Genetics and the mystery of Schizophrenia: What lies ahead….

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The Family Illness

I had so many reasons not to think about schizophrenia, about the terror it caused me as a child. When I was six, I watched my brilliant brother change from an engaging 16-year-old to a zombie who stared into space for hours. Two years later, I saw my older sister turn cruel and loud, screaming for what seemed like hours. I was too young to know anything about schizophrenia, but I knew something was terribly wrong. Like many with this disease, neither my brother or sister could find satisfactory treatment, resulting in my brother's leaping off a cliff to his death and in the regular recurrence of my sister's psychotic rages.

Schizophrenia isn't the multiple personality of movie stereotype, but it is a horrible mental illness, causing aural hallucinations and provoking paranoid delusions that can make peculiar behavior seem normal to the sufferer. It often can be treated, but it isn't yet curable. And although public awareness of mental illness has come a long way in my lifetime, it's difficult not to feel cursed by the shadows it casts.

For much of my life, I have tried to believe that the madness was behind me. After all, my brother committed suicide 15 years ago, while I was still in college, and I've been out of touch with my sister for close to 20 years. They no longer inhabit my present life, but their illnesses haunt me like ghosts.

At this point in my life, that ghost has taken on a terrifying new shape. It haunts me now with the question: Would I have a child with schizophrenia? Talking with geneticists did not dispel my fears; in fact I soon learned that any children of mine would indeed have an increased risk of developing the illness that destroyed my siblings' lives. Although my fiancé has no relatives with schizophrenia, our kids would be as much as eight times more likely than the average person to have schizophrenia. But even for my children, schizophrenia is not a huge risk - their chances range from 3 to 8 percent. In the general population, schizophrenia occurs in one out of every hundred people. Several scientists told me that other considerations - such as the fact that both my siblings had schizophrenia - may increase the odds. Another factor could be the severity of my sibling's cases: Both became wildly, uncontrollably ill.

These odds are all the scientists can offer me. Unlike some other hereditary diseases, the genes for schizophrenia have not yet been isolated; there is no test. All we can provide are our family histories; all we can get in return are percentages.

If only the science were further along. Still, we try desperately to read our futures in the little information we have. The genetics of mental illness will be much better understood in 20 years, scientist say, but there isn't much chance of current research having practical applications within the next five years - when it would be useful to me. In the end, I have to face the fact that no one can tell me whether a child of mine would be healthy or ill.
And so the dilemma remains, particularly for people like me who carry the memories of our siblings at the same time that we feel the pressure of encroaching age. We cannot wait for research to provide the answers. We must make our peace - and our decisions - with the knowledge at hand.

Clea Simon is an editor at the *Boston Globe*. This piece is adapted from her recently released book, *Mad House: Growing Up in the Shadow of Mentally Ill Siblings* (Doubleday), portions of which appeared in *The Washington Post.*

Schizophrenia (SZ) is perhaps the most debilitating and tragic mental illness known. It leads to a complete breakdown of personality, and for many of its sufferers, is a life sentence without hope of parole. It effects at least 1% of the population worldwide regardless of race, gender and economic condition. Symptoms usually develop during young adulthood and continue to haunt its sufferers for their lifetime. Positive symptoms include delusions, hallucinations and disordered thought, while the negative symptoms are social withdrawal and emotional flattening. Complete recovery from the psychotic and emotional symptoms is very rare. Unfortunately, the illness is also perhaps the most elusive and mysterious among the mental afflictions in terms of its molecular, environmental and genetic etiology. Moreover, the symptoms manifest themselves in such varying degrees of qualitative and quantitative intensity, that it very hard to define a specific set of symptoms and behaviors associated with SZ. Some researchers even suggest a mental health continuum from depression to bipolar depression to schizophrenia and varying intensity within its symptoms, rather than looking at the illness as a discretely defined entity. There is presently no biological test that can confirm the presence of the illness.

Schizophrenia is a complex multifactor disorder, and like other multifactor disorders such as cancer, does not follow classical mendelian inheritance patterns. The genetics of Schizophrenia, lika almost every mental disorder, are indeed very complex. Twin and family studies have revealed, however, that there is indeed a genetic component to the development of predisposition and finally to the manifestation of positive and negative symptoms of SZ. Therefore, families with one ill member have a greater chance of developing this illness later on. It has been hypothesized by many

researchers that 60% of the factors that give rise to Schizophrenia may be related to genetic susceptibility. However, researchers have not yet been able to identify a single predominant “SZ gene” . This is complicated by studies that show that there is infact no single gene but a combination of genes acting with small effect to lead to the development of predisposition and pathology; and the more genes necessary for the disorder, the harder it is to detect any one of them. Furthermore, there is evidence that environmental factors interact with genetic predisposition in subtle ways for this inherited susceptibility to actually develop into a full-blown Schizophrenic psychosis. The nature of these non-genetic effects is yet another mystery that futher complicates the search for distinct causal factors.There is great hope, however, that by locating genes that are central to the development of familial predisposition to SZ, we will get clues to many other non-genetic factors that play a central role in this disorder. Let us look at the degree of pre-molecular genetic epidemiology that has come up in studies of twins and families.

Relationship	Morbid risk (%age)
General population	1
Spouses of parents	2
Parent	6
siblings	9
children	13
MZ twins	48
DZ twins	17
Children of two SZ	46

(L.Gottesman, 1982)

This table, constructed from family studies, clearly shows that there is a strong hereditary influence in the manifestation of SZ. However, with Monozygotic twins, who share 100% of their genes, if one twin has the illness, there is only around a 50% chance that the other twin will also develop pathology. This clearly points to other complex gene environment interactions that may be playing a key role beyond inherited susceptibility in the development of schizophrenia. A good sample of families to study for such familial studies would constitute families wih effected individuals manifesting very similar symptoms, so that the group carries the same form of the gene. However, as many as 1600 sibling pairs might be required for fine resolution mapping of an actual gene of small effect. Linkage, linkage-equilibrium and association studies have been used to narrow down the candidate genes for SZ.

There are presently three main lines of inquiry that researchers are using to investigate the underlying defects in brain function and development associated with SZ. These are: I) examination of the mechanism of action of the drugs that alleviate or worsen the symptoms of SZ; II) examination of the neurodevelopment anomalies in the brains of SZ patients II) examination of candidate genes that confer susceptibility to SZ. These three approaches are now coming together in hope of offering a unified theory about the cause, symptoms and cure for SZ in the near future. With the unraveling of the human genome, the possibilities for the studying the distinct and very important role of genetics in SZ is indeed very exciting for observers, and could contribute a lot to knowing about the other factors that drive the onset, symptoms and alleviation from symptoms of the illness. As the function of genes in brain development is better understood, researchers can begin to develop ways to mediate in processes that cause this

illness. Sawa and Synder (2002) talk about how these different approaches are converging owing to the recent development of powerful brain imaging techniques, pharmacological studies and genetic research:

"The difficulties in pinning down specific abnormalities in SZ are not unique. Other common diseases that similarly derive from multi-genetic influences, such as cancer, diabetes, and various cardiovascular disorders, present similar challenges. SZ and other diseases of the central nervous system are particularly well suited to attack by the multiple tools of modern neuroscience with a confluence of imaging, neuroanatomy, genetic analysis, and psychopharmacology. As genetic linkage studies proliferate, highly reproducible defects are emerging that mesh with research on neurotransmitters and neuroanatomy."

In the 1950s, the first drug that helped alleviate symptoms of SZ was discovered; Chloropromazine. Before that no pharmacological treatment existed for SZ. These class of drugs, known as "neurpleptics" (Latin meaning 'seizing the neuron') worked by blocking the D2 subtype of the dopamine receptors in the limbic areas (primarily the prefrontal cerebral cortex) which regulate emotional behavior. These drugs were revolutionary at the time, and did confer substantial relief from the positive symptoms (hallucinations, extreme paranoia, disordered motor function) of SZ. On the other hand, administration of Amphetamines, which work by releasing dopamine in the brain, was found to worsen symptoms. Increased dopamine function was therefore associated with greater manifestation of symptoms, and any drug that decreased dopamine function in the prefrontal cortex therefore had anti-psychotic effects. New drugs like Clozapine, however, can help relieve both the negative and positive symptoms of SZ, and do not have side effects as potent as the classical neurpleptics. Clozapine manifests its influence by blocking the 5-HT2 subtype of the serotonin receptor, more than it does at the dopamine D2 receptors. This had led to a speculation about the role that serotonin might play in the pathophysiology of SZ.

These drugs have indeed alleviated symptoms of Schizophrenia. But their efficacy

is still very limited and their anti-psychotic effects vary from individual to individual for reasons not yet known. The great difficulty in designing anti-SZ drugs arises from our ignorance of the molecular causes of the disease and the absence of reliable animal models. It is indeed very hard to model SZ symptoms in animals. However, Phencyclidine (PCC), a widely abused illicit drug, causes symptoms that are indistinguishable from SZ. It acts by blocking the N-methyl-D-asparate (NMDA) subtype receptor for the neurotransmitter Glutamate. Partial deletion of the gene encoding a form of the NMDA causes effects that mimic PCC administration. If SZ involves decreased NDMA receptor activity, drugs that activate this receptor might be helpful. But designing these drugs is not simple, because Glutamate administration is very complex.

Brain imaging techniques like Magnetic Resonance Imaging have given researchers leads to inherited brain defects observed in SZ patients, even before the full onset of symptoms. Some of the genes causing SZ might be active during early brain development. Studies have shown that SZ is largely a neurodevelopmental and not a neurodegenerative disorder. Brains of patients show consistent increase in ventricular size, with noticeable changes in the prefrontal cerebral cortex and hippocampus - brain areas that are responsible for regulating emotion and higher cognitive function, both of which are significantly impaired in SZ. Other studies indicate that the neurons in SZ patients are smaller in size. All of these abnormalities in brain development give clues to the role of genetics in the flawed synthesis of the SZ brain. Abnormalities in protiens with a key role in brain development may significantly contribute to the illness. Reelin, for example is a molecule that acts as a stop signal for neuronal migration and thus facilitates normal brain patterning during development. SZ patients show a 30-50%

reduction in Reelin expression in the prefrontal cerebral cortex and the Hippocampus. However, a multitude of different chromosomal abnormalities have been attributed to these brain defects, and no highly reliable candidate gene has then been singled out. Sawa and Snyder confirm this finding in their paper:-

"The existence of multiple loci conferring susceptibility to SZ suggests that the disease is caused by the interactions of many different genetic components"

Genetic loci that indicate susceptibility to SZ have been mapped to a number of chromosomes including 1q21-22, 1q32-43, 6p24, 8p21, 10p14, 13q32, 18p11, and 22q11. The genetic complexity of Schizophrenia can however be reduced by studying rare, inherited forms of the disorder. The deletion of chromosome 22q11, called 22q deletion syndrome (22qDS), has been observed in 2% of SZ patients. Moreover adults with this syndrome show a very high occurrence of SZ (about 25-30%). Further study of the inheritability of 22qDS and the function this chromosome performs in brain development will indeed advance study of the genetic basis of SZ. The gene encoding catechol-O-methyl tranferase (COMT) is an interesting candidate as the causal gene for 22qDS. Interestingly, COMT is the enzyme responsible for the degrading of dopamine. Studies with mice have shown that targeted deletion of the COMT gene leads to higher levels of dopamine only in the prefrontal cerebral cortex, a neurological state that drug studies show us worsens the symptoms of SZ. Further, it is amazing that COMT, which regulates dopamine, is localized to 22q11, where a micro deletion leads to a elevation of SZ susceptibility. There are also other promising gene candidates, like the DISC-1 gene, and the gene which occurs on chromosome 13 and encodes the serotonin receptor 5 $HT_{2A.}$ .This receptor appears to influence the activity of commonly used anti-psychotics like

clozapine. Microarray technology for studying gene expression has proved a useful tool for analyzing the genetic pathology of SZ.

Even if there are many complex factors at play in the development of SZ, mediation aimed at just one factor may be a successful prevention strategy. For SZ, where genetic predisposition plays such a major role, genetic identification can prepare individuals medically, emotionally and financially for possible onset of SZ.

The recent convergence of neurodevelopmental, neurotransmitter and genetic studies of SZ has brought us closer to understanding the molecular basis for the illness. The National Institute for Mental Health (NIMH) has recognized that the genetic study of mental disorder is indeed a valuable tool. It is committed to "search for the genes that create mental illness, affect the course of illness, and impact treatment". Eventually, it is hoped that understanding the pathophysiology of SZ will lead to increasingly specific treatments and even to prevention. At the core of this daunting endeavour, amid the labyrinth of complex genetic and environmental factors is the realization that better treatments will eventually come out of discovering the true causes of SZ. The search for these susceptibility genes, however daunting at this point, will indeed be an exciting and life changing experience for many.

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