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Schizophrenia

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Characteristics

Schizophrenia is a severe neurodevelopmental disorder with a worldwide prevalence of around 0.3-0.7% (1). The etiology of schizophrenia is unknown, but it is thought to result from a combination of complex genetic and environmental factors. This includes physical factors e.g., complications during pregnancy and birth, infection, and autoimmune disease; as well as psychological factors that may trigger psychosis, such as stress and drug abuse (2). Several neurotransmitter systems are thought to be involved in the pathogenesis, including dopamine, glutamate, GABA, and acetylcholine.

Schizophrenia is associated with substantial morbidity and mortality. Antipsychotics are the mainstay of treatment, however, their efficacy is poor for many patients. Antipsychotics are thought to exert their therapeutic effects by the post-synaptic blockade of D2 dopamine receptors in the brain.

The symptoms of schizophrenia fall in to three main categories: positive, negative, and cognitive. Positive symptoms are generally not found in healthy individuals, but may come and go or persist in individuals with schizophrenia. Positive symptoms include reality distortion (e.g., delusions, hallucinations), and thought disorders. These symptoms often respond well to treatment.

Negative symptoms are deficits in normal emotions and behavior, and may be mistaken for depression. Symptoms divide into reduced expression of emotion (e.g., speaking without moving or with a monotonous voice) and avolition (a lack of motivation to start or continue with a task). No treatment has established efficacy for these pathologies.

Cognitive symptoms may also be difficult to recognize. They include poor executive functioning (understanding information and using it to make decisions) and trouble focusing or paying attention. And again, no treatment has established efficacy.

Genetics

Schizophrenia is highly heritable, as shown by family, twin, and adoption studies. For example, for identical twins, if one twin develops schizophrenia, the other twin has about a 50% chance of also developing the disease. The risk of the general population developing the schizophrenia is about 0.3-0.7% worldwide (3).

The search for "schizophrenia genes" has been elusive. Initial linkage studies looked at parts of the genome associated with schizophrenia, and many candidate genes were identified, including *APOE*, *COMT*, *DAO*,

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DRD1, *DRD2*, *DRD4*, *DTNBP1*, *GABRB2*, *GRIN2B*, *HP*, *IL1B*, *MTHFR*, *PLXNA2*, *SLC6A4*, *TP53*, and *TPH1* (4). However, some of these have later been questioned (5).

Microdeletions and microduplications have been found to be three times more common in individuals with schizophrenia, compared to controls. Because these deletions and duplications are in genes that are overexpressed in pathways related to brain development, it is possible that the inheritance of multiple rare variants may contribute to the development of schizophrenia (6).

Several genetic disorders feature schizophrenia as a clinical feature. The 22q11.2 Deletion Syndrome comprises many different syndromes, of which one of the most serious is DiGeorge syndrome. Children born with DiGeorge syndrome typically have heart defects, cleft palate, learning difficulties, and immune deficiency. Schizophrenia is a late manifestation, affecting around 30% of individuals (7). Microdeletions and duplications in chromosome 1, 2, 3, 7, 15 and 16 have also been associated with schizophrenia (8).

In 2014, a genome-wide association study looked at the genomes of over 35,000 patients and 110,00 controls. The study identified 108 SNPs that were associated with schizophrenia, 83 of which had not been previously reported. As expected, many of these loci occurred in genes that are expressed in the brain. For example, the SNPs included a gene that encodes the dopamine D2 receptor, *DRD2* (the target of antipsychotic drugs), and many genes involved in glutamine neurotransmitter pathways and synaptic plasticity (e.g., *GRM3, GRIN2A, SRR, GRIA1*). More surprisingly, however, associations were also enriched among genes expressed in tissues with important immune functions (9).

In 2016, a study based on nearly 65,000 people investigated the association between schizophrenia and variation in the Major Histocompatibility Complex (MHC) locus—a region on chromosome 6 that is important for immune function. The study focused on the *C4* gene (complement component 4) that exists as two distinct genes: *C4A* and *C4B*, which encode particularly structurally diverse alleles.

The study found that the alleles which promoted greater expression of *C4A* in the brain were associated with a greater risk of schizophrenia. By using mice models, the study showed that C4 is involved in the elimination of synapses during brain maturation. In humans, "synaptic pruning" is most active during late adolescence, which coincides with the typical onset of symptoms of schizophrenia. It is therefore possible that the inheritance of specific *C4A* alleles could lead to "run away" synaptic pruning, increasing the risk of schizophrenia. Further research may even determine C4 as a potential therapeutic target (10).

Diagnosis

Currently, the diagnosis of schizophrenia is made via a psychiatric assessment using the criteria presented in the American Psychiatric Association Manual of Psychiatric Diseases, which is now in its 5th edition, and is known as DSM-V. To make a diagnosis, specific characteristic symptoms of schizophrenia must be present for at least 6 months, together with a disruption in social or occupational function, in the absence of another diagnosis that could account for the symptoms.

The use of chromosome microarray analysis has been suggested as a diagnostic test for schizophrenia. Microarray analysis can detect copy number variants (CNVs), which are large regions of the genome that have been deleted or duplicated. The prevalence of clinically significant CNVs in schizophrenia is around 5%. For autism and intellectual disability, the prevalence is around 10-20%, and CNV testing with microarray analysis is now a routine first-line diagnostic test for these conditions.

For an individual with schizophrenia, a positive test result for CNV may have implications for medical management, because of the association of CNVs with physical diseases and genetic counseling, and because offspring have a 50% risk of inheriting the CNV (3, 11).

Management

Treatment of manifestations: Antipsychotic medications are the mainstay of treatment and help reduce symptoms and improve behaviors in patients with schizophrenia. The type, dose, and route of administration of antipsychotic medications depends upon the clinical scenario. Adverse effects are common, and may require the dose or type of drug to be altered.

Antipsychotics may be given with counseling and other types of psychosocial interventions. For refractory (treatment-resistant) symptoms, an alternative antipsychotic or an additional antipsychotic may be required.

During pregnancy, antipsychotic drugs should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus. Neonates exposed during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder. While in some cases symptoms have been self-limited, in others neonates have required intensive care unit support and prolonged hospitalization.

Surveillance: Routine monitoring for the symptoms and signs of extrapyramidal adverse effects is needed in individuals taking antipsychotics. These adverse effects include akathisia (feeling of restlessness that may be accompanied with motor restlessness), dystonias (involuntary contraction of large muscle groups), and parkinsonian syndrome. Patients should also be monitored for signs of tardive dyskinesia (involuntary facial movements) and drug-specific adverse effects. For clozapine, because of the risk of neutropenia, the patient's white blood cell count and absolute neutrophil count must be regularly monitored. For thioridazine, the risk of prolonged QT interval may lead to Torsades de pointes.

Prevention of secondary complications: Patients should be regularly monitored for weight gain and metabolic problems such as hyperglycemia and hyperlipidemia, which are common side effects of antipsychotic medications.

Genetic Testing

Genetic testing is available for several of the susceptibility loci for schizophrenia, including clinical and research tests registered in the NIH Genetic Testing Registry (GTR). Additional tests may be found in the 'Related section' of the main GTR record for schizophrenia.

GTR also has registered tests for genetic conditions with schizophrenia as a clinical feature.

Genetic Counseling

Genetic counseling is recommended for people who have a family member with schizophrenia. Recurrence risk counseling is based on empiric familial risk for families with individuals with schizophrenia (12).

The lifetime risk of schizophrenia for the general population is estimated to be 0.2 to 0.7% (13).

The recurrence risk of schizophrenia in the siblings of a patient is 10%, and in the children of patients, the risk is approximately 10%. The risk for second-degree relatives is approximately 3-4% (14, 15).

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Version History

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