaller effect may be detected. Importantly, a GWAS design lacks the power to detect rare sequence variants of large effect, and it is rare variants that may collectively play a major role in the etiology of schizophrenia.[124] While preliminary findings from the first whole exome sequencing studies in schizophrenia are solely in the realm of scientific discovery at this time, they provide evidence in support of a de novo mutational paradigm at the sequence level.[149,150] In time, these studies may provide clinically relevant findings. However, the most notable evidence today for clinically important rare genetic variants in schizophrenia comes from studies of CNV – that is, structural genomics.

Rare copy number variation and emerging genetic subtypes

The discovery that there is substantial structural genomic variation in the human genome that contributes to both normal variation and to susceptibility for disease is one of the major scientific advances in recent years.[5,64,151–155] Consistent with early reports of the association of schizophrenia with rare microscopically visible chromosomal abnormalities[156] and the established association with 22q11.2 deletions,[43,66,67,69] there is now substantial evidence for the importance of diverse rare structural variants in causing schizophrenia.[3,5] These structural variants are mainly comprised of specific examples of large (eg, >500 kb) CNV that are consistently enriched in schizophrenia samples, and absent or extremely uncommon (ie, "rare") in control populations.

Associations with schizophrenia

Following the discovery of 22q11.2 deletions in schizophrenia, the next tier of large, rare CNV findings includes a set of emerging genetic subtypes of schizophrenia (Table 3).[3] In contrast to 22q11.2DS, the epidemiology and basic genetic parameters such as penetrance and expression remain uncertain for these genomic disorders, and there has been little to no study of the dosage-sensitive genes that may cause the associated phenotypes.[64] Collectively, however, this second tier of CNV may be as or more common in schizophrenia than 22q11.2 deletions.[3,5] Those variants identified to date include large (>500 kb), rare, recurring (flanked by segmental duplications), hemizygous losses (deletions) and gains (duplications) at several loci (Table 3). All involve numerous genes and are consistently identified in large-scale case-control CNV studies of schizophrenia, albeit each individually at apparently low prevalence. A recent review has suggested pooled odds ratios for schizophrenia of 8 or higher for four of these five genomic disorders,[5] and for 15q11-q13 duplications of maternal origin, an initial report based on four cases suggested an odds ratio for schizophrenia of 7.3.[157] As with 22q11.2 deletions,[3] these rare structural variants may be expressed as other psychiatric illnesses and/or developmental conditions, such as autism spectrum disorders (ASDs) and epilepsy (Table 3). On the other hand, the few studies of rare CNV in bipolar disorder indicate little overlap of these forms of schizophrenia with this major mood disorder.[5,158] This would be consistent with the historical clinical separation of schizophrenia and bipolar disorder based on presentation, course, and outcome, and the perhaps less "neurodevelopmental" nature of bipolar disorder. The variability of expression of 22q11.2 deletions and these other rare structural variants is shining new light on schizophrenia and on the genetically related spectrum of neuropsychiatric disorders.[3] There are also other potential susceptibility factors for schizophrenia of likely smaller effect (Table 4),[5] such as hemizygous deletions at 15q11.2[159–164] and 17q12,[162,165] and duplications at 1q21.1[159,164,166] and 16p13.11.[160,167] These appear to be similarly or more variable in their expression and less penetrant with respect to schizophrenia, or indeed any major phenotype, than 22q11.2 deletions and the five emerging genetic subtypes.[64,168–179] All await more detailed study, especially of expression in adults.

Table 4 outlines some of the many remaining issues with respect to clinical translation for possible genetic subtypes of schizophrenia. For instance, there are limited or inconsistent data on CNV inheritance status or comorbidity in most of the existing studies, and numerous systematic methodological issues that complicate the assessment of prevalence and penetrance.[3,180] Truly inclusive population-based prevalence samples of schizophrenia (eg, community catchments) are difficult to obtain, and many of the initial large case-control studies may have implicitly or explicitly excluded subjects with dysmorphic features, birth defects, learning difficulties, and/or known syndromes.[3] Such systematic ascertainment biases in sample collection for large-scale case-control studies suggest that the prevalence of genomic disorders in schizophrenia may be underestimated. As an example, the expected prevalence of 22q11.2 deletions in schizophrenia is about 1%,[65,181] but a pooled estimated prevalence based on large consortium-based case-control studies is approximately 0.3%.[5] There are also few data concerning fundamental issues such as the possible effects of sex, ethnicity (most studies to date have involved Caucasians), or sampling from genetic isolates. Nonetheless, this initial wave of genome-wide studies of CNV provides replicated associations of schizophrenia with specific rare variants. This supports a more general mutational mechanism involving large rare CNV that substantially elevate risk for schizophrenia, especially more developmental forms of the disease.[3,182]

Neurodevelopmental implications

Notably, many of the structural variants associated with schizophrenia implicate a dosage effect of neurodevelopmental genes involved with neuronal proliferation, migration, or synapse formation.[2,182] Although there are few studies that have examined age at onset of schizophrenia,[166] it may be that
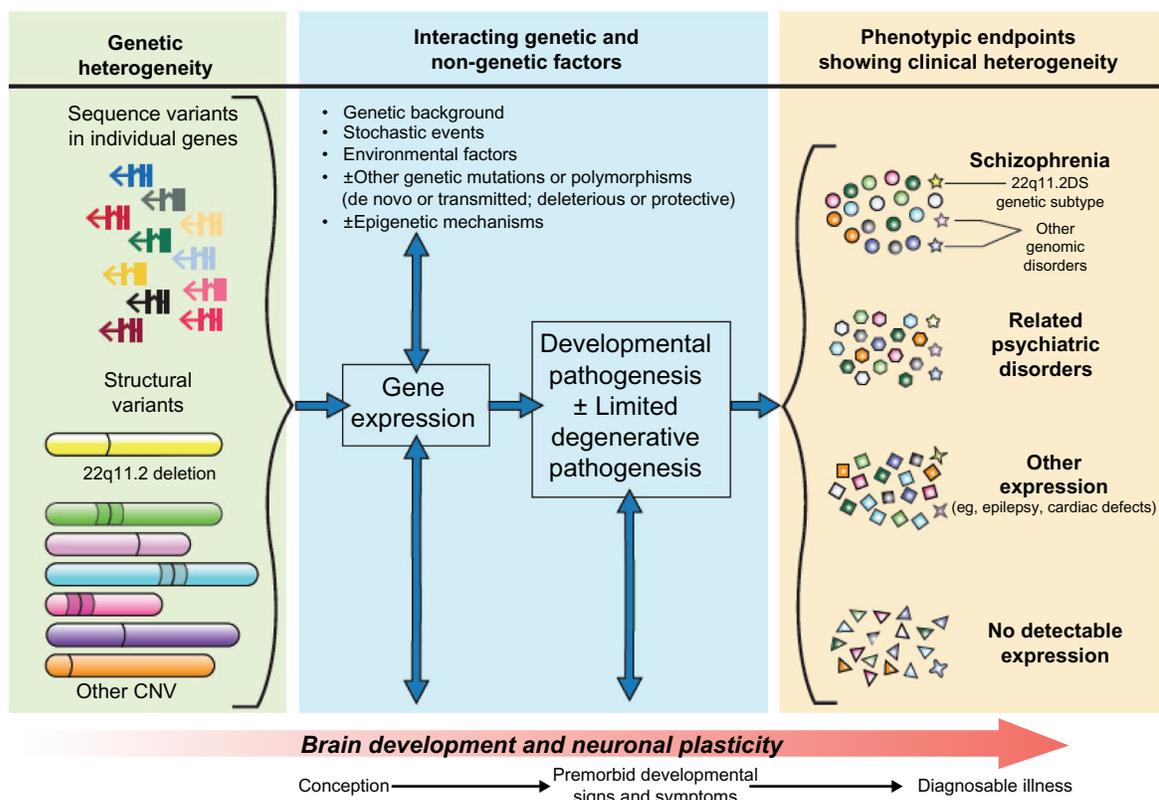

Figure 1 Neurodevelopmental model of schizophrenia, informed by new molecular genetic discoveries. One or more transmitted or de novo sequence or structural mutations, involving one or more genes, and acting individually or interactively, is proposed as the initial causal event. The pathway from genotype to phenotype is formulated as a dynamic process beginning at or before conception, and involving gene expression (including, but not limited to, protein activity) and interaction with normal brain development and neuronal plasticity mechanisms, and likely multiple other genetic and non-genetic factors. Different phenotypic endpoints are possible, and specific factors that dictate variable expression of ostensibly the same genetic loading are largely unknown and may be variant-specific. These resulting phenotypes could include clinically diagnosable schizophrenia, other psychiatric illnesses, other conditions including disorders of development, or no detectable expression. For example, a 22q11.2 deletion (yellow structural variant) may be expressed as schizophrenia and/or a related psychiatric disorder and/or another developmental disorder (yellow stars).
Note: Adapted from AS Bassett, EW Chow, S O'Neill, LM Brzustowicz, Genetic insights into the neurodevelopmental hypothesis of schizophrenia, *Schizophrenia Bulletin*, 2001, 27, 3, pp. 417–430, by permission of Oxford University Press.[35]
Abbreviation: CNV, copy number variation.

rare CNV have a greater impact on such genes in individuals with younger onset (eg, childhood, age <12 years) compared with onset at older ages.[182] This would be consistent with a previously reported greater prevalence of chromosomal abnormalities and 22q11.2 deletions in childhood-onset schizophrenia.[183] Several other lines of evidence, including brain imaging, premorbid clinical signs, and associations with minor dysmorphic features, have previously indicated that early changes in neurodevelopment may be involved in the pathogenesis of schizophrenia.[2,35,184] The current genetic neurodevelopmental model of the etiopathogenesis of schizophrenia (Figure 1) has important consequences with respect to the potential for pre-symptomatic prediction and, ultimately, attenuation, delay, or prevention of psychosis, as well as present-day genetic counseling (outlined below).

Clinical relevance

Use of 22q11.2DS as the benchmark for clinical applicability of molecular genetics in schizophrenia highlights the gaps that currently exist at the level of translating recent genetic results involving other large rare CNV to inform clinical management of patients (Table 4). Optimism about eventual direct benefits for patients and their families stems from the observations that effect sizes are generally large and that the spectrum of disorders involved in variable expression may tend to be multisystem and/or developmental in nature. This may be related to the multiple genes usually involved in large CNV, and in turn suggests that penetrance for any observable phenotype, as opposed to schizophrenia per se, will be fairly high. Meaningful prediction of some associated conditions would then be possible, creating opportunities for anticipatory care and improved medical management, as already exist for 22q11.2DS.[3] Eventually, such genetic variants may also assist in diagnostic subtyping of schizophrenia.

Psychiatric disorders in general appear to have a poorly understood, nuanced connection to the various associated structural variants.[153] Determinants of disease specificity may be other, perhaps more common, genetic, epigenetic, stochastic, and/or environmental modifiers. There has been little research as yet on such additional factors (Table 4).[185] Likely the research that will have the most clinical impact will involve unbiased sampling, family studies, and detailed study of the variable expression and natural history of individual variants. This will in turn facilitate specific care recommendations and prediction of comorbidities, and eventually prognosis and drug response (Table 4).[3] To date, in order to gain sample sizes sufficient to detect signals in genetically heterogeneous populations, many researchers have sacrificed: (1) detailed phenotyping of the probands, (2) the ability to return to individual participants after analyses, and (3) the familial context necessary to assess de novo status and segregation patterns. These features represent, from a clinician's point of view, unfortunate consequences of the study design of much of the large-scale genetics research conducted thus far in the twenty-first century. The longstanding practice of DNA sample anonymity, and other formal barriers between research participation and clinical care, is more and more at odds with a conflicting "duty to warn" in this new era of molecular medicine, where actionable and clinically relevant information is increasingly likely to be obtained.[186,187] Researchers, clinicians, and genetic counselors must begin to consider new strategies for when and how to routinely return to genotypic information and subsequently inform research participants and their clinicians of medically pertinent findings, keeping in mind that the interpretation of any particular variant is subject to change as new data accrues.

Lack of data on potential utility at this time, especially given limited resources, suggests that clinical genome-wide microarray testing is not yet justified for individuals with schizophrenia, except for the minority with syndromic and/or neurodevelopmental features such as mental retardation or multiple congenital anomalies.[3,61,65] Similarly, calls for routine targeted clinical testing on the basis of a single study where penetrance and information about expression remain unknown (eg, 7q36.3 duplications of various sizes implicating the *VIPR2* gene[188]) appear dangerously premature. The effectiveness of personal genomic information in tailoring interventions and improving health outcomes has not yet been convincingly demonstrated for emerging genetic subtypes of schizophrenia, nor for susceptibility factors that may be relevant for this complex disease. There are also limited to no data with respect to the ethical, legal, social, and economic implications of widespread personal genomic testing.[189] As for other diseases like ASDs,[61,190] careful consideration and professional consensus are needed to decide how to apply such genomic knowledge in clinical practice. Use of well-recognized standards and guidelines for clinical genetic testing, such as the ACCE Model Process for Evaluating Genetic Tests (available from: www.cdc.gov/genomics/gtesting/ACCE/), may be helpful in this regard. Their application quickly exposes the many gaps in our fundamental knowledge base with respect to the clinical and analytic validity, and clinical utility, of genetic testing for most CNV in schizophrenia, particularly compared with other diseases

Table 4 Pathway to clinical utility for copy number variation and genomic disorders associated with schizophrenia (as of 2011)

Clinically relevant issues	Established genetic subtype	Emerging genetic subtypes	Potential susceptibility factors[a]
	22q11.2 deletion	1q21.1 deletion 3q29 deletion 15q11-q13 duplication 15q13.3 deletion 16p11.2 duplication	Various, including: 1q21.1 duplication 15q11.2 deletion 16p13.11 duplication 17q12 deletion
Replication of association in unrelated cohorts	●	●	●
Estimation of population incidence and de novo vs inherited rates	○[b]	[c]	[c]
Estimation of prevalence within general schizophrenia population	●	○[d]	○[d]
Estimation of penetrance for schizophrenia (± for any feature)	●	○[e]	○[e]
Assessment of clinical expression of the schizophrenia illness	●		
Elucidation of neuropsychiatric expression across the lifespan	●[f]	○[g]	○[g]
Elucidation of other expression across the lifespan	●[f]	○[g]	○[g]
Search for genetic modifiers of expression	○		
Search for early clinical predictors of psychosis	○		
Evaluation of transmission patterns and reproductive fitness	●		
Development of clinical screening criteria	●		
Evaluation of prognosis and long-term outcomes	○		
Identification of opportunities for improved management	○		
Creation of clinical practice guidelines	●		
Description of treatment response (pharmacogenomics)	○[h]		
Identification of specific treatment targets			

Notes: See text and Table 3 for references. [a]Seemingly less penetrant for schizophrenia, and/or with less evidence as yet for association, than the emerging genetic subtypes, see text for details; [b]population incidence estimates based mainly on prevalence in infants with major congenital anomalies (eg, congenital heart disease[289]);[59] [c]one non-standard attempt to estimate the de novo rate using available case-control data;[290] [d]estimated from available case-control data;[5] no studies of consecutive patients, nor any involving only a single centre or community catchment; [e]attempts to estimate penetrance did not use standard genetic methods, but instead available case-control data;[64,291] [f]adults with 22q11.2DS may have a diminished lifespan;[75] [g]some data, primarily derived from association studies of other developmental diseases. Little to no data regarding lifelong expression (ie, in adulthood), or expression in carriers not ascertained through a major phenotype; [h]clinical observation suggests that response to treatment is not substantially different in 22q11.2DS-schizophrenia,[9,43] but there remain limited published data. ● = Much evidence or progress; ○ = some evidence or progress.

and genetic variants such as breast/ovarian cancer and *BRCA1* and *BRCA2* mutations.[191]

Genetic risk and counseling issues

Genetic counseling for schizophrenia largely continues to focus on recurrence risk based on family history, but recent molecular genetic discoveries are now having a significant impact in specific cases. Post-onset (ie, phenotype first), the identification and disclosure of a well-established genetic variant (eg, a 22q11.2 deletion) that is strongly associated with a stigmatized illness like schizophrenia may be highly valued by the patient and family for its explanatory value.[186,192] Such variants also provide the potential to inform reproductive decision making, including the possible availability of prenatal detection.[3] Even in the absence of such genetic variants, genetic counseling for schizophrenia may still represent an informative and therapeutic intervention. However, there are limited empiric data about potential benefits at present.

Genomic disorders and genetic subtypes

Identifying genetic subtypes of schizophrenia offers new possibilities with respect to recurrence risk prediction. In the case of an individual with 22q11.2DS-schizophrenia and no other affected relatives (including the spouse or partner), for example, knowledge of the proband's 22q11.2 deletion bifurcates the risk scenario. Transmission of the 22q11.2 deletion would imply a recurrence risk for schizophrenia of approximately 20%–25% in each offspring, whereas a failure to transmit the deletion would theoretically decrease that risk to the standard population rate (~1%). With no knowledge about the 22q11.2 deletion status, offspring would have an a priori averaged (though individually far less informative) recurrence risk for schizophrenia that is comparable to the standard empiric recurrence risk of 13%.[20,147] Also, identification of a de novo 22q11.2 deletion, or other putatively causal de novo CNV, in an individual with schizophrenia would be expected to lower the recurrence risk for siblings and nieces/nephews to nearly the population rate.[10] We note from experience that for schizophrenia the risk of recurrence in siblings and nieces/nephews is the dominant concern expressed in most genetic counseling sessions, given the significantly decreased reproductive fitness associated with schizophrenia and concomitantly few direct offspring.[57,193,194]

As new diagnoses of specific genomic disorders and increasing evidence for their involvement in schizophrenia flood clinical practice, the need for more psychiatric genetic counseling research and training will be increasingly apparent. First, the association of specific large rare CNV with schizophrenia, as outlined above (Tables 3 and 4), effectively means that incidental predictive "genetic testing" for schizophrenia is now a reality of clinical practice, because of the use of clinical microarrays as a first-tier diagnostic test for developmental delay/mental retardation, multiple congenital anomalies (even in utero), or ASD.[10,61] Proposed benefits and disadvantages of predictive testing are discussed elsewhere.[147,195,196] Genetic counselors, however, may be reluctant to disclose the possibility of psychotic illness to parents even in the context of well-established risk factors such as 22q11.2 deletions. Stigma,[197] lack of knowledge about the illness and its treatment, and concerns about generating anxiety[79] may play a role in deferral or non-disclosure,[198] despite some evidence that opportunities to anticipate and prepare for such an illness would have been valued by the parents.[186] Second, genetic counseling of the adolescent and adult patients themselves may be complicated by cognitive impairments and/or psychiatric symptoms.[147,199] There are

surprisingly few empirical studies of the optimal content and process, and of the effectiveness and ensuing outcomes, of genetic counseling in these instances,[199,200] even for well-recognized genomic disorders like 22q11.2DS[57] or Williams syndrome.[201]

On the other hand, clinical microarrays also give results unrelated to current genomic disorders and about which there is much uncertainty with respect to interpretation. Today, proposed workflow algorithms for determining pathogenicity are likely to label most individual CNV identified, other than the relatively established like those underlying 22q11.2DS and other genomic disorders, as "variants of unknown significance" or "VOUS."[153,202] This is of particular concern for smaller (atypical) rare CNV at loci that may be associated with emerging genetic subtypes of, or possible susceptibility factors for, schizophrenia. The nature of schizophrenia poses additional challenges. For example, parents of adult patients are less likely to be available for testing to determine de novo/inherited status, and patients may be poor historians with respect to medical and/or family history. Clinical interpretation of many CNV findings will thus remain a major challenge for the foreseeable future.

Familial schizophrenia

Individuals from multiplex families arguably have the greatest need for risk prediction and genetic counseling. However, empiric recurrence risk figures cannot be quantitatively modified to account for multiple affected relatives or a bilineal (ie, maternal and paternal) family history.[147,203] The sole exceptions relate to the situations where both parents, or one parent and one sibling, are affected, for which some recurrence risk data are available.[9,147,204] There is also no ability to adjust risk to take into account relatives with schizophrenia spectrum conditions and/or other neuropsychiatric diseases.[147,203] Also, unlike in Huntington disease before mutation identification,[9,205,206] knowledge of linkage or association information where it exists for individual families cannot be meaningfully incorporated into illness prognostication, given the modest effect size of alleles identified.

As for any individual with schizophrenia, clinicians should be aware of features consistent with testable conditions like 22q11.2DS. However, 22q11.2 deletions are less likely to be co-segregating with schizophrenia in multiply affected families, as they are associated with a strong negative selective pressure.[57] Other large rare CNV associated with schizophrenia, for example, microduplications not associated with multisystem/syndromic features,[157,180] may have less effect on reproductive fitness and thus a higher

likelihood of contributing to the burden of illness in multiply affected families, though this remains to be shown. There is growing empirical[207] and theoretical[208,209] evidence that, as for Parkinson disease,[210] familial and "sporadic" schizophrenia may not be molecularly distinct entities. This underscores the need for a greater focus in future studies on both the inheritance status of genetic variants shown to be associated with schizophrenia, and on the extent of co-segregation of these variants with other neuropsychiatric illness and developmental conditions within families.

Idiopathic schizophrenia

Often overlooked in our collective enthusiasm for the promise of new genetic discoveries are the sobering realizations that the vast majority of cases of schizophrenia are "idiopathic" and that, as for most conditions,[211] family history remains the cornerstone for individualized disease prediction. When the schizophrenia is not a syndromic form of the illness,[9] of genetically testable origin,[61] or originating in the context of a multiplex family, patients and their relatives are unlikely to be seen by a genetics professional unless presented with an unrelated concern.[147] Much has been written and repeated over the past several decades about the optimal content and process of "multifactorial" genetic counseling,[9,147,196,204,212–214] despite low rates of genetic counseling referrals[215] and a continued scarcity of evidence in support of the desirability[216] or effectiveness[217] of the genetic counseling intervention. To assess these key issues, and also prepare for the growing role of personalized molecular genetic information, there is an urgent need for data-driven reports of the genetic counseling of patients with idiopathic schizophrenia and their relatives.

Recent advances in schizophrenia genetics may still be germane to contemporary genetic counseling however, even in the absence of personalized application. For example, presenting schizophrenia to consultands as a neurodevelopmental disorder (Figure 1),[35] with psychosis as a later stage manifestation often preceded by a prodromal period,[2] has the potential to further modify false beliefs that upbringing, lifestyle decisions, or other "triggers"[204] are either necessary or sufficient to cause an illness that otherwise would not have developed. Proof that de novo mutations play an important causal role in some cases may help in dispelling a popular misconception[218] that "genetic" and "inherited" are synonymous terms. Especially in the absence of an affected first- or second-degree ancestor, de novo mutation is a highly plausible theory of causation that may decrease a sense of family blame or shame. Finally, presenting evidence for genetic and epigenetic differences between monozygotic twins can help to explain discordant twin pairs without needing to resort to the unsupported assumption of powerful environmental factors in these rare cases.[219–222] The role of independent environmental factors[29] may be less, and that of gene-environment interactions[25,223,224] and stochastic effects[225,226] may be greater, than initially supposed.

As yet, the full "risk architecture" of schizophrenia, and the extent to which risk factors may be modifiable, is unknown.[2] With respect to idiopathic schizophrenia, there is a forced reliance on family history and associated crude empiric recurrence risks, unmodified quantitatively by any other clinical or demographic variables.[203] Few attempts have been made to update or validate these recurrence risks, despite the potential increase in the proportion of individuals with schizophrenia who partner with someone else with schizophrenia (ie, assortative mating),[227] new conceptualizations of the genetically relevant schizophrenia spectrum,[3] and increasing opportunities for molecular characterization. Initial attempts to generate a "risk score" from multiple variants with weak association with schizophrenia may be promising avenues for future research,[131,228,229] but are not yet meaningful in a clinical genetic counseling context. In addition, the factors of primary interest in genetic counseling (ie, those that increase individual recurrence risk substantially) do not necessarily have much effect on average risk, the primary focus of most retrospective studies of schizophrenia, and vice versa.[230] Partial risk prediction as afforded by proven moderate to high penetrance variants such as 22q11.2 deletions may be the best case scenario. There are likely to be fundamental limits on precise individualized genetic risk prediction due to the complex architecture of common traits, including common variants of very small effect, rare variants that cannot be fully enumerated, and complex epistatic interactions, as well as stochastic and possible environmental factors.[231] The potential "added value" of genome-wide data (eg, derived from next-generation sequencing) in tailoring risk estimates would also need to be weighed against many other factors. These include the cost of, and expertise needed for, the molecular analysis (which is still prohibitive for widespread use, particularly in publicly funded health care systems) and the interpretation of results (as great or greater than molecular analytic costs, and less likely to decrease over time).[231] Such barriers will impede widespread application of new genetic technologies in clinical practice more generally for the foreseeable future. Personal genome sequencing as a single universal genetic test that is cost-effective and of broadly applicable clinical utility remains a distant, though much wished for, prospect.[232]

Conclusion

Schizophrenia is a complex neuropsychiatric disease with documented clinical and genetic heterogeneity, and little is known about the associated pathophysiology apart from strong evidence for neurodevelopmental origins. The elucidation of specific causes and mechanisms for schizophrenia that is beginning to be derived from advances in molecular genetics and related research promises to help many families afflicted with this illness. However, much work needs to be done to move the recent surge of genetic research discoveries into the clinic. In particular, specific large rare structural variants (CNV) have been convincingly implicated in targeted studies over two decades (with respect to 22q11.2 deletions) and more recently in several large-scale genome-wide case-control studies of schizophrenia. Clinical interpretation of most individual loci remains unclear as yet because the associated epidemiology and basic genetic parameters (such as penetrance and expression) are not yet well characterized. For now, 22q11.2 deletions represent the cutting-edge of clinically applicable molecular genetics in schizophrenia. New opportunities in risk prediction and genetic counseling are exciting avenues for future research.

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Disclosure

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