Heredity and Vulnerability in Predicting Schizophrenic Causations: A biobehavioral Approach.

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Abstract

For centuries, the devastating and puzzling effects of schizophrenia on humans have raised great concerns among mental health clinicians, researchers and even the public. Due to the ravaging effects, which are hallmark of this ailment, psychiatrists, psychologists, as well as neuroscientists are in continuous controversial debate as to what may constitute the actual etiology of schizophrenia. For some researchers, the pathogenesis of schizophrenia and other psychotic disorders reveals excesses or abnormalities in dopamine activity at various points in the brain, which they believed link schizophrenia to heritability. The gene, catechol-O-methyltransferase, which regulars the activities of dopamine in the frontal cortex of the brain can be defective, and known to be responsible for the genetic transmission of schizophrenia (Pendleton, 2010). For this reason, it is believed that children, who inherited this “defective gene”, stand a greater than 90% chance of becoming symptomatic of the positive symptoms of schizophrenia. On the other hand, the human genome-wide association (HGA) or the human genome project (HGP), maintains that even though genes play a great role in mental disorder, but no single gene has been identified to have an “absolute” effect on heritability of schizophrenia. So far, research of family history, monozygotic twins, as well as experimentation with amphetamine, chlorpromazine, and phenothiazines have been used to buttress the argument that the dopamine receptor genes are responsible for the heritability of schizophrenia. This line of argument is called the dopamine hypothesis. The counter argument, the ecological vulnerability theory (or the 50:50 vulnerability theory), on the other hand, disagrees with the absoluteness of dopamine hypothesis. They maintained that research findings and evidence-based reports have also shown cases where offspring (even identical twins) of parents with schizophrenia were never symptomatic of schizophrenia or other major mental illnesses. The aim of this paper is to review and analyze relevant scientific literature and clinical reports so as to present to my readers an updated,
balance and comprehensive account of the present scientific and clinical opinion on the heritability of schizophrenia and other major psychosis.

Introduction

Like in every controversial debate, people tend to gravitated toward an inclination that supports their belief systems and aspirations. The same thing can be said of the dopamine hypotheses. The strong genetic component of the hypothesis has spilt mental health clinicians and researchers into two camps, namely “lumpers” and “splitters” (Hedaya, 1996). Lumpers believe that the symptoms manifested by schizophrenic patients may be the result of underlying abnormality, defect, or deficit in integrative functioning in the central nervous system. For example, Wexler (1991) remarked that the basic problem in schizophrenics is their inability to handle complex tasks which as a results of abnormal activities in the frontal cortex. For this reason Wexler believed that when a schizophrenic patient is presented with almost any task that activates a group of cortical neurons, there is a failure of those neurons to recruit, activate, connect, or link to additional cortical brain regions for effective coordination (Frederickson, 2008; Salgado-Pineda et al, 2007; O'Reilly et al, 1999; Weinberger, 1994). The importance of such linkage is that it helps the individual to get ready for the next response.

On the debate of dopamine hypothesis, the lumpers, do not emphasize the heritability of these defects but maintain that the low frontal cortex dopamine secretion is hampered at the base of abnormal neural linkage. On the other side of the camp, splitters think of schizophrenia as the result of the unfortunate inheritance of three semi-independent genes. These genetic defects would then cause a cluster of symptoms, each gene being responsible for the separate symptom domains of schizophrenia (Kendle, 1994). According to the 16th Surgeon General of the United States, David Satcher (2000), the effects of genes in the causes and onset of mental illness, especially schizophrenia, bipolar disorder (manic depressive illness), depression, autism, attention-deficit/hyperactivity disorder, anorexia nervosa, panic disorder, and a number of other mental disorders are well understood (NIMH, 1998) because from studying the family history and from initial molecular analyses of the genomes of families, it is clear that heredity (genetic transfer) plays a considerable role in the transmission of vulnerability of mot of the mental disorders from generation to generation (Clarke et al, 2010; NIMH, 1998).

Judging from the diversity in research opinion, an absolute acceptance of the dopamine hypothesis will be foggy, especially as to its heritability position. It is important, therefore, to investigate and ascertain whether the dopamine receptor genes really carry heritable traits capable of replicating themselves in offspring or that they only make individuals predispose to

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1 In every classification or hypothesis, people are divided in groups or camps. Those classifiers who tend to find similarities between things and prefer to lump smaller groups into larger groups, and on the other hand those who tend to find differences and prefer to split larger groups into smaller groups. Generally speaking, sometimes the lumpers prevail and in another times the splitters.
the illness. Even if the dopamine receptor genes really carry heritable traits, do we know whether the affected chromosome-genes have the propensity to disrupt mechanisms of the neurotransmitters? Furthermore, claims made by the three schools of researchers must be examined to verify whether those claims are scientifically attainable and sustainable. First, the splitters strictly believe that schizophrenia runs in families. Second, the lumpers, believe that the irregularity or disruption of the neurochemical transmission might damage the neural pathways thereby resulting in poor reception of messages intended for their zones, which may not be necessarily as a result defective genes, but due to birth defects from prenatal malnutrition, complications, medications, illicit drug, infectious diseases, as well as neglect, abuses and traumas. For this reason, the ecovulnerability theorists hold a view contrary to the dopamine hypothesis and maintain that psychological, genetic, and ecological factors are responsible for the etiology of schizophrenia (Clarke et al, 2010).

Definition and scope

Schizophrenia is a severe psychopathology and psychotic disorder (Rosenzeig et al., 1999) that affects more than 50 million people worldwide (Mann, 1996, Berquier & Ashton, 1999). Schizophrenia comes in varieties of forms, symptoms, and severity that range from distorted and bizarre thought processes to psychomotor abnormality. Owing to its total and devastating impairment or breakdown in normal human functions, and the number of the world’s population affected, researchers are confronted with multiple questions about the nature of schizophrenia. Judging from the sporadic and recurring total loss of cognitive and motor controls, and often the incurable episodic nature of schizophrenia, many researchers have come up with the notion that this ailment is genetic. As a mental illness the affects thought processes and emotion, rather than “split-personality” or multiple personality, schizophrenia is distinguished from other serious mental illnesses by the presence of a multiple and an unusual array of positive and negative symptoms. Positive symptoms are characterized by the presence of the following signs and symptoms:

a) Thought disorder (loose associations, incoherent thoughts and speech)
b) Hallucinations (which can be auditory, visual)
c) Delusions (e.g., paranoia)
d) Bizarre behaviors (mania or irrational or excited motor activities).
e) Somatization (physical manifestation or compliant presented as a medical problem).

Negative symptoms, on the other hand, are characterized by the absence or lack of behaviors, such as emotion, speech, social interaction, and action, which include:
a) Avolition\(^2\) (general lack of desire, drive, or motivation to pursue meaningful goals),
b) Blunted or flat affect (a lack of emotional activity on the part of an individual
c) Alogia or poverty of speech (a general lack of additional, unprompted content seen in normal fluent speech).
d) Anhedonia (inability to experience pleasurable emotions from normally pleasurable life events such as eating, exercise, social interaction or sexual activities.

These symptoms are by no means concrete and exhaustive because there are varieties of other situations that change or alter how signs and symptoms of schizophrenia are expressed, which include, but are not limited to individuality, personalities, age at outset, gender, cultures, education, and even socioeconomic levels. In this case, it will be wrong to think that every schizophrenia follow systematically and chronologically all the aforementioned symptoms. For example, while addressing cultural variations in expressing symptoms, Ajaelu (2004) described the following signs and symptoms of schizophrenia as prevalent in Africa:

- Holding conversations with oneself or talking to and laughing with oneself (delusion)
- Formication or tactile hallucination (skin sensation as to insects crawling over or within the skin or seeing, hearing, feeling, touching smelling, tasting things that aren't there).
- Eating disorders (mostly non-discriminatory eating habits)
- Lethargy (mostly lack of energy, weakness, dizziness, light headedness)
- Restless thoughts
- Talkativeness
- Wandering (itinerancy)
- Sleeplessness,

According Ajaelu (2004), the significant and sometimes overwhelming disparity in diagnostic nomenclature between the symptoms expressed by Africans and the International Statistical and Classification of Diseases and Related Health Problems (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) commonly used by mental that clinician and researchers in

\[^2\] The avolition symptom, characterized by a general lack of desire, drive, or motivation to pursue meaningful goals, may appear in some cases as "apathy" (indifference, lack of concern, lethargy, or droopiness). Actually, some people with schizophrenia are highly motivated and pursue goal directed tasks. In this sense, avolition ("dysbulia" or "abulia, i.e. a lack of ability to turn desires or plans into active bodily motion) can be interpreted as a disconnection between mental reality and physical actualization. For example, patients with dysbolic or abulic symptoms cannot get their body to do what their "mind" commands. Furthermore, "apathy" or "amotivational" associated with schizophrenia can be as a result of avolition. In fact, depending on personality, culture, and socioeconomic levels, the signs and symptoms may drastically change from one patient to another.
Africa leads to misdiagnosis, poor scientific studies, and undertreatment. It was also discovered that about 75% of mental problems are reported as medical (somatization) problem and treated by medical doctors who are not skilled in psychosomatic illnesses. About 20% are expressed or reported as spiritual or demonic attacks and are treated by spiritual or traditional healers. In fact, only 0.3% of Africans use psychiatric treatment as their first choice of action. However, psychiatric treatment as a last resort, when medical, spiritual, and traditional healing did not work. This time, the family members or caregivers are overburdened and overwhelmed financially and emotionally and could not afford long-term psychiatric expenses as well as the “shame” and loss of opportunities such commitment would bring to the family (Ajaelu, 2004).

The globally, the median prevalence \( \frac{a}{a+b} \) where “a” is the number in the population with schizophrenia at a given time; “b” is the number in the population at risk of developing the disorder at a given time) of schizophrenia was 4.6/1,000 for point prevalence, 3.3/1,000 for period prevalence, 4.0 for lifetime prevalence, and 7.2 for lifetime morbid risk (McGrath, 2010; Bhugra, 2005). Demographically, Bhugra maintained that there is no remarkable prevalence rate between men and women, that is, men and women are equally affected (Bhugra, 2005), but McGrath (2005) rejected such findings and maintained that schizophrenia affects more boys than girls and for every five cases of schizophrenia diagnosed, three boys and two girls. The outliers in the above cited findings are unremarkable and therefore inconsequential to any conclusion that there isn’t much difference for genders. However, we much take notice of the differences in symptom onset because according to McGrath (Health Report, 2005) boys become symptomatic earlier than girls. Another area of interest is socioeconomic group, which also shows no remarkable differences across socioeconomic spectrum. Both low and high income persons as well as countries and cultures did show any significance differences (Bhugra, 2005). Even though schizophrenia has a low mortality rate (MaGarth et al, 2008), it known to have a very high disability-adjusted life year (DALY) and the fifth leading cause years lived with disability (YLD). For example, a research that included East Asia, Europe, Latin America, North Africa, and the Middle East indicated that, on average, only 15–20% of patients with schizophrenia were in paid employment while about 69% were living in dependent housing (Karagianis et al, 2009). In sub-Saharan Africa, about 94% of people with schizophrenia are homeless and live out of begging or eat out of garbage dumps.

The Dopamine Hypothesis of Schizophrenia

The dopamine hypothesis of schizophrenia or the dopamine hypothesis, perceived under a psychoneuroendocrinlogcial component, is a model that attributes the symptoms of schizophrenia (like psychoses) to psychiatric, neurobiological, endocrinological and neurological disturbances through single transduction or genetic disorder caused by abnormalities in genes or
chromosomes. This model is derived from the fact that a large number of antipsychotics have dopamine-receptor antagonistic effects, but the dopamine overabundance theory does not completely explain all the features of schizophrenia (Frederickson, 2010).

The most explicit studies made toward the heritability theory are through the families of persons with schizophrenia, especially with monozygotic (MZ) twins and dizygotic (DZ) twins. For example, Kendler (1983), vehemently believes that genes account for approximately 60-70% of the variance in transmission of schizophrenia. His claims, however, are based on his various studies of more than 800 MZ and 1000 DZ twins. In these studies, it was discovered that paranoid and schizotypal personality disorders are higher in relatives of schizophrenics (Kendler, 1995; Kety et al. 1994).

Apparently, one cannot hold firm to the accuracy of these studies if they are not entirely based on the presupposition that a gene that directs the production of the dopamine receptor (D2) is associated with schizophrenic episodes (Crowe, 1995, Nathan & Gorman, 1998). The reason is that since heredity involves the deoxyribonucleic acid (DNA) mapping, there should be a chronological connotation that vividly demonstrates that the so-called ruptured or damaged D2, is a result of DNA cloning from the parents. The DNA mapping or cloning effects, at this juncture, must not be confused with chromosomal developmental abnormality due to poor prenatal development. In 1987, however, researchers believed that they had finally found a gene responsible for major psychiatry disorders (schizophrenia). Chromosome 11 was identified. It was subsequently believed that this chromosome holds the genetic mapping that directs the production dopamine receptor (D2) (Carpenter, 1993). Dopamine receptor is found in abundance in the mesocortical and mesolimbic tracts. This tract has clinical importance in depression, mania, and schizophrenia. It is not surprising however, that D2 is linked with genes that are responsible for transmitting schizophrenia to offspring.

The concern in this regard is whether it is scientifically possible that children of schizophrenics can inherit the defective chromosome 11 that subsequently recycles itself in family history. If this is true, how can the ecological vulnerability (ecovulnerability) theory that upholds predisposition (episode implied, but not absolute) be reconciled with destined (episode is absolute) schizophrenic states? Ecologically, psychologists as well as biologists believe that environmental events can actually turn some genes related to memory, emotion, learning on or off within seconds (Hedaya, 1996). Is it possible then to conclude that during mutation, environmental factors disrupt or distort the normal developmental process, thereby resulting to a defective chromosome? Resolutions of these thought-provoking questions are at the center of this paper. First let us to understand what genetic transfer or heritability means.
1) Methods of Accounting for Heredity and Genetics.

Conventional wisdom has been that problems with exact phenotyping will always make GWA studies difficult for mental disorders (Craddock et al, 2010; Gunter, 2009). Behavioral geneticists, in their efforts to study human heredity and genetics, typically yield to statistical estimates of the total variance in a trait that is attributable to genetic variation within a group. With this method, the definition of heritability rotates around the statistical estimate of the proportion of the total variance in some trait within a group that is attributable to genetic differences among individuals within the group (Tavris & Wade, 1997). Even though heredity and genetics are connected, it must be understood also that the two do not mean the same thing. In order to explain the difference, this topic will be discussed under the following concepts: a) Biochemical b) Ecological Vulnerability (ecovulnerability), and c) Genetic analysis of the dopamine receptor gene.

a) Biochemical Concept of Human heritability

The genetic traits in each individual are located on chromosomes, which consist of strands of deoxyribonucleic acid (DNA). During intercourse, the male’s sperm, which contains 23 chromosomes, is deposited with the possibility that it will encounter the female ovum, which also contains 23 chromosomes. The unity of mating results in one fertilized egg with a total number of 46 chromosomes. Except the chromosomes, which determine a person’s anatomical sex characterization (YX for male and XX for female), the others, called genomes, are responsible for the expression of particular traits or characteristics in the individual person. The DNA houses thousands of genes that content the specifications and characteristics of each couple. The major function of DNA is to transfer genetic characters, by way of coded instruction, from parents to the embryo. The genes, therefore, are the basic units of heredity. Within each gene, the sequence of four molecules, called bases, constitute a basic chemical code that helps determine the synthesis of a particular protein by specifying the sequence of amino acids.

Research experiences have shown that the transfer of genetic characters from parent to offspring does not always follow a mathematical or logical sequence. It cannot be said that because this couple is tall, their offspring will be tall. Most human traits, even those that are seemingly straightforward such as height and eye color, depend on more than one gene pair. This situation makes it complicated to track down the genetic factors responsible for any behavioral character in an offspring. One method being used to search for genes associated with mental disorders, involves Linkage studies. These studies take advantage of the tendency for some genes in close proximity on a chromosome to be inherited together across the generations. The researchers started out by looking for markers. DNA segments vary considerably among individuals and
those locations on the chromosomes are already known. They then look for patterns of inheritance of these markers in large families in which a particular condition is common.

If a marker tends to exist in individuals who have a certain condition and is absent in those who don’t have the condition, then the variant of the gene involved in the condition is apt to be located nearby on the chromosome. The researchers have some idea then where to search for it. For example, this method of linkage studies was used to locate the gene that causes Huntington’s disease. This break through in neurogenetics stirred up the added conviction among neuropsychologists that there could be a possible neurological explanation for the causes of schizophrenia. In the case of Huntington’s disease (the neurological disorder said to have killed Woody Guthrie) only one gene is responsible, yet the research took a decade of painstaking work. Then consider that schizophrenia has several genes involved.

The complexity of the human genome makes it difficult to claim “absolute” genetic heritability of schizophrenia. Even though science understands why individuals bear characteristic resemblances with their parents, it is obvious that “each of us, with the exception of identical twins, is a unique genetic mosaic, one that never existed before and never will again” (Tavris & Wade, 1997, p.88). To explain each person’s genetic uniqueness, Tavris and Wade maintain that chromosomal replication, division (meiosis and mitosis), and mutation drastically and spontaneously alter genetic codification. The result is that children who share everything with their biological parents can be quite unlike their parents-in purely genetic terms (1997). Can the same theory apply to the heritability of schizophrenia?

b) Ecological Vulnerability theory

The supporters of the vulnerability theory are in the midway between the biological etiology (lumpers), genetic etiology (splitter), and behavioral etiology. They seem to acknowledge neuropsychological and genetic presence in the causes of schizophrenic episode, but they reject the view of schizophrenia as a persistent, progressive chronic disorder leading to complete deterioration of personality (Clarke, 2010; Craddock et al, 2010). They believe that the heritability of the schizophrenic traits do not automatically result to the episode (state), but makes the individual more vulnerable than the person without the genetic traits. The vulnerable individuals who are not subjected to high magnitude stresses and strains, or who learned to adjust properly to situations, may not experience any episode even though their parents did. Supporters of the vulnerability theory further hold that the persistent chronic episode found in the majority of the sufferers is chiefly a result of iatrogenic (wrong treatment method and hospitalization) and ecogenic (noxious and impoverishing environment) circumstances rather than of the natural consequence of the disorder itself. It must be remembered that the iatrogenic and ecogenic effect
on the individual may start immediately after conception. This is why Hedaya maintains that environment and genes share each other, and each can actually influence the other at any given time (1996). Danie Freedman (1975) replicated the idea when he stated that schizophrenia and other major disorders involve a variety of environmental stressors acting on genetic or other biological vulnerability.

Vulnerability theorists have proposed a number of models for the explanation of the causes and persistent nature of schizophrenia. These models range from molecular-biological model (psychogenetic model) to a field-theory model (influenced by ecological factors). They are based on the phenomenological concept that the actual etiology of schizophrenia is concomitant and interwoven in such a way that the network of human neurobiogenetics and ecology are in interplay.

Figure 1: The scientific model of etiology of Schizophrenia (or the 'stress-vulnerability' model)
The above diagram projects the basic concept that no one element is solely responsible for the causes of schizophrenia. Rather genetic trait, developmental abnormality, internal environmental status, and neurophysiological implications intermingle to cause schizophrenia. The progenitors of genetic models believe that what an individual inherits from parents is predisposition to “episode” rather than a “trait”. (Zubin, 1975). No one is born with schizophrenic trait, not even the monozygotic twins, but one can inherit defective genes which puts the individual on the edge. Therefore, such a person is not destined to suffer the ailment if every other condition is kept under control.

If an individual had a schizophrenic genetic trait, prenatal complications, nutritional problem, and lagged maturational development (Gottesman, Aston, and Moldin, 1999), he or she stands a greater chance of becoming schizophrenic than the same sibling who had normal developmental processes (Kety et al., 1994). Since monozygotic twins share equally in these areas of human development, their affectability should be counted as a developmental factor rather than inheritability (Thapar A. Holmes et al., 1999). Researchers also indicate a higher risk of schizophrenia for individuals born with cerebral injury but with no known history of schizophrenia in their families.

The internal environment model has been the most controversial concept among ecovulnerability theorists, and it has stimulated the search for biochemical abnormalities in schizophrenia. The quest, however, to study schizophrenia from the network of the central nervous system (CNS) started as early as the 1940s. More than ever, research recently shifted to the metabolic actions of the synaptic mechanisms which recognizes the presence and the possibilities of chemical imbalances in metabolic processes, hormonal distributions, and drugs, and their affects in the psychological function they mediate (Kety, et al, 1994). Kety and his colleagues believe that the psychological processes, which are mediated through biochemical reactions of the synapses control the individual’s power of perception, cognition, attention, motivation, mood, and other emotional and mental states. The impairment of synaptic metabolism may affect the emotional ability of individuals, which can be complicated by other factors, like iatrogenic factor and ecology.

c) Genetic analysis of dopamine receptor gene

While family, twin, and adoption studies suggest that genetic factors play a major role in the etiology of schizophrenia, the mode of genetic transmission remains clouded and uncertain. Researchers have maintained that the complex traits of schizophrenia are probably represented by more than one locus in the human genome. Many investigators have based their findings in numerous factors, which focus on DNA, gene mapping technique, and the dopaminergic system (Rice, 2008). According to the research of Gureje and colleagues, Thirty-six consecutively
admitted patients with schizophrenia and 20 with mania were studied for the morbid risk of psychosis in their first-degree relatives. Using the family history method of ascertainment, the morbid risk for schizophrenia in the relatives of schizophrenic probands was 4.12% compared with 1.42% in the relatives of manic probands. While this difference was not statistically significant, that between the morbid risk for affective psychoses in the relatives of manic patients (7.81%) was significantly higher than for the relatives of schizophrenic patients (0%).

All genetic variations originate from a change in DNA sequence called mutation. A large number of agents in our environment are known to cause mutations, which include ionizing radiation and many other different chemical reactions. However, mutations can occur spontaneously during the process of DNA replication. The differing DNA sequences of a gene are called “alleles”. If an individual has the same alleles on both members of a chromosome pair (from both parents), he or she is said to be a homozygote. Difference in alleles of DNA sequence, however, means that the individual is heterozygote. It is known that many of the different physical characteristics, such as height, skin and eye color, are determined by genetic variations. Some of the genetic variations are inconsequential while others cause diseases.

A number of laboratory techniques have been employed to determine gene variation that causes schizophrenia. For example, protein electrophoresis, which recognizes differences in proteins on the basis of their electrical charges, has been used to determine amino acid variation in human beings. This method has been rejected because it cannot detect all the variations in the amino acid sequences.

A new deoxyribonucleic acid (DNA) based research method, which detects amino acid variations at DNA level has been recognized by many geneticists. This technique, known as Restriction Fragment Length Polymorphism (RFLP), is developed from the availability of large number of bacterial enzymes which cleave or cut DNA at the specific recognized sites known as restriction or recognized sites (Asherson, P. Curran, S., McGuffin, P., 1999)

Using this technique, many studies have been made of schizophrenic-gene replication. Bruce Bower reported investigation of more than 100 families that suggests a gene located on chromosome 13, which contributes to at least some cases of schizophrenia that usually appears at younger ages (1998). A specific sequence on chromosome 8 also shows signs of boosting susceptibility to schizophrenia for some people who possess the signature sequence on chromosome 13 (Bower, 1998). The genetic epidemiologist, Ann Pulver, maintains that what is exciting is that we have the first evidence to support the theory that different sets of genes can create a susceptibility to schizophrenia. Earlier efforts to locate susceptibility of schizophrenia have had mixed results. Some evidence indicates that an unidentified gene on chromosome 6 contributes to disorganized thinking, delusions, and hallucination typical of this mental ailment.
In order to support their views, researchers have used DNA blood samples of those diagnosed with schizophrenia and members of their extended families. The studies reflect a genetic link was found in areas of chromosomes 13 and 8 in both the individuals diagnosed with schizophrenia and in their families. A genetic link found only in chromosome 13 characterized families in which several members had mood disorder, as well as hallucinations and delusions. In similar research, Sevilla Detera-Wadleigh of the National Institute of Mental Health in Bethesda, Maryland is believed to have found the same chromosome 13 sequence in family members of individuals diagnosed with bipolar disorder, or manic depression. This finding argues that if heritability is composed of DNA traits, the gene on chromosome 13 can inherited and can increase the likelihood of schizophrenia in the offspring of those suffering the ailment. This finding has been challenged because of its lack of precision and because of limited access to other areas of great importance in determining heritability.

Molecular biologists have resorted to the “gene mapping technique” to study genes-chromosome interplay and heritability. These techniques are used widely in the study of CNS structure and function. The methods permit investigation of different proteins, step by step, from gene transcription to the post-transcriptional processes. They are being applied also in the investigation of enzymes responsible for the synthesis of neurotransmitters and receptors.

Furthermore, Seaman et al (1994) studied the dopamine D4 receptor gene in a group of schizophrenia and control subjects. These studies are carried out in order to determine the frequency of the dopamine receptor gene variants in which serine or glycine substitutions have occurred. When administered with glycine substitutions, 23 out 183 control, representing 12.6% of the population, and three out 24 schizophrenia, representing 12.3% revealed a replacement of thiamine by guanine. The identical prevalence of this variant between two groups indicates that the variant is not associated with schizophrenia. This variant, however, was found only in black subjects, but none of the 147 Caucasians (113 controls and 34 schizophrenics) revealed this variant.

Concentrations of serine and glycine in the cerebrospinal fluid (CSF) and plasma have shown some evidence of the genetic control of these amino acid variations. cerebrospinal fluid levels of several amino acids showed a similar pattern in a twin sample (Hagenfeldt et el 1998). Devor and waziri (1993) reported significant genetic control of plasma concentrations of serine and glycine in 28 nuclear families with 108 members . The authors suggested that the control of the plasma concentration was carried out via single major gene locus and the glycine metabolizing enzymes, SHMT, was a likely candidate for this single gene locus.

2) Balancing the Dopamine hypothesis Debates
The dopamine hypothesis states that schizophrenia is caused by functional hyperactivity of the dopaminergic system in the brain. This hypothesis accounts for all the aberrations that occur in the synthesis, release, reuptake, and metabolism of dopamine, and changes in the dopamine receptors throughout the CNS. They will be discussed under the following sequence:

a). The Biochemical activities of Dopamine.

Dopamine is one of the neurotransmitters. Neurotransmitters, on the other hand, are electrochemical substances released from pre-synaptic axonal terminals into the post-synaptic receptor (Crow, et al 1979). The neurotransmitter that will occupy us here is the catecholamines that are released in the form of epinephrine, norepinephrine, and dopamine (Friedhoff et al., 1977). The calcium ion plays an important role in the release and responses of the transmitters. Irregularities in calcium ion may delay the arrival of action potential and the opening of the Ca+ + gates to allow the entry of the Ca+ + into the pre-synaptic terminal (Gomes, 1980). On the other side of the neurotransmitter are the receptors or post-synaptic terminal. They are the constituents of cells that have the ability to recognize a neurotransmitter, neuropeptide (kety et al., 1994), hormones, and other chemical substances.

In neurons that localize dopamine (DA) as their transmitter, the biogenic amino synthetic pathways stored with Dopa decarboxylase, the enzyme that synthesizes DA. DA acts on two types of receptors, both of which are linked to adenylate cyclase- cAMP second messenger systems (crowe, 1995). Investigators have identified several subtypes of DA receptors that are categorized as D1, D2, D3, D4, and D5. This categorization follows the order of their discovery (Rosenzenweig et al., 1999). With the exception of D1 and D5, all other DA receptors, D2, D3, and D4 share the same properties and are similar to each other. However, the stimulation of D1 receptors causes an increase in cAMP levels, whereas stimulation of D2 receptors decreases the cAMP (Nader et al., 1997). There are also autoreceptors on the presynaptic terminal, which are thought to exert an inhibitory feedback effect on the DA neuron. Dopaminergic synapses have been of great interest because of the evidence that antipsychotic drugs that are effective in alleviating the symptoms of schizophrenia have the common effect of interfering with transmission at the dopaminergic synapse in the brain (Rosenzweig et el., 1999).

Recent research studies indicate that the primary mode of operation of antipsychotic drugs is to bind to, and block, the D2 receptors. In contrast to these blocking actions of antipsychotic drugs, it is known that drugs that are DA agonists such as amphetamine, that enhance or mimic the actions of DA, can induce schizophrenia-like behavior. It has been tempting therefore to believe that schizophrenia is due to hyperactivity of the DA neuron in the brain. But how this
hyperactivity of the DA can be a transmitter to a generation of siblings is yet to be cleared (Schneider & Tarshis, 1987).

The molecular mechanism, activities, and metabolism of the dopaminergic synapses can be explained as follows: The synthesis of the enzymatic pathway starts with the action of tyrosine (Tyr). The Tyr catalyzed and converted to dihydroxyphenylalanine (DOPA). The DOPA is transported and stored within the neural network as dopamine (DA). Storage of DA is blocked and inhibited by the actions of reserpine (Res). DA is released by the actions of exocytosis. During the onward transmission from pre-synapses to receptors or post-synapses, the DA binds itself to D1 receptor, acting through stimulatory G protein (G2) to increase the level of CAMP, or binds with D2 receptor, acting through inhibitory G protein to lower levels of CAMP. Most of the antipsychotic medications/drugs, such as butyrophenones, block the action of the D2 receptor.

Argument from D2 receptor

Many eminent researchers have come to the gripping that the mere fact that the D2 receptors have been identified as the cause of schizophrenia does not give the whole picture of the origin or etiology of this ailment. Keeping in mind that several factors can upset the chemical activities of the D2 receptors leading to the increase of the cAMP, we are not yet satisfied that the D2 receptor gene can be inherited. On this topic we will try to know how much the individual can inherit from the defective D2 receptor genes. In medicine, for example, the type of diabetes in which the receptors do not recognize the presence of insulin has been linked to genetic trait, which is inheritable.

The introduction of both RFLPs and VNTRs, and PCR are geared toward the determination and accessibility of the genetic variation at DNA levels (Yang et al., 1993, Saha, et al., 1994, Sokoloff et al 1992). The linkage analysis makes it possible to determine the location of genes on chromosomes. Most of these techniques are used to determine the “association” levels between the two different alleles. The term “association” in genetics refers to a statistical relationship between two traits, which may or may not be genetic or heritable. However, when two gene loci, one allele of a marker and the other one of a disease gene, are located close to each other on the same chromosome, the two are transmitted together within the family (A.J. Publisher, 1998). All the dopamine receptors subtypes (D1-D5) have been cloned and each of the genes of the dopamine receptors have been found to have a number of mutations. The ongoing studies in this direction are to determine whether the occurrence of these mutations has something to do with the cause of schizophrenia. The results are still controversial in some areas because most of the studies report no significant differences between the schizophrenic and the normal population.
with regard to the occurrence of dopamine receptor gene mutation (Sunahara et al 1991, Sobel et al., 1995).

Similarly, genes for enzymes tyrosine hydroxylase and COMT have been identified and localized (Rao et al 1994, Daniel et al 1996). Mutations in these genes do not appear to be associated with schizophrenia. It is of great interest to note that the recent effort to determine the genetics of schizophrenia have produced spectacular results from hundreds of family populations all over the world (Sedvall et al 1995, Sedvall and Farde, 1995). Several studies involved in this effort have agreed that a region on the short arm of chromosome 6 appears to be associated with schizophrenia. Although even this area of chromosome 6 is fairly large and contains about 700 genes, none of the dopamine receptor genes (1-5) have been known to occur in this region (Malmberg et al 1993).

Conclusion

It has long been known that schizophrenia runs in families. People who have a close relative with schizophrenia are more likely to develop the disorder than are people who have no relatives with the illness. For example, a monozygotic (identical) twin of a person with schizophrenia has the highest risk—40 to 50 percent—of developing the illness. A child whose parent has schizophrenia has about a 10 percent chance. By comparison, the risk of schizophrenia in the general population is about 1 percent.

Scientists are studying genetic factors in schizophrenia. It appears likely that multiple genes are involved in creating a predisposition to develop the disorder. In addition, factors such as prenatal difficulties like intrauterine starvation or viral infections, perinatal complications, and various nonspecific stressors, seem to influence the development of schizophrenia. However, it is not yet understood how the genetic predisposition is transmitted, and it cannot yet be accurately predicted whether a given person will or will not develop the disorder.

Several regions of the human genome are being investigated to identify genes that may confer susceptibility for schizophrenia. The strongest evidence to date leads to chromosomes 13 and 6 but remains unconfirmed. Identification of specific genes involved in the development of schizophrenia will provide important clues into what goes wrong in the brain to produce and sustain the illness and will guide the development of new and better treatments. To learn more about the genetic basis for schizophrenia, the NIMH has established a Schizophrenia Genetics Initiative that is gathering data from a large number of families of people with the illness.

That there is a genetic vulnerability to schizophrenia is not a controversy for a variety of reasons. It has been shown that sibling schizophrenic patients have been at increased risk of the disorder
only when they are biological siblings, not adopted. What this genetic vulnerability is, of course, is not known, as no single gene has been identified as a risk factor for schizophrenia. That the gene or genes involved interact with some environmental factor is clear since identical twins share the disorder only about 50% of the time. According to Schwartz and Africa (1988), an individual has an 8% risk of schizophrenia if his or her sibling is schizophrenic, a 12% risk if one parent is affected, a 14% risk of sharing the disorder with a fraternal twin, a 38% risk if both parents are affected, and a 47% risk when two individuals share the same exact genes.

In real life experience, these figures can vary extensively, giving the individual the course to think that the vulnerability theory rather than strict biological inheritability is more attainable than the notion that schizophrenia is inherited.

- twins reared apart are not assigned at random to foster or adoptive parents - since homes are selected purposely to with regard to characteristics of the child and characteristics of the family. This would partially account for the IQ correlations attributed to inheritance

- twin studies may not be generalizable to the population at large as twins are more susceptible to prenatal trauma leading to retardation. The inclusion of retarded cases may increase the twin correlation in intelligence test scores. Heritability indexes refer to the population on which they were found at the time and is not applicable to an analysis of test performance between two population groups e.g. ethnic groups.

- heritability does not indicate the degree to which a trait can be modified e.g. even if the heritability of a trait, like intelligence were found to be 100% it wouldn’t mean it couldn’t be modified. (Anastasi & Urbina, 1997).

Nevertheless, “no single gene has yet been isolated and identified for any psychiatric condition”(Hedaya, 1996, p.39). Notwithstanding this limitation, both neuroscientists and psychiatry researchers have continued to fuel the notion that heritability is a prime factor in the etiology of schizophrenia (McGuffin, 1995).
References


