The Role of Genetics in the Etiology of Schizophrenia

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• Evolution • SNP • CNV • Complex disorders
• Polygenic • GWAS

This article introduces the reader to the genetics of schizophrenia: its background; the status of a variety of genetic findings; new developments (which are many since the last review)[1]; and current and future challenges. Schizophrenia is a devastating psychiatric disorder with a median lifetime prevalence of 4 per 1000 and a morbid risk of 7.2 per 1000.[2] The age at onset is typically in adolescence or early adulthood,[3] with onset after the fifth decade of life and in childhood both being rare.[4,5] Although the prevalence for males and females is similar,[2] the course of schizophrenia is often more severe and with earlier onset for males.[3,6] The standardized mortality ratio (ratio of observed deaths to expected deaths) for all-cause mortality is 2.6 for patients with schizophrenia compared with the general population,[2] with excess deaths mainly from suicide during the early phase of the disorder, and later from cardiovascular complications.

Schizophrenia commonly has a chronic course albeit with fluctuating patterns, and cognitive disability. Its hallmark is psychosis, mainly characterized by positive symptoms, such as hallucinations and delusions, which are frequently accompanied by negative (deficit) symptoms, such as reduced emotions, speech, and interest, and by disorganization symptoms, such as disrupted syntax and behavior. Severe mood symptoms, up to and including manic and major depressive episodes, are present in many cases. There are no diagnostic laboratory tests for schizophrenia; instead, the diagnosis relies on clinical observation and self-report. It is then remarkable that ongoing epidemiological study over the last century using the clinical phenotype, but with variable ascertainment and assessment rules, has consistently shown the importance of genetic factors in schizophrenia.

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THE PHENOTYPIC CONUNDRUM

The definition of caseness is fundamental to research design decisions. Bipolar disorder, schizoaffective disorder, and schizophrenia share some phenotypic aspects in common, both in terms of symptoms and also therapeutics, with all responding to antipsychotic drugs. Kraepelin[7] defined dementia praecox as a group of psychotic conditions with a tendency toward poor prognosis. He grouped under the term ''manic-depressive psychoses'' a set of conditions that included periodic and circular insanity, simple mania, and melancholia, which he thought did not result in deterioration. Kraepelin believed that dementia praecox and manic-depressive psychoses had specific and separate causes. Reality proved to be more complex, however, and in 1933 Kasanin[8] coined the term ''schizoaffective psychosis'' to refer to a disorder with mixed features of schizophrenia and affective disorder. Compared with the general population, family studies show that the clinically intermediate diagnosis of schizoaffective disorder is more common in families ascertained from probands with schizophrenia and in families ascertained from probands with bipolar disorder.[9–14] The diagnostic distinction between schizophrenia or bipolar disorder and schizoaffective disorder is not reliable.[15] The specific time criterion for affective symptoms relative to the schizophrenic symptoms is not well defined and varies in different modern classifications.[16,17]

COMPLEX GENETICS

Knowledge of the molecular mechanisms of schizophrenia pathophysiology remains very incomplete. False starts and research dead ends have taught the field the need for caution; the biological complexity of schizophrenia is much higher than was anticipated. This complexity also applies to simple Mendelian disorders, which although easily analyzed by studying pedigrees, can present unexpectedly intricate biology. Yet, the architecture of schizophrenia is incommensurably more difficult than simple genetic disorders. The idea that one or a few common major gene effects explain schizophrenia was empirically tested in genome-wide linkage scans but results mostly fell short of genome-wide significance.[18] That schizophrenia is very complex should not be surprising. First, the brain is more complicated than any other organ; the number of neuronal interconnections and permutations thereof in humans is enormous (approximately 2×10^{10} neocortical neurons and approximately 10^{14} synapses),[19,20] and knowledge of the physiological basis of higher brain functions is very incomplete. Second, the absence of well-defined, focal, and specific neuropathology has contributed to making schizophrenia particularly impervious to molecular progress, but this is starting to change (discussed later).

Schizophrenia belongs to a group of pathologies known as ''complex genetic disorders.'' Understanding of complex genetic disorders is still evolving as new experiments uncover novel mechanisms of disease. It is commonly thought that many genes are involved in each disorder with each gene conferring only a small effect on the phenotype. The individual risk variants are without diagnostic predictive value, and any estimations of risk are probably going to change in the future as large epidemiological samples become available for analysis.[21] Epistatic interactions between these genes and among their products, and interactions with environmental risk factors are considered highly plausible. The study of genetic interactions using genome-wide data remains largely unexplored because of need to correct for an enormous number of statistical comparisons. Knowledge is shifting from oligogenic models to a polygenic model of schizophrenia, but its genetic architecture still remains largely unknown. The current evidence strongly suggests that the mutation frequency