

SCHIZOPHRENIA & GENETIC RISKS

*A Guide to Genetic Counseling
(Second Edition)
for Consumers, Their Families,
and Mental Health Workers*

by

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A CAUTIONARY PROLOGUE

An acceleration of print and broadcast media attention to such exciting developments in molecular genetics and the neurosciences as the cloning of Dolly the sheep, gene therapy for some rare diseases, pre-implantation screening for “healthy” embryos, inventions of new technologies to study gene expression (DNA microarrays), and fully automated gene-sequencing machines to facilitate rapid genotyping and mapping/sequencing of the human genome give us reasons for cautious optimism about winning the struggle to understand the causes of schizophrenia in the foreseeable future.

But, such genuine developments, often distorted by media hype, must not be allowed to raise false hopes of an immediate solution to the problems of preventing and treating schizophrenia and other major mental disorders. As of the summer of 1998, no specific genes have yet been identified that will lead to the development of schizophrenia, but a number of gene regions on a few chromosomes have been identified that are statistically reliable indicators of increased risk at the group, but not the individual, level.

The objective of this brief pamphlet is to provide basic facts about schizophrenia and its familial distribution (with suggested resources) so that consumers, their families, and mental health workers can start the quest to become informed enough to initiate appropriate actions, if any. We present this update to our previous edition in response to the remarkable and continuing demands to NAMI for such information.

You will need much more information than that contained in this booklet before you can make the critical decisions you may want to make about such topics as marriage, divorce, pregnancy, abortion, health insurance, and estate planning. These areas are intensely personal ones, at the core of an individual’s sense of identity and self-worth. Adding to the tension is the complication that decisions are often contemplated at the height of vulnerability to both valid and incompetent advice. We are mindful of the phrase, “The road to Hell is paved with good intentions.”

What is genetic counseling?

When Sheldon C. Reed coined the term *genetic counseling* in 1949—the year after the founding of the American Society of Human Genetics and the year the first modern American textbook in human genetics was published—he was formalizing various activities that “genetic social workers” had provided to families on an individualized basis from early in this century. The hope was to prevent or minimize the risk of recurrence of a serious disorder presumed to be wholly or partly genetically influenced. The quality of the advice varied with the competence of the counselor and the stage of knowledge about the origins of various medical disorders.

The good track record of genetic counseling was established with such diseases as the inborn errors of metabolism, Huntington’s disease, chromosomal errors, and the many simple forms of mental retardation. These diseases run in families with relatively simple patterns of transmission, and siblings of people affected have a 25-percent (for recessive disorders) or a 50-percent (for dominant disorders) chance of being affected. Schizophrenia, major depressive disorder with psychosis, bipolar affective disorder, cancers, diabetes, and heart disease, among other numerous common human afflictions, all belong to a group of more “complex” disorders that involve both an important genetic *and* an important environmental component. Such disorders, not present at birth but developing over the life span, are observed to *aggregate* within families at higher rates than in the general population (say eight percent of siblings versus one percent), but not to *segregate* into the neat one-in-four or one-in-two Mendelian ratios noted above.

Such disorders require the individualizing of empirical risks on the basis of clinical experience and observations of earlier families. In respect to schizophrenia, the risks to offspring or to siblings increase with the severity of illness in the first case identified in a family (sometimes termed *proband*), with the number of other relatives in the pedigree also affected and whether one or both sides of it are involved, and with younger ages of onset in the proband.

Great strides have been made in the science of genetic counseling, but there is still a large element of “art” in the process, especially for the mental disorders. We are convinced that the amazing strides made in the identification of individuals at risk for developing the simpler genetic conditions and for treating them at the molecular level will rapidly spread to the complex disorders where four or more genes plus non-genetic factors are involved. A corps of psychiatric genetic counselors must be trained and prepared for the heavy workload such advances in public health will place upon them.

It is imperative to state that genetic counseling in a democratic society is conducted in an atmosphere of protected privacy, informed consent, and without coercion from governmental agents. The National Human Genome Research Institute has established a program for ethical, legal, and social implications (ELSI) that derive from the Human Genome Project (see Recommended Resources). The psychological aspects of genetic counseling have been discussed in depth by Dr. Seymour Kessler (also see Recommended Resources).

What is schizophrenia?

Schizophrenia is one of the most serious and disabling mental illnesses, and tragically, it has its greatest impact during the most productive years of life. It has been estimated that the cost of care over a lifetime for an individual, once diagnosed, comes to one million dollars from combining direct (hospital, outpatient care, medications) costs and indirect (loss of wages, familial care) costs. Schizophrenia is associated with several characteristic disturbances in the way an individual thinks, perceives, feels, and relates to others. An affected individual also frequently lacks interest in and the drive to work or to engage in other activities. The essential features of this disease are the presence of psychotic symptoms (delusions, hallucinations, disturbances in thought) that grossly impair a person's sense of reality during the active phase of the illness and cause him or her to function below the highest psychosocial level previously achieved. Accurate diagnosis demands an evaluation of symptoms and life history by an experienced professional to exclude a number of deceptive "imitators" caused by various prescription and street drugs, physical illnesses, and other brain or genetic disorders.

In our efforts to prevent this illness, we must first understand the causes. One of the most consistent findings is that genetic factors contribute to the development of schizophrenia in a major way, in addition to environmental and experiential factors.

Frequency

The lifetime risk by age 60 for developing schizophrenia in the general population is approximately one percent. (One in 100 newborns in the U.S. population today will eventually become affected.) This is a common illness compared to other genetic conditions like Huntington's disease, or phenylketonuria, which have lifetime risks of between one in 20,000 and one in 10,000, respectively. In fact, more than two million Americans over the course of their lifetimes have already been struck with schizophrenia; it is five times more common than multiple sclerosis, six times more common than insulin-dependent diabetes, and 60 times more common than muscular dystrophy. Other conditions known in the aggregate as "schizophrenia spectrum disorders" are important in the context of genetic counseling, but accurate figures for their lifetime prevalence are lacking. Included in this category would be schizoaffective disorders, other nonaffective psychoses within families with schizophrenia, and schizotypal/schizoid/paranoid personality disorders.

Facts relevant to familiarity and to genetics

- The risk of developing schizophrenia to the offspring of two parents who are free from schizophrenia-like conditions in themselves or their close relatives is approximately one percent.
- The *average* risk of developing schizophrenia in offspring, given that one parent has the disorder, is approximately 13 percent, but ranges from two percent to 35 percent as a function of severity and the number of other affected relatives.

- The *average* risk of developing schizophrenia in offspring, given the rare situation that both parents have the illness, is approximately 46 percent.
- The *average* risk of developing schizophrenia in the sibling (brother or sister) of an individual with the disorder is approximately eight percent when no other close relatives have schizophrenia.
- The risk of schizophrenia to the relatives of an individual with the illness increases markedly with the degree of genetic relatedness. Therefore, first-degree relatives (parents, siblings, offspring) of an individual with schizophrenia have a greater risk for developing the illness compared to second-degree relatives (grandparents, grandchildren, uncles, aunts, nieces, nephews, half-siblings) of that individual.
- The identical (one-egg, or monozygotic) twin of an individual with schizophrenia has a risk of developing the disorder (48 percent) about three times that of a fraternal (dizygotic) twin (17 percent) and nearly 50 times that of individuals in the general population. These results from studies conducted before 1992 have been reconfirmed and extended in five new studies reported after 1995 around the world.

The following facts demonstrate the great importance of systematic or chance environmental factors in contributing to the liability for developing the illness.

- More than half of the monozygotic twin pairs in recent scientific studies are discordant for schizophrenia (only one member of the pair has the illness), despite sharing all their genes in common.
- Identical twins who are discordant (one ill, one well) for schizophrenia each transmit the predisposition that developed into schizophrenia to their offspring at the same high rate. This shows that individuals can pass on genes involved in the disorder while not being affected themselves; that is, genes predisposing to schizophrenia are not sufficient to guarantee the development of the disorder.
- Children of a parent with schizophrenia placed early for non-familial adoption still develop schizophrenia as adults at rates considerably higher than the one-percent population rate, sometimes as high as rates in home-reared offspring of parents with schizophrenia.
- Pre-pubertal childhood-onset cases of schizophrenia appear to represent a very rare but severe form of schizophrenia; childhood psychoses appearing before age eight do not seem to be genetically related to schizophrenia.
- Illicit drugs such as speed, crack, acid, and PCP (angel dust), as well as alcohol withdrawal, can result in symptoms similar to those observed in genuine schizophrenia. The risks for schizophrenia to relatives of individuals who only develop psychotic symptoms over the course of a physical illness or after illicit drug ingestion are not usually different from those in the general population. However, some street drugs may reveal a low “genetic loading” for schizophrenia that becomes triggered by drug exposure.

A BOTTOM-LINE SUMMING UP

What does it mean that genes are involved in causing schizophrenia?

Genes are chemical structures passed from parents to offspring that are the blueprints for the assembly and regulation of proteins. Proteins are the building blocks of our nervous system and all other parts of our bodies. There is an indirect and complex path between genes and schizophrenia mediated by proteins and physiological systems. Genes are not robot-like, hard-wired circuits that absolutely determine that an individual will develop schizophrenia. It is the complex, epigenetic interplay between both genetic and environmental factors that determines who, if anyone, will become affected.

If genes are involved in causing schizophrenia, does that mean that environmental factors are not important?

Absolutely not! The vast majority of schizophrenias are most likely caused by specific genetic factors in combination with nonspecific genetic and environmental factors.

Without such environmental effects, many cases of schizophrenia might not develop. “Nonspecific” refers to environmental influences (like general stress) that would not cause schizophrenia in people who are not genetically predisposed. Therefore, the environmental “triggers” involved as proximal factors in causing schizophrenia are events or influences that most people would not find overwhelming.

No major, specific environmental influence by itself has consistently been identified as a significant risk factor for developing schizophrenia the way cigarette smoking is for lung cancer or the way severe combat is for post-traumatic stress disorder. We do know that illicit drugs like PCP, cocaine, and LSD should be avoided at all costs (especially if schizophrenia runs in one’s family) because of their powerful abilities to induce psychotic, schizophrenic-like symptoms. There is some evidence that these substances may trigger full-blown schizophrenia in genetically predisposed individuals—all the more reason why relatives of affected individuals should avoid these drugs. A list of probable “toxic” experiential factors that may contribute liability to relapse and acute episodes of schizophrenia would include insults to the brain, demoralizing or threatening physical environments, emotionally intrusive experiences, emotionally demanding experiences, emotional understimulation, and chronic disruptions to attention or information-processing. Intense, dramatic efforts to change personality via “encounter groups” should be discouraged in those with a probable disposition.

Given that genes are involved in causing schizophrenia, does that mean schizophrenia cannot be treated or prevented?

Absolutely not! Genetic involvement in a complex condition does not preclude the effects of environmental or genetic “assets” in reducing suffering or in preventing the illness from developing. Psychiatric medications like risperidone

(Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), and clozapine (Clozaril) are such environmental assets that help to treat (but not cure) many of the prominent symptoms of schizophrenia. The effectiveness of such medications is amplified by the addition of assertive community treatment and family educational programs.

Do we know which genes cause schizophrenia?

Not yet. At the present time, we have not specifically identified any genes as the ones causing schizophrenia, but tremendous national and international efforts have been launched to locate them. Statistical evidence is accumulating that implicates specific gene regions in a small number of chromosomes, and several investigative teams point to the same region. However, even with the best example to date of a “small” region on the short arm of Chromosome 6, the region may contain as many as 2,000 to 4,000 genes. The blameworthy gene in this “crowd” is yet to be indentified; when it is, it will then become one of the genetic risk factors. In the case of heart disease, high levels of “bad” cholesterol are risk factors; in fact 17 different genes have been identified so far that regulate cholesterol levels, but no high-cholesterol person need share more than a few with any other high-cholesterol person.

Are there prenatal or postnatal genetic tests that tell who will develop schizophrenia?

No. Such tests have only been identified for rare, simpler genetic conditions, like Huntington’s disease or cystic fibrosis, that are transmitted in families in very predictable ways. Just as we do not yet have prenatal tests for genetically influenced illnesses with complex patterns of inheritance like diabetes, heart disease, or cancer, we do not have them for schizophrenia. Postnatal tests on children for genetically influenced disorders where major therapies are not available have been deemed unethical and are prohibited. Thoughtful discussions about the ethical issues involved are essential and must occur before any such diagnostic test becomes widely available.

If schizophrenia is transmitted through genes, why do most families with a relative with schizophrenia not have affected individuals in every generation?

The vast majority (nearly 90 percent) of people with schizophrenia have neither parent who is affected, and 81 percent have neither parents nor siblings affected. A sizable majority—about 63 percent—of individuals with schizophrenia do not have any first- or second- degree affected relatives. This makes sense from a genetic point of view because schizophrenia has a complex, irregular pattern of genetic transmission in families, and not all individuals genetically predisposed to schizophrenia will have schizophrenia themselves. Therefore, some of these clinically healthy individuals can pass on some of these predisposing genes in their families with “silent” effects. A close analogy would be seen in the parents of professional basketball players who are over seven feet tall; neither parent, while taller than average is “affected” with extreme height, but each transmits enough of the “tallness genes” to produce a son who develops into a person significantly taller than either parent.

Who is genetically predisposed to schizophrenia, and will all such individuals eventually develop the illness?

Individuals at greatest risk are the closest relatives of individuals with schizophrenia. Just having an ill relative does not mean you will develop schizophrenia. The range of risks varies greatly by genetic closeness to an ill relative. Computer programs that take into account all available family data can be used for more precise risk prediction. A promising avenue for future research involves studying behaviors that are correlated (associated) with liability to schizophrenia and that also are inherited within families. These may include disturbances in attention/concentration, disturbances in how the eyes follow moving objects, extreme shyness or suspiciousness, and performances on certain psychological tests like the Minnesota Multiphasic Personality Inventory (MMPI). As this research continues, we will be able to increase the accuracy and efficiency of risk prediction to a practical level. Imaging the structure and function of the brain is another promising method for identifying risk factors for developing schizophrenia.

Should individuals affected with schizophrenia have any children?

A simple “yes” or “no” answer cannot do justice to this very personal and delicate question that goes to the heart of personal liberty and civil rights in a democratic society. Most adult individuals suffering from schizophrenia never marry; if they do, they have a high divorce rate. As a group their fertility (number of children) is greatly reduced, with only 20 percent of males and 40 percent of females having one or more children. Possible upward changes in such rates may be occurring as a consequence of improvements in treatment and outcome.

The very high genetic risks to offspring for such severe dominant diseases as Huntington’s disease (50 percent) or to the two normal but “carrier” parents for recessives such as Tay-Sachs disease or cystic fibrosis (25 percent) have a major impact on decisions about child-bearing. The decision of a person with schizophrenia about whether or not to have a child should not be primarily based on a consideration of the more variable and lower genetic component of the risks to offspring. Rather, the decision should be based on an objective evaluation of the affected person’s ability to deal with the emotional stress and tension-related risks of relapse associated with the demands of parenting. Individual counseling is necessary in each case to assist with rational and fair decision-making about marriage and child bearing. Concerned individuals or couples should seek professional guidance from a genetic counseling center before making decisions in these matters.

Should relatives of individuals with schizophrenia be hopeful about genetic research in the near future?

Absolutely! Rapid advances are continually and sometimes unpredictably being made in the brain sciences and in molecular and quantitative genetics. The potential for unraveling the genetics of schizophrenia benefits from the entire body of research in human and animal genetics. As our recommended resources make clear, cautious optimism characterizes our attitude, and we encourage its adoption by consumers, their families, and their mental health workers.

RECOMMENDED RESOURCES

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INTERNET ADDRESSES

www.nami.org

Home page for the National Alliance for the Mentally Ill and a gold mine of linked addresses.

www.faseb.org/genetics

Home page for professional societies dealing with genetics and with genetic counseling, including addresses of counselors and their areas of expertise. Even if not specialists in mental illnesses, they are likely to be knowledgeable about good referrals.

www.ncbi.nlm.nih.gov

Home page for the National Center for Biotechnology Information with an outstanding collection of further links to government resources such as the National Library of Medicine and the National Institutes of Health. Links to the most up-to-date map of the human genome and to the wealth of knowledge about single-gene disorders and traits in humans available in Victor McKusick's Online Mendelian Inheritance in Man (OMIM). From this address you can access the wonderful National Library of Medicine's MEDLINE with instant recovery of abstracts and even entire articles, at no cost, from the vast biomedical and neuroscience journal databases.

www.grb.nimh.nih.gov

Home page for the genetics research of the NIMH; describes ongoing research funded by the NIMH to find genes that influence the development and functioning of the brain; complex behavior; and schizophrenia, bipolar disorder, and autism. Provides a wealth of links to resources on the Internet.

www.mentalhealth.com

An address loaded with links to details and treatment of the major mental disorders; maintained by Canadian authorities.

www.schizophrenia.com

A very informative page directed toward consumers and their need for information; maintained by a dedicated brother.

www.neuroguide.com

An omnibus entry point to resources about the neurosciences generally; edited by a neurologist.

www.bioethics.gov

A guide to the work of the presidential committee on the limits to the uses of human beings as research subjects in psychiatric and other kinds of research. The site also deals with definitions of informed consent for those patients who need guardians and with such futuristic concerns as the cloning of human beings.

www.medscape.com/Home/Topics/psychiatry/psychiatry.html

This site provides free updates to the literature on schizophrenia and other severe mental illnesses for the most recent 36 months. First to offer full-text access to the *Schizophrenia Bulletin*, a direct link to MEDLINE, a medical dictionary, a guide to drugs, and a search function for its contents. (Type "schizophrenia" and it will present 100 important items, including an updated summary to the *APA Guideline for Treating Adults with Schizophrenia*.)