Genetic Insights Into the Neurodevelopmental Hypothesis of Schizophrenia

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Abstract

The original neurodevelopmental hypothesis of schizophrenia presented by D.R. Weinberger in 1987 focused on pathogenesis and did not address etiology. Available evidence indicates that genetic factors are the principal cause of schizophrenia. It is imperative that any pathogenetic model for schizophrenia takes into account what is now known about genetic mechanisms of illness. Recent advances in molecular genetics can provide insights into the neurodevelopmental expression of the illness and what future genetic discoveries are likely to contribute to our understanding of schizophrenia. In this article, we propose a genetic model of etiopathogenesis that is consistent both with a modified neurodevelopmental hypothesis and our current knowledge about schizophrenia and molecular genetics.

Keywords: neurodevelopment, schizophrenia, genetics, pathogenesis.

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The idea that abnormalities of neurodevelopment are likely to be involved in the pathogenesis of schizophrenia stems back to Kraepelin (Lewis 1989). The hypothesis was reintroduced in 1987 (Weinberger 1987), spurred by observations of structural brain changes at the onset of illness using modern imaging techniques (Turner et al. 1986). Weinberger's original hypothesis posited that a "lesion," perhaps involving specific brain regions, occurred at a certain point during development and remained static, with later clinical manifestations being the result of interaction of this "lesion" with normal brain development and likely an external factor to trigger onset (Weinberger 1987). This hypothesis has influenced much of schizophrenia research in the past 14 years and has been a key force in reestablishing schizophrenia as a brain disease.

In addition to brain imaging findings (Lewis and Mezey 1985; Degreef et al. 1992*a*, 1992*b*; Hirayasu et al. 1998; Nopoulos et al. 1998; Zipursky et al. 1998), support for a neurodevelopmental pathogenesis for schizophrenia has come mainly from longstanding clinical observations of premorbid features that are present long before diagnosable psychotic illness (Bleuler 1950; Kraepelin 1971). These features include consistent evidence of subtle early developmental delays (Fish et al. 1992; Jones et al. 1994) and multiple other premorbid clinical signs (Done et al. 1994; Jones et al. 1994; Olin and Mednick 1996; Yung and McGorry 1996; Cannon et al. 1999; Parnas 1999; Erlenmeyer-Kimling et al. 2000). Elevated rates of nonneurological congenital dysmorphic abnormalities in schizophrenia (Green et al. 1989; Lane et al. 1997; Griffiths et al. 1998) have also been presented as support for development abnormalities involved in pathogenesis. On the other hand, the general absence of both gliosis on neuropathology (Arnold 1999; Harrison 1999) and an inexorable dementing process in the clinical course (Harvey et al. 1999; Fucetola et al. 2000) suggest that schizophrenia is not a classic neurodegenerative disorder. However, there is some evidence, primarily from imaging studies, that a limited degree of neurodegeneration may form part of the pathogenesis of schizophrenia (Woods 1998; Lieberman 1999).

With respect to the etiology of neurodevelopmental abnormalities in schizophrenia, although recognizing genetic factors as important, discussions have tended to emphasize environmental factors that would occur early enough in development to affect both the central nervous system (CNS) and other systems to account for associated minor congenital abnormalities (Murray 1994). This emphasis may have been facilitated by the use of terms such as "insult" and "lesion" to describe the initial event (Weinberger 1987; Murray 1994), as well as the generally greater familiarity of psychiatric researchers with

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environmental factors than genetic factors. However, the initial events leading to neurodevelopmental abnormalities are most likely genetic in nature, and gene expression likely plays a primary role in subsequent pathogenic processes that could include both neurodevelopmental and limited neurodegenerative mechanisms. Genetic effects are dynamic, not static (Rutter and Plomin 1997). In this article, we first review support for genetic causation and our understanding of the complex genetics of schizophrenia, outlining how recent molecular genetic discoveries can lead to an understanding of previously puzzling clinical observations and complex pathogenesis. We then present a revised neurodevelopmental genetic model of the pathogenesis of schizophrenia that attempts to account for the complex features observable in schizophrenia (table 1).

Support for Genetic Causation of Schizophrenia

There are three main observations supporting genetic causation as the principal etiologic pathway to schizophrenia (McGuffin et al. 1994):

1. The risk for schizophrenia is far greater for close family members of an individual with schizophrenia than it is for individuals in the general population (Gottesman and Shields 1982; McGue et al. 1983; Kendler et al. 1985; Moldin and Gottesman 1997).
2. The risk for schizophrenia is far greater for monozygotic twins of individuals with schizophrenia than it is for dizygotic twins of individuals with schizophrenia (Gottesman and Shields 1982; Moldin and Gottesman 1997; Franzek and Beckmann 1998; Cardno et al. 1999).
3. The risk for schizophrenia is far greater for biological relatives of individuals with schizophrenia than it is for adoptive relatives (Rosenthal et al. 1971; Gottesman and Shields 1982; Lowing et al. 1983; Moldin and Gottesman 1997).

There are also observations that indicate complexity in the genetics of schizophrenia, however. These include non-Mendelian inheritance patterns at the population level, only one individual affected with schizophrenia in most nuclear families, and monozygotic twin concordance less than 100 percent. In addition, individuals with schizophrenia, even within the same family, have a variable age at onset, course, and severity of illness, and family members have higher than expected rates of schizoaffective disorder, nonaffective psychotic disorders, certain personality disorders (Kendler and Diehl 1993), and affective disorders (Maier et al. 1993).

Consideration of certain traditional genetic models, such as fully penetrant single-gene autosomal recessive conditions that are diagnosable at birth (such as cystic fibrosis) but with limited therapeutic interventions avail-

Table 1. Factors that should be accounted for by an etiopathogenetic theory of schizophrenia

Developmental and Prodromal Features of Schizophrenia
Subtle developmental delays
Congenital non-central nervous system dysmorphic features
Prodromal clinical signs and symptoms
Phenotype of Schizophrenia
Variable age at onset of schizophrenia (childhood - geriatric)
Variable severity of clinical phenotype
Variable course of illness with deterioration of functioning but not inexorable decline to dementia and death
Subtle changes of brain structure and function observable at onset of illness
Absence of reactive gliosis but no consistent neuropathology identifiable with current methods
Possible subtle neurodegenerative processes after onset of illness
Evidence of Genetic Etiology of Schizophrenia
Strong evidence that genetic factors cause the illness and only weak evidence of environmental factors
Familial forms of schizophrenia with significant evidence of several genetic loci
Syndromic form of schizophrenia (22q Deletion Syndrome)

able or autosomal dominant conditions that may have later onset followed by inexorable degeneration (such as Huntington disease), has not been helpful for schizophrenia. These traditional genetic models may encourage the fallacy of genetic determinism—that all gene carriers will develop the (untreatable/unmodifiable) disease (Rutter and Plomin 1997). These models may also make it appear necessary to generate environmental explanations for the non-Mendelian observations in schizophrenia genetics. Although there is little evidence for environmental factors as the primary cause of schizophrenia (McGuffin et al. 1994), environmental factors are likely to be important modifying factors for age at onset and other manifestations over the course of illness. As a result, new genetic models that can provide a molecular understanding for the genetic complexities that are clinically observable in schizophrenia are needed. Fortunately, advances in molecular genetics are providing possible answers. Even "simple," single-gene Mendelian disorders show evidence of complex genetic mechanisms that are likely operating in most genetic disorders (Dipple and McCabe 2000).

Molecular genetic mechanisms now discernible in other disorders, together with emerging evidence in studies of schizophrenia, may therefore aid in providing genetic insights that could be helpful for modifying the neurodevelopmental model of schizophrenia.

Complex Genetic Mechanisms Likely To Be Involved in Schizophrenia

Genetic Heterogeneity. As with most genetic conditions, there are likely to be several genetic forms (genetic heterogeneity) of schizophrenia; this may be part of the mechanism underlying schizophrenia's non-Mendelian presentation at the population level. Although there is usually not a direct relationship, genetic heterogeneity may also account for some of the clinical heterogeneity observed in schizophrenia. Alzheimer's disease (AD) is a disorder familiar to psychiatric researchers that illustrates genetic heterogeneity. For example, if one considers the general population of individuals with AD, this would include rare syndromic AD associated with Down syndrome (trisomy 21, a readily identifiable genetic syndrome), several rare familial forms with identifiable phenotypic characteristics such as early onset, and individuals with susceptibility loci that increase their risk for developing late-onset AD. Although several more genes for both early- and late-onset forms of AD remain to be localized and identified, the consistent neuropathology and existence of syndromic and familial forms of the illness have greatly assisted in the identification of four AD-related genes (St. George-Hyslop 2000). These genes are beta amyloid precursor protein gene (ßAPP) on chromosome 21, presenilin 1 gene (PS1) on chromosome 14, presenilin 2 gene (PS2) on chromosome 1, and apolipoprotein E gene (APOE) on chromosome 19. Mutations in PS1, PS2, and ßAPP account for approximately 50 percent of familial AD and less than 3 percent of AD in the general population (Martin 1999). In contrast, APOE acts as a susceptibility gene: one of the three common coding sequence polymorphisms (variations)—the ϵ4 allele—increases risk for late-onset forms of AD (St. George-Hyslop 2000). However, the APOE ϵ4 allele is neither essential to any form of AD nor specific for AD, and may be more generally involved in brain response to injury (St. George-Hyslop 2000).

There is emerging evidence of genetic heterogeneity in schizophrenia. Two studies of schizophrenia that involved scanning the entire human genome for genetic linkage have found significant (Lander and Kruglyak 1995) evidence for schizophrenia susceptibility loci on chromosomes 1q (Brzustowicz et al. 2000) and 13q (Blouin et al. 1998; Brzustowicz et al. 1999). These loci are involved in familial schizophrenia (i.e., schizophrenia in families with several closely related affected members). Both these loci linked to schizophrenia appear to be transmitted in an autosomal recessive manner. Significant evidence for the action of chromosome 1q and chromosome 13q loci in the same set of families (Brzustowicz et al. 2000) supports the possibility of a multiple-gene model for schizophrenia that may include epistasis (gene-gene interaction) (Risch 1990). Further evidence for genetic heterogeneity in schizophrenia comes from the recent description of a syndromic form of schizophrenia, 22q Deletion Syndrome, associated with a deletion on chromosome 22 involving multiple genes (Bassett and Chow 1999; Bassett et al. 2000).

Thus, similar to AD, schizophrenia is likely to involve at least one syndromic form, at least two genes involved in familial forms, and presumably many more genetic forms that remain to be determined. Even with substantial genetic heterogeneity, recent genetic linkage results for schizophrenia (Brzustowicz et al. 2000) and other genetic disorders suggest that gene localization and identification in schizophrenia should be possible. Genetic heterogeneity may even be advantageous in terms of explaining complex pathogenesis. For instance, deafness has long been known to have considerable genetic heterogeneity, but research involving families multiply affected with either syndromic or nonsyndromic forms of deafness has led to the identification of more than 35 loci (Kimberling 1999) and 18 genes related to hearing impairment (Bork et al. 2001). These molecular genetic discoveries have often involved genes that were not a priori candidates, and have led to new understandings of the

etiology, nosology, and pathogenesis of human deafness (Kimberling 1999). Even in AD, where there was consistent neuropathology to guide the research, the understanding of the molecular etiopathogenetic mechanism implicating amyloid protein metabolism has been significantly facilitated by each of the molecular genetic discoveries (St. George-Hyslop 2000). Gene finding is more challenging in complex disorders such as schizophrenia, but major advances in understanding the mechanism of illness at the molecular level will likely depend on identifying disease-related genes (Hyman 2000).

De Novo Mutations. Related to the issue of genetic heterogeneity is the possibility of de novo (sporadic), in addition to transmitted (familial), mutations in schizophrenia. New mutations could provide another possible explanation for non-Mendelian inheritance patterns in schizophrenia and the common observation of only one affected individual in a nuclear family (McGuffin et al. 1994). One known example is the chromosomal deletion associated with the 22q Deletion Syndrome subtype of schizophrenia, which often occurs as a de novo mutation (Lindsay et al. 1995; Leana-Cox et al. 1996; Bassett et al. 1998). Nonsyndromic forms of schizophrenia may also, in some cases, be secondary to de novo mutations in susceptibility genes and may therefore appear "sporadic" in some cases (McGuffin et al. 1994). The observation of later paternal age in schizophrenia (Hare and Moran 1979) provides indirect evidence for possible de novo mutations because the likelihood of mutations in sperm increases with age (Penrose 1955; Evans 1988).

Modifying Factors Involved in Complex Genetic Mechanisms. As for most heritable disorders (Vogel and Motulsky 1997; Dipple and McCabe 2000), interacting genetic and nongenetic factors are likely to influence gene expression in schizophrenia. Collectively these factors probably account for the small proportion of "nongenetic," or nonheritable, variance in heritability calculations (McGuffin et al. 1994). Interacting genetic factors involving other genes could include genetic background, transmitted polymorphisms or mutations, and de novo mutations. Other interacting factors include random or chance (stochastic) effects that may be particularly important during development (Kurnit et al. 1987), epigenetic mechanisms such as X-chromosome inactivation and genomic imprinting (the differential expression of genes dependent on whether the genetic material was inherited from the mother or the father), and environmental factors (McGuffin et al. 1994). Normal neuronal plasticity is thought to comprise certain of these components (genetic background, stochastic effects, and environment) (Kandel and Squire 2000), which are likely to be modifiers of expressed genes during development and throughout life (Vogel and Motulsky 1997). These modifiers of gene expression may present as complex genetic mechanisms observable clinically as incomplete penetrance, variable expressivity, or clinical heterogeneity.

Incomplete penetrance. Studies of offspring of discordant monozygotic twins have found that offspring of both affected and unaffected monozygotic co-twins show similar rates of schizophrenia (Gottesman and Bertelsen 1989; Kringlen and Cramer 1989). These studies indicate that monozygotic twin discordance is the result of nonexpression of genetic susceptibility (incomplete penetrance) (McGuffin et al. 1994), not purely environmentally caused phenocopies of schizophrenia as is commonly believed. Discordance in monozygotic twins is a commonly observed phenomenon in genetics. Monozygotic twins with Down syndrome, for example, are often discordant at birth for individual features of Down syndrome, such as congenital heart defects (Kurnit et al. 1987). How does this occur when both twins have "identical" genotypes and have shared the same intrauterine environment? There are several plausible explanations (Vogel and Motulsky 1997). First, there are stochastic (random or chance) factors at work from the time of conception; for example, determining which particular cell in the developing embryo lies next to another particular cell at a certain point in time, which changes the microenvironment (Kurnit et al. 1987). Clinical variability among individuals with the same genotype may thus be determined by chance alone (Kurnit et al. 1987). Second, there may be minor, but potentially significant differences in the intrauterine environment, such as inequalities in fetal blood supply that may have an effect on growth and development. As most recently highlighted by research on the human immunodeficiency virus, identical twins may be discordant for developing infection despite exposure to the same viral agent in utero. Third, these stochastic or intrauterine environmental differences can trigger epigenetic mechanisms such as imprinting or X-chromosome inactivation, which may also differentially affect individuals with the same inherited genotype, even in monozygotic twins. These postzygotic differences have been observed in discordant monozygotic twins with Fragile X mental retardation (Kruyer et al. 1994) and Rett's syndrome (Van den Veyver and Zoghbi 2000). Fourth, after conception de novo mutations may occur at any time causing both genotypic and phenotypic differences between individuals who originally inherited the same initial genotype. Such a "second-hit" mutation could produce either a protective or a deleterious effect on the individual who carries a genetic susceptibility to schizophrenia. As an illustration of such a protective effect associated with the observation of incomplete penetrance, a recent molecular genetic study of deafness reported that an autosomal dominant modifier locus

appears to suppress the deleterious effects of an autosomal recessive locus for deafness on another chromosome (Riazuddin et al. 2000). Thus, both nongenetic (e.g., chance or epigenetic) and genetic (e.g., de novo mutations) mechanisms may explain the incomplete penetrance observed in discordant monozygotic twins in schizophrenia (McGuffin et al. 1994).

Variable expressivity. Variable expressivity (variable extent and intensity of phenotypic signs among individuals with the same genotype), a common feature of most genetic conditions (Vogel and Motulsky 1997), is also likely in schizophrenia. Schizophrenia spectrum disorders such as schizoaffective disorder, nonaffective psychoses, and schizotypal and paranoid personality disorders likely represent variable expressions of the same disorder as schizophrenia (Kendler and Diehl 1993). Family studies (Maier et al. 1993) and twin studies (Farmer et al. 1987) have indicated that, although schizophrenia and mood disorders may be largely separate entities, in some families these two conditions may be genetically related. Interestingly, one of the significant linkage findings in schizophrenia is to a region on chromosome 13q (Blouin et al. 1998; Brzustowicz et al. 1999) that has recently been reported to show significant linkage to bipolar disorder (Detera-Wadleigh et al. 1999). Also, a broader definition of schizophrenia, including nonaffective psychotic disorders and schizotypal and paranoid personality disorders, was involved in the chromosome 13q32 linkage finding (Blouin et al. 1998; Brzustowicz et al. 1999). This variability is not necessarily the result of multiple different genes. As exemplified by neurofibromatosis, even single-gene disorders demonstrate variable expressivity, the mechanism of which is unknown but likely includes genetic background, and epigenetic and nongenetic factors (Vogel and Motulsky 1997).

Clinical heterogeneity. Clinical heterogeneity (variable age at onset and severity of the same illness) is also a feature of most genetic disorders, and although genetic heterogeneity may be involved in some conditions, even single-gene disorders demonstrate clinical heterogeneity that are presumably the result of modifiers of gene expression. In AD as a whole, for example, age at onset varies from early to late. Early onset is associated with several single-gene familial forms, as well as AD associated with Down syndrome (i.e., genetic heterogeneity is involved). However, other mechanisms modifying gene expression in AD must also exist because age at onset even in single-gene familial early onset forms varies over a 25- to 45-year time span (St. George-Hyslop 2000). In late-onset forms of AD the $\epsilon 4$ allele of the APOE gene may be associated with lowering age at onset in a dose-dependent relationship (St. George-Hyslop 2000), indicating a molecular genetic mechanism for this component of clinical heterogeneity in some forms of AD. The APOE $\epsilon 4$ allele may also be associated with increased prevalence of psychotic features in AD (Weiner et al. 1999). In addition, there is evidence of interaction of an APOE genotype with other modifying factors. Patients with APOE $\epsilon 4$ alleles and a history of head injury have a 10-fold increase in risk for AD compared with a 2-fold increased risk with the APOE $\epsilon 4$ allele alone (Tang et al. 1996). Susceptibility loci for the same condition may have variable susceptibility to specific modifying factors, including possible environmental factors such as head injury (St. George-Hyslop 2000). The search for other molecular modifiers of gene expression continues in AD. However it is interesting to note that, unlike for schizophrenia, there has not been a focus on identifying environmental triggers for onset of AD, even though onset does not occur for several decades after birth.

22q Deletion Syndrome: A Syndromic, Genetic, Neurodevelopmental Subtype of Schizophrenia

A syndromic form of schizophrenia, 22q Deletion Syndrome (22qDS), has recently been identified with multiple features that are consistent with a neurodevelopmental model of pathogenesis for schizophrenia and that illustrates some of the complex genetic mechanisms involved in schizophrenia. This syndrome involves a physical genetic abnormality: a small deletion on chromosome 22q11.2. This deletion is detectable with a specialized type of chromosomal analysis—fluorescence in-situ hybridization—that uses a molecular probe from the commonly deleted region (Driscoll et al. 1993; Morrow et al. 1995). Approximately 25 percent of individuals with this syndrome develop schizophrenia (Murphy et al. 1999) and up to 2 percent of individuals with schizophrenia may have 22qDS (Karayiorgou et al. 1995), indicating that 22qDS is a syndromic genetic subtype of schizophrenia (Propping and Nothen 1995; Bassett and Chow 1999). The clinical, structural brain findings and cognitive profile of 22qDS-schizophrenia are all similar to other forms of schizophrenia (Bassett et al. 1998; Chow et al. 1999*a*, 1999*b*). However, 22qDS has multiple other associated features as well.

Neurodevelopmental Features. Neurodevelopmental features of 22qDS include psychiatric, congenital physical, cognitive, and brain structural aspects. The syndrome in general is associated with learning disabilities ranging from borderline to severe (Swillen et al. 2000). Average intellectual levels in 22qDS schizophrenia appear to be in the borderline mental retardation range (Bassett et al. 1998; Murphy et al. 1999). Minor and major congenital defects in other, non-CNS, organs are commonly associ-

ated (Cohen et al. 1999), including palatal anomalies and dysmorphic features, which are similar to those seen in general population samples of schizophrenia (Bassett et al. 1998). Brain structural abnormalities lend further support to involvement of a neurodevelopmental process. There are high rates of developmental anomalies, such as cavum septum pellucidum and cavum vergae (Chow et al. 1999*b*), in addition to the typical ventricular and gray matter findings of schizophrenia. Age at onset of schizophrenia varies (Bassett et al. 1998; Murphy et al. 1999) and includes childhood onset (Nicolson et al. 1999).

Complex Genetic Features. The available data on the syndromic 22qDS subtype of schizophrenia therefore indicate that, although more genetically homogeneous than general population samples of schizophrenia, 22qDS schizophrenia also displays considerable variable expressivity. This is consistent with the high degree of variability in the physical phenotype observed in general in 22qDS, even within families (Demczuk and Aurias 1995) and between monozygotic twins (Fryer 1996; Hatchwell 1996), with the same extent of deletion. Indeed, the syndrome is under-recognized, especially in adult populations, because features may be so subtle (Bassett and Chow 1999; Cohen et al. 1999). With respect to the behavioral phenotype expressed as a psychiatric illness, although schizophrenia is most common, other psychiatric disorders, including mood disorders, may be expressed (Pulver et al. 1994; Papolos et al. 1996; Cohen et al. 1999; Murphy et al. 1999), and many adults with 22qDS have no diagnosable psychiatric phenotype.

Molecular Genetic Mechanisms. The chromosomal deletion in 22qDS usually occurs as a de novo mutational event (Lindsay et al. 1995; Leana-Cox et al. 1996), likely during gametogenesis. The molecular structure of the 22q11.2 region, which includes several long tandem repeat sequences, is thought to make the region prone to rearrangements and deletions (Morrow et al. 1995; Shaikh et al. 2000). The deletion is transmissible in an autosomal dominant manner, with offspring having a 50 percent chance of inheriting the deletion. However, because de novo mutations are common and, as in schizophrenia (Bassett et al. 1996), reproductive fitness is reduced, 22qDS usually presents as a "sporadic" condition. Transmission of 22qDS from an affected parent is found in less than 10 percent of cases identified (Lindsay et al. 1995). Syndromic schizophrenia associated with 22qDS thus provides an example of nontransmitted schizophrenia resulting from a spontaneous mutation.

Interestingly, there is no apparent correlation between the severity or pattern of the expressed phenotype and the extent of the deletion for 22qDS, which is most commonly 3 megabases in length (Morrow et al. 1995; Carlson et al. 1997*b*). This has led to speculation that individual genes in the deletion region involved in early embryonic development are key to expression of the phenotype and that other factors, such as interacting genes and environmental and stochastic factors, likely modify this gene expression (Demczuk and Aurias 1995).

Molecular Pathogenesis. Abnormal neural crest cell migration has been proposed to be involved in the pathogenesis of 22qDS (Scambler et al. 1992; Demczuk and Aurias 1995; Carlson et al. 1997*a*). This could involve disruption of retinoic acid signaling, which also plays an important role in forebrain, limb, face, and cardiac development (LaMantia 1999), and the development and functioning of the dopamine system (Goodman 1998). Although many genes, including genes involved in neurodevelopment, have been mapped to the commonly deleted region on chromosome 22q11.2 (Budarf and Emanuel 1997), the contribution of these genes to the behavioral phenotype and other developmental anomalies of 22qDS is still not well understood. However, speculating about which genes, developmental or otherwise, may be involved in this or any other form of schizophrenia is premature given the lack of consistent neuropathology in the disorder and our limited understanding of the molecular biology of brain development and plasticity (Kandel and Squire 2000).

A Molecular Genetic Model for Complex Neurodevelopmental Pathogenesis: Rett Syndrome

Other conditions that are further along in understanding of individual gene involvement may help illustrate how a molecular genetic approach can assist in understanding both neurodevelopmental pathogenesis and complex genetic features. Rett syndrome, a severe psychiatric disorder with childhood onset, has previously been presented as an example of a progressive neurodevelopmental disorder that may be instructive for schizophrenia (Woods 1998). The value of this disorder as a model has increased since the discovery of a specific underlying genetic defect that can cause Rett syndrome: mutations in the methyl-CpG-binding protein 2 gene (MECP2) on the X chromosome (Amir and Zoghbi 2000). There is an emerging understanding of etiopathogenesis of this disorder that, although clearly different in many ways, displays several characteristics similar to those in schizophrenia with respect to neurodevelopmental origins and complex genetic mechanisms.

Progressive Neurodevelopmental Phenotype. Rett syndrome (MIM 312750) (McKusick 1998), known as "Rett's disorder" in *DSM–IV* (American Psychiatric Association 1994), is a severe pervasive developmental disorder. Individuals with Rett syndrome appear to develop normally until 6 to 18 months of age, then neurologic function deteriorates, with development of severe mental retardation and stereotypic hand movements and loss of acquired purposeful hand skills (Amir and Zoghbi 2000; Van den Veyver and Zoghbi 2000), reaching a plateau at about age 4 years (Amir and Zoghbi 2000). The principal clinical features in Rett syndrome involve the CNS; however, mild congenital dysmorphic features may also be present (Van den Veyver and Zoghbi 2000). Thus, like schizophrenia, Rett syndrome exhibits an apparently normal initial phenotype when a clinical diagnosis could not be made (although subtle early signs may be present), followed by functional decline.

Also similar to schizophrenia is that there are no consistent laboratory findings in Rett syndrome (Amir and Zoghbi 2000), and brain imaging and pathological studies have indicated a neurodevelopmental rather than a neurodegenerative process, with increased ventricular size and no evidence of gliosis (Woods 1998). However, individuals with Rett syndrome may later develop spastic paraparesis and other neurologic symptoms (Amir and Zoghbi 2000), indicating some subsequent evolution of pathology. This possible progression of clinical features after the illness is diagnosable may be similar to the clinical deterioration in functioning and subtle signs of neurodegeneration that are sometimes seen in schizophrenia (Woods 1998).

Complex Genetic Features. Rett syndrome was diagnosed initially only in females and was believed to be uniformly lethal in males. However, identification of mutations in the MECP2 gene has revealed a broad range of phenotypes and some hints as to the complex genetic mechanisms involved in this disorder. Rare familial forms of Rett syndrome have allowed researchers to identify males with Rett syndrome and severe mental retardation (Amir and Zoghbi 2000; Meloni et al. 2000), and female carriers of familial Rett syndrome who have only subtle learning difficulties (Amir and Zoghbi 2000). This vast range of variable expression was unexpected given the strict diagnostic criteria for the condition in the identified patients (probands) with Rett syndrome. Some gene carriers, including an unaffected member of a pair of monozygotic twins discordant for the Rett phenotype, have no apparent clinical features (Van den Veyver and Zoghbi 2000), thus providing evidence of incomplete penetrance. The molecular mechanisms underlying these phenotypic observations are not fully understood, although epigenetic and other interacting mechanisms appear likely (Amir and Zoghbi 2000; Van den Veyver and Zoghbi 2000). Most cases of Rett syndrome, however, are sporadic because the mutations in the MECP2 gene usually arise de novo, likely because of several "hot spots" for mutation in the MECP2 gene (Amir and Zoghbi 2000). Unlike schizophrenia, most individuals with Rett syndrome appear to have mutations in a single major gene. Yet genetic heterogeneity appears likely because mutations in the MECP2 gene account for only 40 percent of familial cases and 80 percent of sporadic cases (Amir and Zoghbi 2000).

Molecular Pathogenesis. Discovery of a causal gene for Rett's syndrome has led to some initial insights into pathogenesis of this neurodevelopmental disorder. Although the phenotype mainly involves neurobehavioral features that become observable during infancy, the MECP2 gene is expressed ubiquitously in most tissues during both early development and throughout postnatal life (Amir and Zoghbi 2000). The MECP2 gene product (MeCP2) binds to methylated DNA in the nucleus and acts with a co-repressor complex to repress transcription of target genes, a function that may be particularly important during development (Van den Veyver and Zoghbi 2000). Although the gene targets of MeCP2 are unknown, some are likely to be critical for neurodevelopment (Van den Veyver and Zoghbi 2000), which may provide a molecular explanation for the predominantly, but not exclusively, neurobehavioral phenotype. Because MeCP2 is a member of a family of transcription repressors with similar functions, other genes that are coding for proteins in this family may be able to compensate for MeCP2 dysfunction in tissues not involved in Rett syndrome pathology or at certain times (Amir and Zoghbi 2000). Identification of molecular targets, possible compensatory genes, and other mechanisms that modify MECP2 gene expression will further elucidate the pathogenesis of Rett syndrome and the modulation of its ultimate clinical expression. Although genes for schizophrenia will likely have different functions than MECP2 given the different phenotype involved, MECP2 and its yet to be identified interacting genes present a model that may be helpful when considering candidate genes for schizophrenia, together with complex interactive modifiers of gene expression.

Genetic Insights Into the Pathogenesis of Schizophrenia

How can our current knowledge of schizophrenia genetics and illustrations of molecular genetic mechanisms from other disorders help to modify the neurodevelopmental hypothesis of schizophrenia? Gene expression is a dynamic process with multiple factors that can modify expression. The genetic mutations that lead to schizophre-

nia, as for Rett syndrome, will likely have active expression during neurodevelopment and through much of the lifespan. Gene expression, coupled with interacting factors, must reach a critical point when onset of diagnosable illness becomes observable, but this point may vary from person to person and possibly from gene to gene. Also, as in Rett syndrome, one or more of the gene mutations leading to schizophrenia likely causes subtle changes in development of both the CNS and other systems. Such a process could therefore lead to observable premorbid clinical symptoms (Done et al. 1994; Jones et al. 1994; Olin and Mednick 1996; Yung and McGorry 1996; Cannon et al. 1999; Parnas 1999; Erlenmeyer-Kimling et al. 2000), structural brain abnormalities (Lewis and Mezey 1985; Degreef et al. 1992*a*, 1992*b*; Hirayasu et al. 1998; Nopoulos et al. 1998; Zipursky et al. 1998), and congenital physical features (Green et al. 1989; Lane et al. 1997) in schizophrenia.

In addition to this early expression, many predominantly "neurodevelopmental" genetic conditions demonstrate a degree of later "degenerative" brain activity. Rett syndrome is an example of this, as previously noted (Woods 1998). Other examples involve some progression of cognitive dysfunction long after the principal neurodevelopmental phenotype has been expressed. In Fragile X mental retardation, for example, individuals with varying trinucleotide repeat mutations and varying levels of initial learning disability have been observed to have a degree of later cognitive decline (Bardoni et al. 2000) related to an unknown molecular mechanism. In Williams syndrome, a microdeletion syndrome involving a small region on chromosome 7q that has a significant neurobehavioral phenotype, distinctive cognitive abnormalities evolve from infancy to adulthood (Donnai and Karmiloff-Smith 2000). This has led to a hypothesis that long-term developmental processes themselves play a crucial role in the evolving phenotype of Williams syndrome, with initial genetic changes subtly altering the course of brain developmental pathways during both embryogenesis and postnatal growth (Karmiloff-Smith 1998). Interaction with ongoing normal processes involving neuronal plasticity that do not strictly relate to development (Kandel and Squire 2000) is also likely, as is a degree of later neurodegeneration (Woods 1998). These mechanisms would be consistent with Woods' (Woods 1998) proposal that schizophrenia is a progressive neurodevelopmental disorder and would represent an evolution of Weinberger's original neurodevelopmental hypothesis of schizophrenia (Weinberger 1987).

The model of etiopathogenesis we propose (figure 1) encompasses the ideas presented in this article. The initial event is most likely to be an inherited or de novo mutation in one or more genes involved in the development of the CNS. Later clinical manifestations would result from the expression of these genetic changes and their dynamic interplay with genetic and nongenetic factors commonly involved in modifying gene expression (Vogel and Motulsky 1997). This process could occur from conception and on through the lifespan and include interaction with molecular mechanisms of normal brain plasticity and possibly neurodegeneration that does not involve gliosis (Margolis et al. 1994; Woods 1998). Modification by multiple other factors, including antipsychotic medications, would also be possible. No specific external factor would be necessary to trigger onset. Thus, a dynamic cascade stemming from initial mutations in one or more genes involved in the development and likely ongoing function of the complex neuronal network of the brain could lead to the structural and functional abnormalities associated with schizophrenia.

The Future

Identifying specific genetic, epigenetic, and nongenetic factors involved in schizophrenia should be possible after major genes related to schizophrenia are found. In other disorders, moving from genes to biological mechanisms has proved to be an essential method for understanding the pathophysiology of illness (Rutter and Plomin 1997; Vogel and Motulsky 1997; Dipple and McCabe 2000). For example, an iterative approach that begins with identifying major genes and leads to insights into pathophysiology may be necessary for determining relationships with polymorphisms in genes of small effect (St. George-Hyslop 2000). Gene-finding studies are at an early stage in schizophrenia. Although no schizophrenia susceptibility gene has yet been identified, the magnitude of recent logarithm of odds (lod) scores suggests that linkage studies of multiply affected families with adequate power to overcome the complex genetic features of schizophrenia, particularly genetic heterogeneity, are likely to lead to the identification of susceptibility genes (Brzustowicz et al. 2000). The identification of even one genetic mutation will provide much-needed information to help elucidate a molecular pathway to schizophrenia that is likely to include abnormalities of neurodevelopment (Woods 1998).

References

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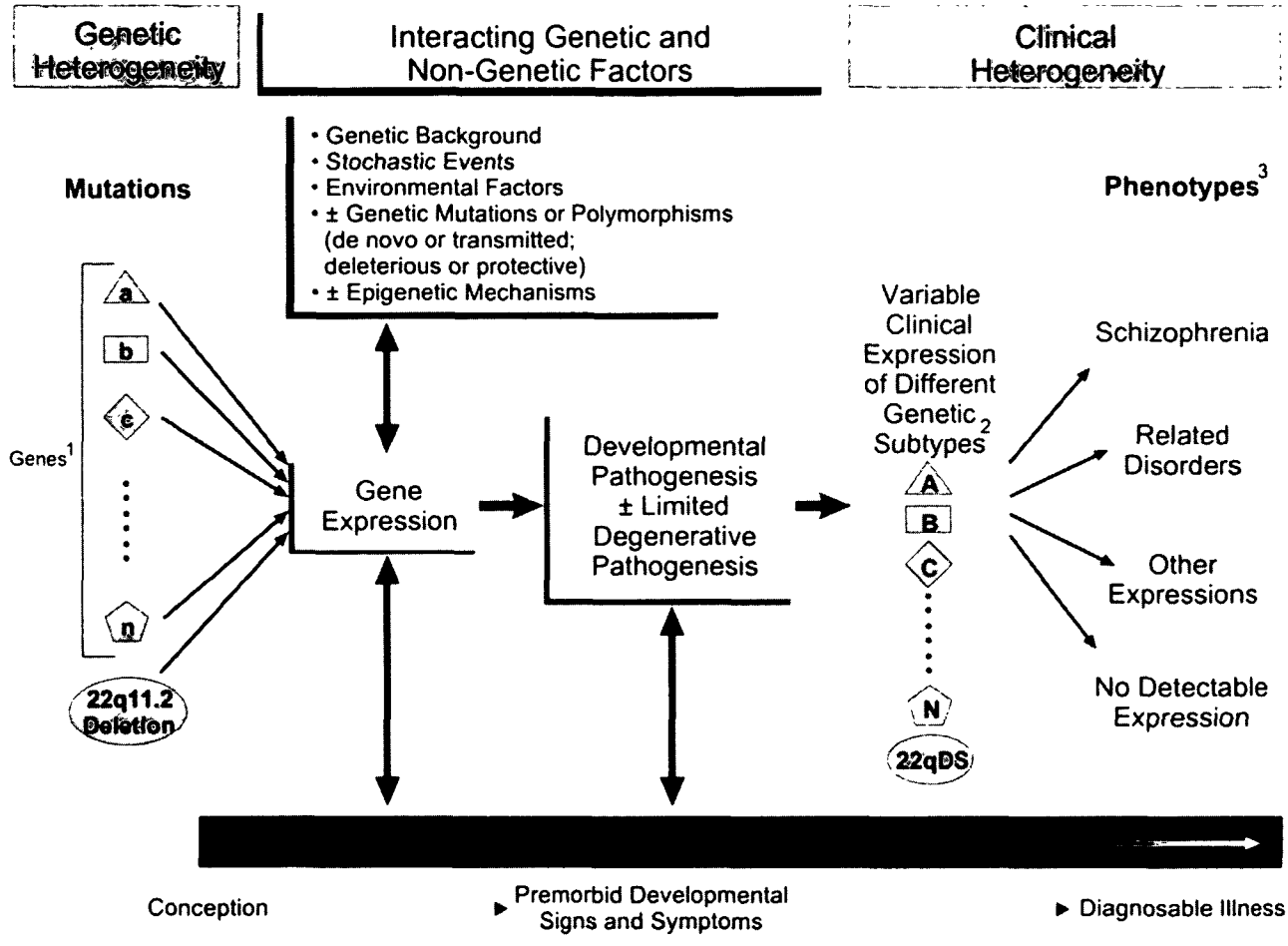
Figure 1. Genetic neurodevelopmental model of the etiopathogenesis of schizophrenia



[1]A transmitted or de novo mutation in one or more major genes, acting individually or interactively, is the initial causal event. In the general population there may be many different major genes involved in causing schizophrenia (genetic heterogeneity), indicated by letters a, b, c...n. In addition, a syndromic subtype of schizophrenia may be caused by a mutational event involving a deletion on chromosome 22q11.2.

[2]After a dynamic process involving gene expression and interaction with normal brain development and neuronal plasticity mechanisms as well as other genetic and nongenetic factors, there is expression of a variety of genetic subtypes of schizophrenia, indicated by letters A, B, C...N, corresponding to the causal genes. These genetic subtypes of schizophrenia are likely to be clinically indistinguishable from one another.

[3]The phenotypic expression of these genetic subtypes could include clinically diagnosable schizophrenia, other psychiatric disorders (variable expression), subclinical expressions such as subtle structural brain or cognitive abnormalities (endophenotypes), or no detectable expression (incomplete penetrance).

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