Schizophrenia and Genetics: New Insights

Anne S. Bassett, MD, FRCPC^{*}, Eva W. Chow, MD, FRCPC, Rosanna Weksberg, MD, PhD,
and Linda Brzustowicz, MD

Abstract

There is consistent evidence that the principal etiology of schizophrenia involves predisposing genetic factors. Recent years have seen several new insights in the genetics of schizophrenia. Several chromosomal regions show significant evidence that they contain schizophrenia susceptibility genes. A clinically relevant genetic subtype of schizophrenia (22q deletion syndrome) has been identified. There is new evidence that spontaneous mutations may play a role. There are new recommendations for genetic counseling. The progress to date suggests that understanding of a neurodevelopmental pathway from genetic susceptibility to schizophrenia will soon be fundamentally altered by molecular genetic advances in this complex disease.

Introduction

Schizophrenia is a serious neuropsychiatric disorder affecting approximately 1% of the general population, and with substantial impact on a much larger proportion of the population, including family members and society at large. There is substantial evidence that the principal etiology of schizophrenia involves genetic factors that predispose an individual to develop the disorder; indeed, multiple genetic and nongenetic factors are likely to be involved [1•,2•]. No individual susceptibility gene for schizophrenia has yet been identified. Recently, however, there has been much progress, and several new developments in the genetics of schizophrenia have emerged. These include the identification of the first clinically relevant genetic subtype of schizophrenia that is detectable by clinical and laboratory evaluations, advances in understanding of possible mechanisms, and multiple localizations of potential susceptibility genes. The authors of this paper will discuss the most promising and clinically relevant advances.

Insight #1: A Genetic Subtype of Schizophrenia

One of the most exciting developments in recent years is the identification of 22q deletion syndrome (22qDS) as a clinically detectable genetic subtype of schizophrenia that may serve as a model to study the etiopathogenesis of schizophrenia, including the neurodevelopmental process involved. 22q deletion syndrome is a genetic syndrome associated with a high (approximately 25%) rate of schizophrenia [3–5] and microdeletions in the long or “q” arm of chromosome 22. This means that individuals with a chromosome 22q11.2 deletion have a

^{*}Clinical Genetics Research Program, Centre for Addiction and Mental Health, 1001 Queen Street West, Toronto, Ontario M6J 1H4, Canada. anne.bassett@utoronto.ca.

higher genetic risk for schizophrenia than any other group of individuals except for monozygotic (identical) co-twins of individuals with schizophrenia [5].

22q deletion syndrome: an under-recognized condition

The estimated rate of 22q11.2 microdeletions in the general population is about one per 4000 live births, making it the most common of all microdeletion syndromes and the second most common genetic syndrome after Down syndrome. The rate of chromosome 22q11.2 microdeletions in a population of individuals with schizophrenia, however, is about 80 times more frequent than that in the general population, occurring in up to 1 in 50 patients [5,6]. 22q deletion syndrome is, therefore, several times more prevalent than childhood onset schizophrenia, and is much more common in the general population than Huntington's disease.

In specific subpopulations of schizophrenia, 22qDS is even more prevalent. For example, the authors have found that as many as 40% of adults with schizophrenia who meet clinical screening criteria for 22qDS have a detectable 22q11.2 deletion [7•,8]. The prevalence of 22qDS also appears to be high in patients with dual diagnoses of schizophrenia and mental retardation (approximately 9%) [9], and in childhood onset schizophrenia [10]. However, several features conspire to make 22qDS ascertainment incomplete, and this genetic subtype of schizophrenia may therefore be misperceived as rare. Responding to this issue, the authors have developed a set of clinical criteria designed to increase the rate of detection of 22qDS in adults [7•].

Clinical features

The physical and neurobehavioral features of 22qDS are highly variable, and are often so mild that the condition goes unrecognized, particularly in adults (*see* Table 1) [11]. The facial features are subtle and variable [7•,12,13], reducing the index of suspicion for a genetic syndrome. Palatal problems are common, but usually take the form of velopharyngeal insufficiency, a neuromuscular problem resulting in a variable degree of hypernasal speech, rather than overt cleft palate [11]. The majority of individuals with 22qDS have learning difficulties, but these are most commonly subtle and may never be detected by the school system. Only 35% to 40% have intellectual functioning in the mild range of mental retardation, though there are case reports of more severe mental retardation [14]. The authors have found that platelet levels are usually in the low normal to below normal range, which may be a useful adjunctive feature in screening patients for 22qDS [15].

Family history

The fact that the 22q11.2 deletion is usually (greater than 90% of newly identified cases) [16] a spontaneous (*de novo*) mutational event may also make the syndrome difficult to recognize because there is no family history of 22qDS or its component features. The term *genetic* may connote only *inherited* to many clinicians; 22qDS is certainly genetic and transmissible, but is not usually inherited. Even in the minority of cases with an inherited deletion, the transmitting parent often has such subtle manifestations that a genetic condition has never been suspected [17].

Molecular testing

Clinical testing for 22qDS only became widely available in about 1995. Specialized testing is required; routine karyotyping does not detect the 22q11.2 microdeletion. The most commonly associated deletions are identifiable with standard molecular cytogenetic studies, now available in clinical laboratories, using a fluorescence in-situ hybridization (FISH) technique and 22q11.2 probes (D22S75 or TUPLE1) [18]. These common deletions include a 3 million base pair (Mb) deletion (greater than 85%) and a 1.5 Mb deletion (8% to 14%) nested within the 3 Mb deletion region [16,19]. 22q deletion syndrome, therefore, represents the first genetic subtype of schizophrenia detectable using a blood test. The main limitation to the available clinical FISH testing is that it cannot detect rare, atypical deletions, though these appear to account for very few 22q11.2 deletions [19].

Typical schizophrenia

The authors' studies of individuals with a 22qDS subtype of schizophrenia (22qDS-SZ) reveal strong similarities in clinical, demographic, neurocognitive, and structural brain features to other forms of schizophrenia. Age at onset, major signs and symptoms of schizophrenia, level of functioning, profile of cognitive deficits, and structural brain findings are similar [12,20–22]. Possible differences from other forms of schizophrenia include a lower rate of comorbid substance use, lower rate of family history of schizophrenia, higher rate of physical congenital anomalies, lower mean intelligence quotient, and equal sex distribution.

Research advantages

The relative genetic homogeneity of 22qDS makes this an especially powerful model in which to study other etiopathogenetic factors because individuals with 22qDS all share the primary genetic predisposition for schizophrenia—a 22q11.2 deletion. This makes 22qDS different from other genetic high-risk groups available for study. For example, most samples of first degree relatives or mono-zygotic co-twins of individuals with schizophrenia are genetically heterogeneous because they derive from multiple different families with various, unknown genetic predispositions. A further advantage of 22qDS is the capability of molecular testing for the 22q11.2 deletion, both to identify this subgroup with elevated genetic risk for schizophrenia and to characterize the specific predisposing DNA alteration (primary genetic lesion). Chromosome 22 was the first chromosome to be “sequenced,” and its interesting genomic structure [23,24] has intrigued researchers attempting to understand the non-Mendelian genetic mechanisms that may underlie the 22qDS phenotype.

Immediate clinical relevance

22q deletion syndrome is a syndromic form of schizophrenia of immediate clinical relevance [5,7•]. Diagnosis of 22qDS may significantly alter medical management. For example, regular assessment for known associated conditions such as hypocalcemia and hypoparathyroidism is important, because hypocalcemia can arise at any time and can lower the seizure threshold. This may have significant implications to medication management if a seizure ascribed solely to psychotropic medications is actually precipitated by undetected hypocalcemia. Individuals with 22qDS appear to respond to the symptomatic medications

currently available for psychiatric illnesses, but there is insufficient information yet with respect to optimal treatments. As for other patients with both schizophrenia and developmental delay, patients with 22qDS may be more susceptible to neurologic side effects. A diagnosis of 22qDS also has important genetic counseling implications. The authors have recently outlined how genetic counseling for this subtype significantly differs from that for other forms of schizophrenia (*see* Insight #4) [25•].

Insight #2: There are Likely to be Several Susceptibility Genes for Schizophrenia

Evidence for genetic heterogeneity: multiple plausible localizations

Recent findings from genetic linkage studies of families with several affected family members (familial schizophrenia) add substantially to the longstanding body of work implicating genetic factors in the cause of schizophrenia [2•,26]. Linkage studies serve to narrow down a region where a gene for schizophrenia may be localized. This is like finding the city or neighborhood a susceptibility gene is in, though not actually identifying which gene it is or precisely which genetic change has occurred to predispose to the illness. Prior to 2001 there was convincing evidence for schizophrenia susceptibility loci on the long arm of both chromosome 1 [27•] and chromosome 13 [28,29]. These studies involved multi-generational Canadian [27•,28] and nuclear (small) and multigenerational American families [29], and found significant [28,29] or highly significant [27•] genome-wide linkage [30].

Significant results

Now there is further evidence helping to confirm a chromosome 1q21-q22 schizophrenia susceptibility locus from multigenerational British and Icelandic families [31] and several new localizations of possible schizophrenia susceptibility genes (*see* Table 2). Besides 1q and 13q, there is significant evidence for linkage of schizophrenia to three more genomic regions from three different genetic isolate populations—the short (“p”) arm of chromosome 2 (2p13-14) in large Palauan families [32•], chromosome 2q37 in Finnish nuclear and larger families [33•], and chromosome 6q25 in a very large northern Swedish pedigree [34•]. A locus on chromosome 15q14 also reached a genome-wide level of significance in a reanalysis [35] of small European-American [36] and African-American families [37].

It is notable that, with the exception of two studies [29,35], all of the significant linkage results have arisen from samples comprised of multigenerational families with large numbers of affected and unaffected subjects per family (Table 2). In contrast, linkage studies with samples comprised primarily of affected sibling pairs or small nuclear families (mostly single generation) have largely been unsuccessful. This is comparable to the successful strategy applied in studying hereditary deafness where large multiply affected families have been useful in identifying dozens of loci [38,39]. Despite the rarity of any single locus in the heterogeneous population of individuals with deafness, these studies have led to important advances in understanding the pathogenesis of hearing loss [38]. The authors of this paper now await the further laborious steps to narrow down the regions of interest identified by significant linkage results, and identify susceptibility genes for schizophrenia.

Suggestive results

Several other chromosomal regions show evidence from multiple suggestive linkage findings to support their possible involvement in schizophrenia susceptibility. A recent review found that three of these regions (6p24-p23, 8p21-p22, and 10p14-p11) had four or more genome scan studies with suggestive linkage findings, and are therefore consistent with regions where true schizophrenia susceptibility loci are most likely to be located [40]. The 5q22-qter region should probably now be added to these loci, given recent studies with similar suggestive linkage results [31,32•,33•,41].

Challenges to replication

Unambiguous (*eg*, logarithm of odds [lod] score greater than 10) linkage findings that are frequent in Mendelian disorders are unlikely to occur in complex disorders such as schizophrenia, where a significant finding needs to be differentiated from a false positive error [42]. Although specific ascertainment strategies and careful methods likely play a role, significant linkage results in complex disorders may be due in part to the draw of a “lucky hand”—a set of families with disease attributable to a specific locus [43]. This provides a partial explanation for difficulties in replicating susceptibility loci for complex disorders after initial significant results [30,43]. The reason is low power secondary to the genetic heterogeneity inherent in complex disorders [43,44]. Indeed, when there are multiple genes for a disorder, the *more representative* a data set is of the illness in the general population, the *less likely* that data set will be to confirm an initial finding of linkage [43]. Furthermore, small nuclear families or affected sibling pairs may generate different results from more densely affected, larger families due to different susceptibility genes segregating [43–45].

Phenotype issues

The significant linkage findings in schizophrenia to date have used conservative diagnostic categorization, a narrow definition of illness usually comprising schizophrenia and schizoaffective disorders or a broader definition including other related disorders (*see* Table 2). Use of diagnostic categorization provides some comfort that the susceptibility loci localized to date are relevant to expression of a schizophrenic illness. However, it is likely that other phenotypic features are involved in the full range of expression of a susceptibility genotype. Interestingly, there is a suggestion that there may be overlap of susceptibility loci for some familial forms of schizophrenia and bipolar disorder [46]. For example, there are significant [47] and suggestive [48] linkage results for bipolar disorder involving the same region of chromosome 13 (13q32) as that for schizophrenia [27•,29]. These findings are consistent with the likelihood of variable expression in schizophrenia, as in most other genetic disorders. Identifying features characterizing individual susceptibility loci could significantly increase power for localizing genes. Alternative phenotypes, which are often termed *endophenotypes* in psychiatry, that consistently subtype the illness in a genetically meaningful way with respect to schizophrenia may be identifiable now that there are significant linkage results using a schizophrenia phenotype.

Insight #3: New Evidence for an Old Idea—Spontaneous Mutations and Schizophrenia

As noted, there are high rates of new mutations with respect to 22q11.2 deletions in 22qDS. Identification of 22qDS patients with transmitted deletions is 10 times less common than identification of patients with deletions due to spontaneous mutations in germ cells (*ie*, both parents with normal chromosomes) [16]. There is now new evidence [49], added to that from several previous studies, which supports the possibility of spontaneous mutations in other forms of schizophrenia, an idea first advanced by Böök [50] in 1953. This possibility is supported by the observation that rates of schizophrenia are slightly higher with advancing paternal age (*ie*, older age of fathers at the birth of individuals who eventually develop schizophrenia) [49,51]. The likelihood of mutations in sperm increases with age [52], thus association of illness with advancing paternal age provides indirect evidence for possible spontaneous mutations. This finding may have more resonance with the general public today because older parents are more common than in previous decades. However, the clinical relevance of a small association between advanced paternal age and risk of schizophrenia is uncertain.

The relevance to research is more tangible. This advancement of an old idea is timely given that the identification of unstable mutations or other genomic instabilities that could underlie an increased frequency of spontaneous mutations has become plausible [1••]. For example, large unstable nucleotide repeats have been found to be responsible for several neuropsychiatric disorders. Large repeats do not appear to be involved in schizophrenia [53], although smaller repeats or other genomic instabilities remain a possible etiology and source of new mutations. A mechanism that included a high rate of spontaneous mutations predisposing to schizophrenia would be consistent with the low rate of family history of schizophrenia usually found in individuals with the illness, and apparently “sporadic” schizophrenia [26]. The authors have previously pointed out how a high rate of spontaneous mutations could help explain the maintenance of the illness prevalence despite low reproductive fitness [54]. The possibility of spontaneous mutations reemphasizes the idea, also noted previously, that “genetic” does not equate with “inherited.”

Insight #4: New Recommendations for Genetic Counseling in Schizophrenia

The authors have recently reviewed the role of genetic counseling in schizophrenia [25•]. Genetic counseling, the process through which knowledge about the genetics of illnesses is shared, provides information on the inheritance of illnesses and their recurrence risks, addresses the concerns of patients, their families and their health care providers, and supports patients and their families dealing with these illnesses. Empiric risks for schizophrenia are available, but must be used in the context of the individual’s family history, in order to tailor the risk assessment to the individual. For example, detailed family history and medical history are necessary to determine whether there is an isolated case of schizophrenia within a family, a more complex family structure with schizophrenia or other psychiatric disorder(s) in several members, or evidence for 22qDS. Access to genetic

counseling should be available to all individuals with schizophrenia, and is particularly important for family planning, although this service is not routinely offered in most clinical settings today.

An important addition to genetic counseling issues in recent years is the ability to identify individuals with a 22qDS subtype of schizophrenia. If 22qDS or another genetic syndrome were suspected, a referral to a geneticist would be appropriate. Genetic counseling regarding the syndrome, its variable expression, available testing, and future pregnancies is an essential component of the comprehensive medical management of patients with 22qDS.

Transmission of a 22q11.2 deletion follows a Mendelian autosomal dominant pattern. Thus, an individual with 22qDS has a 50% chance of having a child with 22qDS with each pregnancy. As with most Mendelian conditions, however, the severity of the condition or any of its physical or neurobehavioral manifestations cannot be predicted. In 22qDS, as in other forms of schizophrenia, there may be varying levels of learning disabilities. Genetic counseling for these patients may, therefore, require unique approaches to help convey the information [25•].

Parents of an individual with 22qDS are also routinely tested for the deletion, because in about 10% of newly diagnosed cases the deletion has been inherited from one of the parents, who then requires an appropriate medical work-up. As previously noted, most newly diagnosed cases of 22qDS arise from a de novo mutation. The authors have found that counseling regarding the chance nature of this occurrence, and its likely timing during gametogenesis may relieve parents of longstanding guilt feelings in regard to their offspring [25•].

The future

New findings in the genetics of schizophrenia and related disorders may have important clinical implications to patients and their families in the near future. Identifying susceptibility genes will likely have an impact on our understanding of pathophysiology, and may in the future alter what information will be available to patients and families for genetic counseling. Consideration of ethical issues, guided by experience gained in other neuropsychiatric disorders [55], will be essential to determine the most appropriate implementation of any future services involving genetic testing for schizophrenia [25•,56].

Insight #5: A Neurodevelopmental Pathway from Genetic Susceptibility to Schizophrenia

It has long been recognized that genetic factors are involved in a pathway from an initial causal event (susceptibility) to clinical expression of schizophrenia [1•,2•]. The authors have recently proposed a model of etiopathogenesis that brings molecular genetic and other etiologic factors together with the popular neurodevelopmental hypothesis of schizophrenia [1•]. This model emphasizes the dynamic nature of genetic effects and their role in pathogenetic processes that likely include changes in neurodevelopment.

Individual genes are an important component in eventual illness expression, but increased understanding from the human genome project has clarified that other genomic or epigenetic

mechanisms may also be important, and may explain the non-Mendelian segregation patterns observed in schizophrenia [1••]. In addition, there is some evidence for gene-gene interactions, stochastic (chance) factors, and non-genetic factors playing a role in expression, likely as modifying factors [1••,26]. For example, there is preliminary evidence for genetic factors being involved in modifying age at onset of schizophrenia [57], as has been recently found in Alzheimer disease and Parkinson's disease [58]. Also, our group has found that mild childhood head injury (age 10 years or younger) is associated with younger age at onset in familial schizophrenia [59].

Even single gene Mendelian disorders show evidence of complex genetic mechanisms and interacting factors likely to influence expression [60]. Indeed, it is the norm in the genetics of human disorders to have reduced penetrance (a genetic susceptibility that in some individuals is not expressed) and variable expression (a genetic condition that is expressed with variable severity). Schizophrenia will be no exception to this [1••], as illustrated by studies of offspring of discordant monozygotic twins, which show that the unaffected co-twin and the twin with schizophrenia have about the same risk of having an affected offspring [61,62••]. Indeed, as in other complex traits [38,63], the genetic heterogeneity of schizophrenia will likely prove advantageous in developing an understanding of the pathogenesis of the disorder, and in providing multiple targets for new treatment possibilities.

Conclusions

Gene discoveries, aided by the Human Genome Project, are predicted to revolutionize medicine [64], and these genetic advances will encompass psychiatry as well as other disciplines. The advances in the past several years in the genetics of schizophrenia promise that further advances will soon be forthcoming, leading to identification of molecular subtypes of schizophrenia [65] and eventually an initial understanding of the pathogenesis of the disease.

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Table 1

Major clinical features of adults with chromosome 22q11.2 deletion syndrome

Clinical feature	Cohen <i>et al.</i> [11] (n=126)	Murphy <i>et al.</i> [3] (n=48)
	Patients, n (%)	Patients, n (%)
Physical		
Facial anomalies (variable)	120 (99)	—
Palatal anomalies (any)	92 (88)	13 (27)
Overt or submucous cleft palate	43 (41)	13 (27)
Congenital heart defects (<i>eg</i> , tetralogy of Fallot, ventricular septal defect)	36 (30)	19 (40)
Neuropsychiatric		
Learning difficulties (any)	104 (94)	—
Mental retardation (IQ under 70)	—	16 (33)
Borderline intellectual functioning (IQ 71 to 80)	—	19 (40)
Psychiatric disorders (any)	45 (36)	20 (42)
Schizophrenia and other psychoses	—	15 (31)

IQ—intelligence quotient.

Table 2

Significant * genome-wide linkage findings for familial schizophrenia (as of April 1, 2002)

Chromosomal region	Study	Sample size (genotyped)		Pedigrees	Subjects		Ethnicity	Genetic model [†]	Marker	Map position, cM [‡]	Maximum score	
		Affected	Unaffected		Affected	Unaffected					LOD [§]	NPL [¶]
1q21-q22	Brzustowicz <i>et al.</i> [27•]	22	79	209			Northern European	Recessive/narrow het	D1S1679	170.84	6.5	—
2p13-p14	Camp <i>et al.</i> [32•]	7	40	87			Micronesian isolate	Recessive/narrow het	D2S358	85	4.8	6.5
2q37	Paunio <i>et al.</i> [33•]	53	96	293			Finnish isolate	Recessive vs narrow	D2S427	224.7	4.43	—
6q25	Lindholm <i>et al.</i> [34•]	1	39	171			Swedish	Dominant broad	D6S253	173.2	7.7	—
13q12-22	Camp <i>et al.</i> [32•]	7	48	79			Micronesian isolate	Recessive broad het	D13S894	24	3.6	1.1
13q31-q32	Brzustowicz <i>et al.</i> [27•]	22	107	169			Northern European	Recessive broad het	D13S793	76	3.81	—
13q32	Blouin <i>et al.</i> [29]	54	276	87			White/African-American	Recessive/narrow het	D13S174	84.87	3.19	4.18
15q14	Freedman <i>et al.</i> [35] **	77	183	83			White/African-American	Dominant/narrow het	D15S118	42.3	3.97	—

LOD—logarithm of odds; NPL—non-parametric linkage.

* Genome-wide significant linkage ($P < 0.05$ per genome scan) by Lander and Kruglyak [30] guidelines for complex traits and simulation studies [29] in all studies expect one, using either parametric (logarithm of odds scores) or non-parametric linkage methods. Linkage results reaching guidelines for highly significant ($P < 0.001$) genome-wide results are the studies by Brzustowicz *et al.* [27•] and Lindholm *et al.* [34•].

[†] Model giving maximum linkage score—dominant or recessive inheritance and diagnoses include as affected: very narrow=schizophrenia only; narrow=schizophrenia and schizoaffective disorders; broad = schizophrenia and schizoaffective disorders as well as nonaffective psychotic disorders=affective disorders=schizotypal and paranoid personality disorders; het=model under heterogeneity.

[‡] Marshfield genetic map, approximate distances in centimorgans (cM) from pter (short arm terminus).

[§] Logarithm of odds scores refer to multipoint analyses except in one study that used two-point analysis [33•].

[¶] Non-parametric lod scores (model free).

** Reanalysis of two previous genome scans [36,37] with nonsignificant results using non-parametric lod score methods that analyzed the sample by ethnic group (European-American [36] and African-American [37]).