Commentary

Retroviruses and the pathogenesis of schizophrenia

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Schizophrenia is a complex disorder characterized by disturbances in multiple domains of brain functioning, including cognitive, emotional, and perceptual processes (1). Although the diagnostic criteria for schizophrenia have high diagnostic reliability, affected individuals may differ substantially in the specific profile of signs and symptoms that they manifest as well as in the severity and course of their illness. This heterogeneity, in concert with interindividual variability in the presence of various biological markers, has contributed to the view that what we recognize clinically as schizophrenia is likely to encompass a set of disorders that differ with respect to their underlying causes and mechanisms of disease. However, the conclusive identification of specific etiological factors or pathogenetic processes in schizophrenia has remained elusive. In this issue of PNAS, Karlsson *et al.* (2) provide intriguing data suggestive of a possible role for retroviruses in the etiology and/or pathogenesis of schizophrenia in some individuals.

The contribution of genetic factors to the risk of developing schizophrenia has been demonstrated in family, twin, and adoption studies. In contrast to the 1% lifetime incidence of schizophrenia in the general population, the incidence of schizophrenia in the relatives of affected individuals is ≈2% in third-degree relatives, 2–6% in second-degree relatives, and 6–17% in first-degree relatives. When one member of a twin pair has the illness, the morbid risk of schizophrenia in the other twin is ≈17% for fraternal twins and approaches 50% for identical twins (3). Furthermore, in adoption studies, the risk of schizophrenia is related to the presence of the illness in the biological but not in the adoptive parents (4). Although regions on a number of chromosomes have been implicated as sites of potential susceptibility genes (5), the specific genes (or combination of genes) that confer risk for schizophrenia have not yet been identified.

A number of environmental factors, usually occurring early in life, also seem to increase the risk for schizophrenia. For example, severe maternal malnutrition during the first trimester or maternal influenza during the second trimester of pregnancy seem to be associated with a doubling of the relative risk of schizophrenia, and perinatal brain damage or maternal preeclampsia may increase the risk by 7- to 9-fold (6). However, because most individuals with a history of these problems do not develop schizophrenia, other predisposing factors must also be present. In addition, because the clinical features of schizophrenia typically do not become manifest until the late second and third decades of life, the impact of developmental processes also needs to be considered.

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Thus, the current data suggest that schizophrenia may represent the shared (but not fully uniform) phenotype of a group of disorders whose etiopathogenesis involves the interplay of complex polygenic influences and environmental risk factors operating on brain maturational processes. Clearly, the complexity of these potential gene–environment–development interactions presents a tremendous challenge for the study of the disease mechanisms operative in schizophrenia. In this context, the report by Karlsson *et al.* (2) is of particular interest, because it suggests that retroviruses, which as discussed below may represent either an exogenous infectious or endogenous genetic factor, may contribute to the appearance of schizophrenia in at least some individuals.

Retroviruses infect a wide range of vertebrate species. Although some infectiously transmitted retroviruses do not seem to be disease pathogens, others, such as HIV, may initiate a disease process that is lethal to the host. During replication, the virally encoded enzyme, RNA-dependent DNA polymerase (reverse transcriptase), copies the retroviral RNA genome into DNA, forming a haploid DNA provirus in the host cell. This provirus can then be inserted into the host's chromosomal DNA. If inserted into the coding region of a gene, the proviral DNA may disrupt the function of the normal protein product of that gene; if inserted adjacent to a gene, the promoter sequences in the retrovirus long terminal repeat can actually lead to an upregulation of the normal gene's expression (7). When proviruses are integrated into the germ cell line of a host, they are transmitted subsequently to the next generation. Such integration and transmission may explain the number of sequences in the human genome that are homologous to known retroviruses. The vast majority of these sequences, termed human endogenous retroviral elements (HERVs), seem to have sustained mutations or deletions that disrupt one or more of their major open reading frames, rendering them translationally defective (7). The extent to which other HERVs are capable of encoding complete viral proteins, of producing viral particles, and/or of contributing to disease pathogenesis remains controversial.

RNA transcripts for multiple HERVs are expressed in normal tissues (8), but the presence of specific HERVs has been reported to be associated with disease states such as multiple sclerosis (9), rheumatoid arthritis (8), and diabetes mellitus (10). However, the reported isolation of a previously unknown HERV from a patient with diabetes and the identification of one of its proteins as a putative superantigen (10) have not been confirmed in subsequent studies (11–13). In addition, sequences of endogenous retroviruses nearly identical to multiple sclerosis-associated retrovirus seem to be expressed in control human tissue (14).

In the case of schizophrenia, retroviruses have attracted interest as possible etiological agents for some time (15), because they could explain some of the enigmatic aspects of the illness. For example, the differential activation and reintegration of endogenous retroviruses during early development may lead to

See companion article on page 4634.

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altered brain function later in life (16), providing a potential link between identified *in utero* and perinatal risk factors and the onset of clinical schizophrenia during the late second and third decades of life. In addition, an endogenous retroviral etiology could provide explanations for the continued prevalence of schizophrenia despite the reduced fecundity associated with the illness and for the relatively uniform incidence of schizophrenia throughout the world (17).

However, evidence of an association between retroviruses and schizophrenia was lacking before the report of Karlsson *et al.* (2), who identified nucleotide sequences homologous to retroviral *pol* (polymerase) genes in the cerebrospinal fluid (CSF) of 28.6% of subjects with schizophrenia of recent onset and in 5% of subjects with chronic schizophrenia. In contrast, such retroviral sequences were not found in any individuals with noninflammatory neurological illnesses or in normal control subjects. The identified sequences are related to those of the HERV-W family of endogenous retroviruses and to the members of the murine leukemia virus retrovirus genus. In addition, RNA transcripts homologous to members of the HERV-W family were found more frequently in postmortem samples of the frontal cortex from subjects with schizophrenia relative to those from control subjects. The authors conclude that the onset of schizophrenia in some individuals may be related to the transcriptional activation of certain retroviral elements in the brain. Whether these transcripts derive from infectious exogenous retroviruses with sequence homology to HERVs, as opposed to the expression of HERVs, cannot be determined from the available data. However, the apparent absence of replication competence as indicated by the presence of stop codons in the sequences isolated from some subjects suggests that exogenous infection may be unlikely.

These interesting findings may inform our understanding of the etiopathogenesis of schizophrenia and provide insight into novel modes of treatment of the illness, in several respects. Although the premorbid features of schizophrenia (e.g., subtle motor abnormalities during infancy) and the prodromal symptoms and behaviors (e.g., social withdrawal and declining academic performance) that herald the approaching onset of the illness are not uncommon, most individuals seem to function normally until they enter the greatest period of risk in late adolescence and early adulthood (1). However, after the onset of the full syndrome of symptoms, substantial functional deterioration typically occurs, especially during the first 5–10 years. Thus, the greater frequency with which HERV sequences were found in the CSF of subjects with recent onset compared with chronic schizophrenia raises the possibility that the activation of retroviral transcripts may contribute to the onset and initial progression of the illness. However, as noted by the authors, the potential confounding influences of differences in geographic source, demographic variables, and handling of the CSF specimens across the two groups of subjects with schizophrenia must be kept in mind. Clearly, longitudinal studies of the same subject cohort, including individuals thought to be at high risk for the illness, will be critical to determine whether the timing of the appearance of HERV sequences in CSF precedes the onset of clinical symptoms and whether their presence changes across the course of the illness. Certainly, one exciting possibility suggested by the findings of Karlsson *et al.* (2) is that early intervention targeted at repressing the expression of these transcripts might have a positive influence on illness course and outcome.

In the absence of such longitudinal data, it is not possible to determine whether the finding of HERV sequences in only a minority of the subjects with schizophrenia represents false negatives caused by the timing of sampling in some subjects. However, given the number of other risk factors that have been associated with schizophrenia, it seems more likely that the presence of these transcripts in a subset of subjects reflects heterogeneity in the pathogenetic processes that are operative across subjects with schizophrenia. Additional studies may help illuminate whether detectable HERV sequences are predictive of specific clinical features, such as age of onset and severity of illness, or biological indices, such as the presence and magnitude of structural brain abnormalities.

Although the observations of the study of Karlsson *et al.* (2) are interesting, their potential significance for our understanding of the etiopathogenesis of schizophrenia rests on the replication of these findings in other cohorts of subjects. Independent replication is an axiom in all areas of medicine, but it is particularly important in studies of schizophrenia where the history of the field includes many examples of exciting findings that subsequently either failed to be confirmed in other cohorts of subjects with the disorder or proved to lack specificity to the illness. Replication of the findings of Karlsson and colleagues will certainly motivate subsequent critical studies designed to identify translational products derived from the HERV transcripts and to determine the mechanisms by which these products may contribute to the types of brain abnormalities observed in individuals with schizophrenia (18).

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