The Origin of Schizophrenia: Genetic Thesis, Epigenetic Antithesis, and Resolving Synthesis

Arturas Petronis

Traditionally, it has been thought that schizophrenia results from the interaction of predisposing genes and hazardous environmental factors. In this article, the paradigm of "genes plus environment" is challenged, and a new interpretation is presented, in which the emphasis on DNA sequence variation is shared with epigenetic misregulation as a critical etiopathogenic factor. Partial epigenetic stability (metastability) of gene regulation is consistent with various nonmendelian irregularities of schizophrenia, such as the presence of clinically indistinguishable sporadic and familial cases, discordance of monozygotic twins, coincidence of peaks of susceptibility with major endocrine rearrangements, and fluctuating course of disease severity, among others. It is also suggested that stochastic epigenetic events might account for a substantial portion of phenotypic variance, which traditionally has been ascribed to environmental effects. This theoretic essay is constructed according to the principle of Hegelian dialectic reasoning (thesis–antithesis–synthesis), which serves the goal of showing that the best outcome of molecular genetic studies in schizophrenia (and perhaps other complex diseases) can be expected when components that effect chromatin structure and gene regulation are taken into account and investigated comprehensively.

Key Words: Schizophrenia, epigenetics, DNA, complex trait, twins, paradigm

Over the last half century, psychiatric research has undergone a major paradigmatic shift. In the 1950s and 1960s, psychiatric literature was full of articles suggesting that the causes of psychosis were related to, for example, complicated id–ego–superego interactions, ego weakness, regression, and disturbed mother–child relationships. Several decades later, genetic developments started dominating the field as twin and adoption studies consistently demonstrated that hereditary factors play a very important role in major psychosis. More specifically, monozygotic (MZ) twins exhibited a significantly higher concordance rate for psychosis compared with dizygotic ones, and the risk for the disease did not decrease if a child born to a parent affected with schizophrenia was raised in a healthy family. Since then, a typical article investigating etiologic factors in major psychosis usually begins with a statement that twin, family, and adoption studies have unequivocally proven the primary role of hereditary factors in schizophrenia and bipolar disorder. The same applies to autism, major depression, and attention-deficit/hyperactivity disorder, among many other psychiatric disorders. The citation index for Gottesman's books pertaining to the genetics of schizophrenia (Gottesman 1991; Gottesman and Shields 1982) is now counted by thousands. Evidence for genetic predisposition was immediately linked to deoxyribonucleic acid (DNA) structure, the main biological discovery of the 20th century. The four nucleotide–based macromolecule became the center in molecular studies of psychiatric (as well as somatic) diseases. Deoxyribonucleic acid sequences and sequence variation (polymorphisms) across individuals became the key element of human genetics textbooks. The phrase from Vogel and Motulsky's *Human Genetics: Problems and Approaches,* "Our goal is to trace genetic differences to the DNA level" (Vogel and Motulsky 1997) represents the *Zeitgeist* of human morbid biology of the last decades. The expectation is that identification of disease-specific DNA polymorphisms and mutations will revolutionize medicine and lead to new diagnostic, treatment, and prophylactic strategies. Governmental and privately funded multimillion dollar human genome projects would have not been such a major priority if not for the putative relevance to the elucidation of the primary causes of common complex diseases.

Thesis: Schizophrenia = Predisposing DNA Sequences + Hazardous Environment

Predisposing DNA sequence variants of some specific genes, however, are not considered to be the only cause of mental dysfunction. In complex diseases, MZ twins (who by definition carry the same DNA sequences) exhibit far from full concordance, and MZ concordance for schizophrenia is 41%–65% (Cardno and Gottesman 2000). Phenotypic discordance in MZ twins has traditionally been interpreted as the evidence of the role of hazardous environment. Even slightly different environments should affect the co-twins differently, and therefore such environments are called "non-shared" (Plomin and Daniels 1987). Although psychodynamic factors are still entertained, thinking regarding environmental effects shifted from the psychological to the biological pole and now deals primarily with such factors as infectious agents and birth seasonality (Torrey et al 1997), adverse events during the mother's pregnancy, prenatal and postnatal development, nutritional factors, and drug abuse, among others (Tsuang et al 2001). Because it is very difficult to uncover the specific impact of a myriad of environmental events on human brain and behavior, it has been generally accepted that it is easier to investigate several dozen genes and genomic loci than the elusive environmental factors. Hence, thus far, molecular genetic research has dominated the field of psychiatric research.

The original genetic strategies that were developed for simple mendelian disorders, such as cystic fibrosis, Huntington disease, and Duchenne muscular dystrophy, have turned out to not be very productive in schizophrenia, bipolar disorder, and autism, as well as in numerous other complex diseases (diabetes, cancer, multiple sclerosis, and asthma, among others). Southern blot hybridization–based genotypings using restriction fragment length polymorphisms and the classic Morton linkage algorithm (which were sufficient for cloning the genes in simple mendelian diseases) have failed to produce meaningful results in complex diseases, and a number of new research strategies and ap-

From The Krembil Family Epigenetics Laboratory, Center of Addiction and Mental Health, and University of Toronto, Toronto, Ontario, Canada.

Address reprint requests to Arturas Petronis, M.D., Ph.D., The Krembil Family Epigenetics Laboratory, Center of Addiction and Mental Health, 250 College Street, Toronto, Ontario M5T 1R8, Canada.

Received June 11, 2003; revised January 28, 2004; accepted February 3, 2004.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2004.02.005

proaches have been developed. A prominent figure in genetics of the last century, Sir Ronald Fisher (geneticist and statistician who demonstrated at the beginning of 20th century that mendelism and biometry are not contradictory theories), once wrote that fashions in science are subject to rapid changes. This well applies to the genetics of complex traits. Parametric linkage analyses have been nearly completely replaced by nonparametric ones, whereas in genetic association studies the case–control design (which provides the best power) still competes with the family-based one (which is the most robust in terms of genetic stratification–related artifacts). In the case–control studies, a new "height of fashion" is genomic controls, which are advantageous compared with demographic ones. In terms of molecular genetic markers, a decade ago, single nucleotide polymorphisms (SNPs) were "pushed out" by the repetitive DNA elements–based microsatellites, but now SNPs are back on stage again. Alleles (single nucleotide variants) are thought to be of low informativeness, however, and some editors have already announced that only haplotype-based genetic studies will be considered for publication (Licinio 2003). There are also substantial changes in the conceptualization of the phenotypes that would be most suitable and productive in genetic analyses. Clinical phenotypes are thought to be too complex and too far from the primary genetic cause. Therefore, endophenotypes (biochemical, physiologic, or other measurable equivalents of a disease) (Gottesman and Gould 2003) and subphenotypes (some specific aspect of the clinical phenotype, e.g., depression with and without suicide attempt) are becoming more popular. Developments in statistical genetics have led to a myriad of new methods, a good understanding of which requires a university degree in mathematics or a related field. All the above aspects of genetic research have been subjects of heated debates, and geneticists cannot reach consensus as to the best methods, strategies, designs, markers, and samples (e.g., Terwilliger et al 2002; Weiss and Terwilliger 2000). What has never been questioned, however, is the key role of DNA. Deoxyribonucleic acid sequence variation remains the central element of the current paradigm of human morbid genetics.

The next section argues that, in addition to DNA sequence variation, other components of the chromosome might be of major importance. Phenomenologic evidence for a hereditary component in the disease might not necessarily imply the primary role of DNA sequence variation; other nuclear factors might be operating. In addition, the idea of quite a substantial contribution of hazardous environmental factors will be critically evaluated.

Antithesis: Schizophrenia = Epimutations + Stochasticity

Chromosomes are much more than just naked DNA. Chromosomes consist of DNA sequences that are wrapped around the histone complex, which forms the nucleosomal structure of chromatin. Each nucleosome is made of approximately 150 base pairs of DNA associated with a histone octamer, composed of a pair of each of the core histones: H2A, H2B, H3, and H4. Although for a long time it was thought that nucleosomal proteins provided just a static DNA packaging device, it is now becoming clear that histones, through the number of chemical modifications, play a very active role in remodeling chromatin structure and regulation of gene activity (Jenuwein and Allis 2001). The functional state of a specific segment of a chromosome is determined by acetylation, methylation, phosphorylation, ubiquitination, and ribosylation of residues of amino acids on the histone tails (Jenuwein and Allis 2001). The DNA sequence itself can also be modified through cytosine methylation (Figure 1) (for the sake of simplicity, only DNA methylation will be used in figures to illustrate various aspects of epigenetics). Functional states of histones and DNA have a direct effect on gene activity, as well as on other functions of a chromosome (e.g., recombination, segregation, mutagenesis) that determine functional and morphologic peculiarities of a cell. Such modifications are called epigenetic (prefix "epi" indicates "beyond," "above"), and by definition, epigenetics refers to regulation of various genomic functions that are controlled by heritable but potentially reversible changes in DNA methylation and/or chromatin structure (Henikoff and Matzke 1997). The primary role of epigenetic factors in the regulation of gene activity makes epigenetics a major topic of interest in understanding pathologic events originating from the cell nucleus (Jaenisch and Bird 2003). DNA sequences, even if they are impeccable, have to be organized in a way that provides the optimal expression of the required genes in a specific cell. Misregulation of gene activity can be as detrimental to a cell as mutant DNA sequences resulting in dysfunctional proteins: the effects of insufficient or excessive amounts of a structurally perfect protein might be as dangerous as those of a mutant protein (Petronis 2001; Robertson and Wolffe 2000).

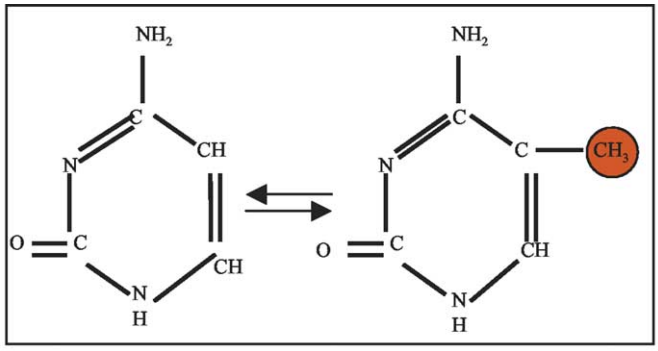

Figure 1. DNA methylation. Cytosines can be either unmethylated (left) or methylated (right).

Epigenetic signals in the somatic cells are inherited during mitotic divisions of cells, and this process is called an epigenetic inheritance system (Maynard Smith 1990). It has been generally thought, however, that during gametogenesis, epigenetic modifications are erased and reset de novo, and therefore epigenetic marks cannot be transmitted from one generation to another. There is now an increasing body of evidence suggesting that epigenetic marks of at least some mammalian genes are not completely erased during meiosis and therefore can be transmitted from one generation to another (Rakyan et al 2001). A dozen genomic loci that exhibit evidence for epigenetic meiotic stability determine a wide variety of phenotypic traits, from coat color to neural tube defects to piebald spotting (Rakyan et al 2002). Transgenerational epigenetic inheritance is quite different from the DNA sequence–based inheritance, however, because the former exhibits a substantially lower degree of stability compared with the latter. Unlike DNA sequences, which usually remain stable throughout the lifetime of an organism, epigenetic modifications can be subjected to quite substantial changes during meiosis, which results in numerous quantitative phenotypic differences in the offspring compared with the parents. Partial stability of epigenetic regulation, or metastability, also

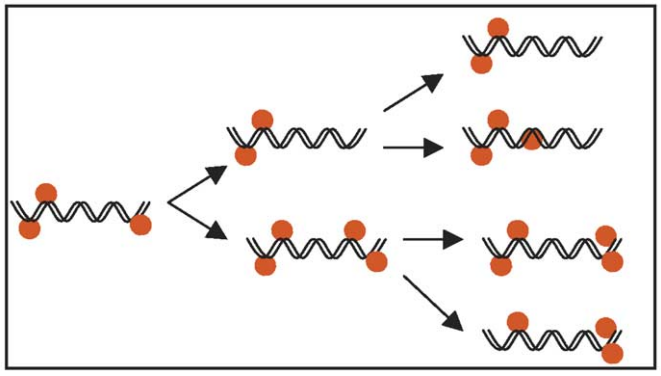

Figure 2. Partial stability, or metastability, of epigenetic factors. Some methyl groups (red circles) might by lost, or de novo methylation might occur, which results in different epigenotypes in the cells with identical genotypes.

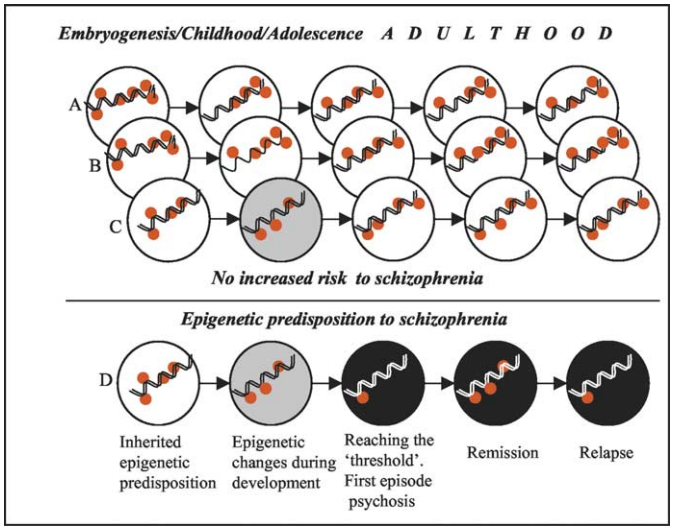

Figure 3. Epigenetic changes during development. Epigenetic status of a gene changes under the influence of various factors: cell differentiation, intra- and extracellular environment, age effects, and stochastic factors. Scenarios **A**, **B**, and **C** demonstrate normal epigenetic development of a hypothetical gene that potentially might predispose to schizophrenia (white circles: healthy individuals; gray circles: borderline psychological abnormalities). Scenario **D** illustrates how a pre-epimutation converts into a serious epigenetic problem, which results in psychosis (black circles). Note that despite an identical starting point, epigenetic developments in **C** and **D** were very different, as were clinical outcomes.

applies to somatic cells, and the daughter chromosomes do not necessarily carry exactly the same epigenetic patterns as the parental chromosomes (reviewed in Rakyan et al 2002; Riggs et al 1998) (Figure 2). Epigenetic regulation of a gene is a dynamic system, and the inherited epigenetic status of a gene is modified by various factors: parental origin, developmental programs (that likely include cell and tissue differentiation) and aging, intra- and extracellular environment (including hormones), and stochastic fluctuations in the nucleus (reviewed in Petronis 2001).

Although thus far there is no direct experimental evidence that epigenetic factors are involved in schizophrenia, shifting the emphasis from DNA sequence variation to epigenetic misregulation may provide a cohesive explanation of various nonmendelian features of this disease and a new theoretic framework for experimental approaches. From the epigenetic standpoint, schizophrenia could be imagined as the result of a chain of unfavorable epigenetic events that begins with a primary epigenetic defect, or pre-epimutation, that occurs in the germline during the error-prone epigenetic reprogramming process (Jablonka and Lamb 1995). Pre-epimutation increases the risk for the disease but, unlike the deterministic DNA mutations in mendelian disorders, a pre-epimutation does not necessarily indicate that the disease is inevitable. Such pre-epimutations might not cause any clinical problems for decades, although they might result in various minor cytoarchitectural changes in brain development and lead to barely detectable neuropsychological aberrations in childhood. Pre-epimutations are subject to further changes during embryogenesis, childhood, and adolescence owing to multidirectional effects of tissue differentiation, stochastic factors, hormones, and probably some external environmental factors (e.g., nutrition, medications, and addictions) (Jaenisch and Bird 2003; Sutherland and Costa 2003) (Figure 3). The peaks of susceptibility to schizophrenia seem to follow the major changes in endocrine homeostasis: late adolescence and early adulthood for both sexes, late forties in women, and the sixth decade in both sexes again, which suggests that hormonal changes might play a significant role in the further dynamics of an inherited epigenetic defect (reviewed in Petronis 2001). The phenotypic outcome depends on the overall effect of the series of pre- and postnatal impacts on pre-epimutation. Only some predisposed individuals will reach the "threshold" of epigenetic misregulation that presents with clinical schizophrenia. Severity of epigenetic misregulation might fluctuate over time, which in clinical terms is treated as remissions and relapses. In addition to its intensity, the spectrum of psychopathology might also vary in the same patients (e.g., delusions and hallucinations might be substituted by predominantly negative symptoms). In aging patients, epimutations might start slowly regressing back to the norm, and this would be seen as fading psychopathology or even partial recovery. The advantages of the epigenetic scenario of schizophrenia, compared with the DNA sequence–based model, is that the former is consistent with long years of ostensible mental health, critical susceptibility periods, fluctuating course, and even clinical improvement after decades of the patient being affected by this debilitating disease.

The meiotic metastability of epimutations allows for rethinking the issue of familiality and sporadicity in schizophrenia. A good illustration of intergenerational epigenetic metastability is shown by the transgene locus *TKZ751* in mice (Allen et al 1990). Depending on the strain of the nontransgenic parent mated with a mouse carrying the transgene, the degree of DNA methylation increased or decreased in the F_1, F_2, and F_3 offspring. Specifically, the transgene locus completely lost methylation in several generations when the transgenic mouse was mated to DBA/2 mice but became fully methylated in the BALB/c background. Furthermore, DNA methylation correlated with decreasing expression of the transgene across generations and spread by 6–10 kilobases with each subsequent generation (Allen et al 1990). In a similar way, some schizophrenia epimutations might regress toward the norm in the germline of a schizophrenic patient, and his/her offspring will not be affected (Figure 4A). Conversely, other epimutations might persist across generations and become even more pathogenic. Such meiotically persistent and progressing epimutations result in increasing clinical severity and earlier age of onset, which is characteristic of genetic anticipation (Figure 4B). It is not clear why some epimutations can be corrected during meiosis and others cannot. On the basis of mice

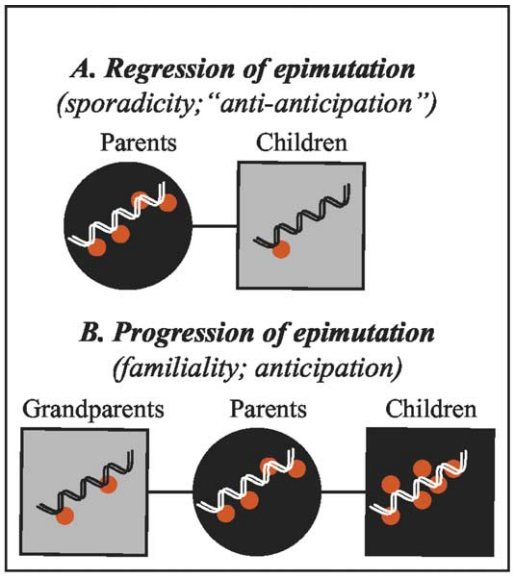

Figure 4. Epigenetic perspective on the familial and sporadic cases of schizophrenia. **(A)** Some epimutations might regress toward the normal in the germline of a schizophrenic patient, and his/her offspring will not be affected. **(B)** Other epimutations might persist across generations and become even more pathogenic, which results in increasing clinical severity and earlier age of onset.

studies, however, (epigenetic) interaction of the homologous parental chromosomes during meiosis could be a possibility.

The epigenetic theory of schizophrenia also challenges the idea of a critical etiologic role of a hazardous environment. First, despite many decades of schizophrenia research (including the psychodynamic period), thus far nobody has been able to identify any specific exogenous factor that would unequivocally increase the risk for schizophrenia. Second, there are significant methodologic problems with the interpretation of the role of such environmental candidates. For example, if childhood head trauma is associated with a higher chance of developing schizophrenia, can it be concluded that head injury increases susceptibility to the disease? Or rather does it mean that trauma results in some mild attention deficit and general developmental delay that could be constituents of premorbid personality? An infamous example of a noncausal association and incorrect primary interpretation of a cause–effect relationship is the age at first drink and risk for alcoholism (Prescott and Kendler 1999). Finally, a fundamental question can be raised: does the relatively high MZ twin discordance for schizophrenia really mean that environmental differences make the twins different? There are at least several pieces of evidence arguing against the environmental effects on phenotypes of genetically identical organisms. First, adoption studies showed that the risk to a disease does not decrease if a child born to an affected parent is raised in a healthy family (Gottesman 1991). Another example is the similar rate for schizophrenia among the offspring of MZ co-twins who were discordant for this disease (Gottesman 1991). The observation that the risk for the two groups of offspring is similar suggests that the healthy co-twin escaped the disease but transmitted the risk factors through the germline to his/her offspring and that environment did not play a critical role. Finally, in normal twins, MZ twins reared together exhibited correlation coefficients (a quantitative measure of phenotypic similarity/difference) for various psychological characteristics very similar to those of MZ twins reared apart (Bouchard et al 1990). The fact that living separately does not make identical twins significantly more different from each other than does living in the same environment argues that the fundamentals of contemporary behavioral science have to be revisited (limitations of the theory of "nonshared" environment cannot be discussed here, owing to space limitations).

From the epigenetic point of view, stochastic events might be a much more powerful mechanism that induces phenotypic differences in genetically identical organisms than environmental effects. The role of stochastic factors is occasionally discussed in the psychiatric literature (McGuffin et al 1994); however, it has been generally accepted that stochasticity cannot be reliably investigated at the molecular level. It is interesting to note that stochasticity is an inseparable component of the epigenetic metastability, which presents with partial epigenetic "infidelity." In studies of clonal mammalian cells (i.e., genetically identical) in culture, fidelity of maintenance and de novo methylation were 97%–99.9% and 3%–5% per mitosis, respectively (Riggs et al 1998). There are many other examples demonstrating that the error rate of replication of epigenetic patterns is significantly higher than that observed for DNA replication (Rakyan et al 2001). Stochastic variations in replication of epigenetic patterns can result in phenotypic diversity in identical genetic and environmental backgrounds. Examples for this could be inbred (genetically identical) agouti and kinked tail mice that show major differences in coat color and shape of the tail, both of which are determined by differential epigenetic regulation (Rakyan et al 2002). Similarly, MZ twins, although carrying identical (or nearly identical) DNA sequences, might exhibit many random epigenetic differences (Petronis et al 2003; Weksberg et al 2002); however, it is possible that only one of the two co-twins might reach the critical mass of epigenetic misregulation that results in some specific phenotype (Petronis et al 2003; Weksberg et al 2002). If the emphasis is shifted from environment to stochasticity, it might become clear why MZ twins reared apart are not more different from each other than MZ twins reared together. It is possible that MZ twins are different for some traits not because they are exposed to different environments but because those traits are determined by metastable epigenetic regulation on which environmental factors have minimal impact at the best. Finally, epigenetic mechanisms might provide a molecular explanation for the riddle of similar risks for the offspring of discordant MZ twins. The key element of this explanation is epigenetic tissue differences. Epigenetic misregulation might reach very different points in the brains of MZ twins, affecting only one of them, but pre-epimutations might be nearly identical in the germline of the affected and unaffected twins, resulting in the same risk to the offspring of the discordant co-twins (Figure 5).

In summary, meiotic and mitotic epigenetic metastability might shed a new light on various nonmendelian irregularities of schizophrenia and help address a series of issues that cannot be explained by the traditional genetic (DNA sequence–based) paradigm (see Table 1 for a summary).

Resolving Synthesis

It is not the intent of this article to say that in the etiopathogenesis of schizophrenia epigenetic factors are important and DNA sequence factors are not. It is very evident that DNA sequences and epigenetic modifications are two absolutely necessary components of a chromosome, and neither of them can be

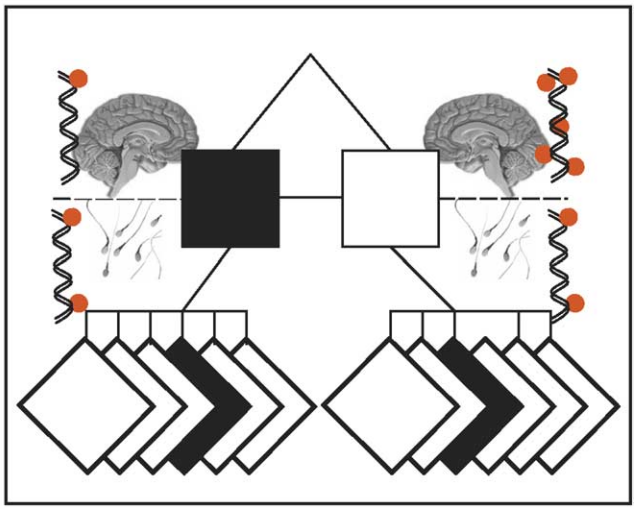

Figure 5. Epigenetic interpretation of the identical risk to the offspring of monozygotic twins discordant for schizophrenia. Monozygotic co-twins might exhibit significant differences of epigenetic regulation in the brain, with only one twin being affected with schizophrenia; however, such co-twins carry very similar pre-epimutation in the germline, which results in identical risk of schizophrenia in their offspring.

ignored. In addition to the "hardware" of DNA sequences, which carry the information for the order of amino acids to produce a structurally and functionally impeccable protein, there is also epigenetic "software," which orchestrates various activities of the genome and regulates what genes have to be expressed at what time and in what compartment in the nucleus. These are the "yin and yang" of the nucleus, and the normal life of a cell is not possible without both functioning properly. There is absolutely no doubt that epigenetic factors cannot be analyzed separately from the DNA sequences: DNA sequences are the "stage" for the epigenetic "play." Epigenetic patterns are built on some specific DNA sequences, and DNA sequence variation is one of the factors that contribute to epigenetic profiles. Because only cytosines can be methylated in humans, DNA methylation (as well as related histone modifications) can be expected to be different in GC-rich regions compared with DNA stretches in which adenine and thymine are the dominant nucleotides. In addition, the CpG dinucleotide is both the primary target in mammalian DNA methylation and also the "hot spot" of DNA mutations, which translates into a different epigenetic potential of DNA sequence variants.

Genetic linkage studies are invaluable for identification of the loci that exhibit parent-of-origin effects (Schulze et al 2003), which would indicate the putative role of genomic imprinting and provide the rationale for application of specific molecular epigenetic approaches (e.g., monochromosomal cell hybrids) that would enable identification of the imprinted genes. Genetic association studies stratified for gender give us clues as to what autosomal genes might be subjected to differential epigenetic regulation in a male or female hormone-specific milieu. Epigenetic studies might help in the understanding of why a specific allele or haplotype becomes a disease risk factor in only male or only female subjects. This is part of a fundamental question of the interaction between DNA variation and epigenetic modification. The latter might provide an insight into the interpretation of the increasing number of findings that haplotypes of some genes (e.g., neuregulin, dysbindin, G72) (reviewed in Harrison and Owen 2003) exhibit strong evidence for association with a disease, but such risk haplotypes, as a rule, consist of noncoding SNPs (sometimes far from the coding part of the gene) and the etiopathogenic mechanisms of such an association are obscure. Different haplotypes might provide a (slightly) different "stage" for an epigenetic "play," but certainly the "stage" is not the only

Table 1. Comparison of Genetic (DNA Sequence–Based) and Epigenetic Models of Schizophrenia

Feature	Genetic Model	Epigenetic Model
Primary Molecular Mechanism of the Disease	Predisposing DNA sequence variation	Epigenetic misregulation
Discordance of MZ Twins	Effects of nonshared environment	Differential epigenetic modification of disease genes in MZ co-twins, mostly due to stochastic factors
Parent-of-Origin Effect	No explanation	Parent-of-origin-specific modification of DNA and histones (genomic imprinting)
Environmental Effects	Somehow interact with the genome to change gene expression	Epigenetic status of a gene(s) can be modified by environmental factors to directly control gene expression
Sex Effects	Linkage to sex chromosomes (if no linkage to sex chromosomes is detected, no explanation)	Differential epigenetic effects of androgens and estrogens
Phenotypic Variability	Different combinations of predisposing genes and hazardous environment	Result of the epigenetic changes induced by stochastic, environmental, and developmental events
Remissions and Relapses	No explanation	Fluctuations in metastable epigenetic regulation; age-related epigenetic changes; epigenetic effects of treatment
Presence of Familial and Sporadic Cases	Major (familial) and minor (sporadic) genes (linkage studies have not been able to detect genes with large effects)	Epigenetic metastability during meiosis
High Frequency Despite Evolutionary Pressure	Evolutionary advantages of genes predisposing to schizophrenia (in unaffected carriers)	High de novo epimutation rate during meiosis
Inconsistent Genetic Linkage/Association Data	Genetic heterogeneity of the disease. Lack of power to detect small additive effects. Evolutionary complexities of haplotype formation.	DNA sequence variation does not necessarily play the primary etiological role in schizophrenia

DNA, deoxyribonucleic acid; MZ, monozygotic.

factor that determines the "play," and the "players" might improvise in different ways. To have a full picture, epigenetic profiling has to be performed alongside DNA haplotyping.

It is also not the intent of this article to say that environmental factors play no role in schizophrenia. Although arguments weakening a putatively major role of such effects were provided, it does not necessarily mean that exogenous factors do not contribute to the risk for schizophrenia on a case-by-case basis. As was mentioned above, the problem is that systematic studies of environmental impact on human behavior are very difficult, retrospective studies are ambivalent, and large-scale, prospective studies are nearly impossible. Instead of investigating environment, is it not a better idea to investigate the impact of such environmental factors on the epigenetic regulation of some specific genes? Such studies can be well designed for inbred animals and eventually tested in humans.

Finally, the "family" of putative etiologic factors—DNA sequences, epigenetics, and environment—has to accept a new member: stochasticity (fractals, randomness). Mendelian genetics did not need and did not know this term because the relationship of a gene and a mendelian trait, as a rule, is completely deterministic. The fact that genetically identical animals (inbred lines and clones) in the absence of environmental variation exhibit very different phenoptypes can no longer be ignored. Phenotypic discordance of MZ twins is likely to be another example, although less straightforward because of the putative impact of differential environment. Interestingly, 80 years ago, Timofeeff-Ressovsky (1925) noticed the same phenomenon in Drosophila and introduced the concept of incomplete penetrance and variable expressivity. Since then, the two terms have been quite frequently used in the scientific literature, but it has been rarely admitted that this is an indicator of our ignorance. The biological "uncertainty principle" implies that even if full biological information about a specific zygote (embryo, newborn) is available, our predictions regarding the future phenotypic outcomes will always be probabilistic.

This work was supported by grants from the Ontario Mental Health Foundation, the National Alliance for Research on Schizophrenia and Depression, the Stanley Foundation, and the Canadian Psychiatric Research Foundation.

I thank Dr. Irv Gottesman (University of Minnesota), Dr. Todd Gould (National Institute of Mental Health), and Mr. Zachary Kaminsky (Centre for Addiction and Mental Health, Toronto) for their valuable comments and advice.

Allen ND, Norris ML, Surani MA (1990): Epigenetic control of transgene expression and imprinting by genotype-specific modifiers. *Cell* 61:853–861.

Bouchard TJ Jr, Lykken DT, McGue M, Segal NL, Tellegen A (1990): Sources of human psychological differences: The Minnesota Study of Twins Reared Apart. *Science* 250:223–228.

Cardno AG, Gottesman II (2000): Twin studies of schizophrenia: From bow-and-arrow concordances to Star Wars Mx and functional genomics. *Am J Med Genet* 97:12–17.

Gottesman II (1991): Schizophrenia Genesis: The Origins of Madness. New York: W. H. Freeman.

Gottesman II, Gould TD (2003): The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry* 160:636–645.

Gottesman II, Shields J (1982): *Schizophrenia: The Epigenetic Puzzle*. Cambridge, United Kingdom: Cambridge University Press.

Harrison PJ, Owen MJ (2003): Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 361:417–419.

Henikoff S, Matzke MA (1997): Exploring and explaining epigenetic effects. *Trends Genet* 13:293–295.

Jablonka E, Lamb M (1995): *Epigenetic Inheritance and Evolution*. Oxford: Oxford University Press.

Jaenisch R, Bird A (2003): Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. *Nat Genet* 33(suppl):245–254.

Jenuwein T, Allis CD (2001): Translating the histone code. *Science* 293:1074–1080.

Licinio J (2003): Molecular psychiatry: Moving away from one-polymorphism genetic association studies. *Mol Psychiatry* 8:247.

Maynard Smith J (1990): Models of a dual inheritance system. *J Theor Biol* 143:41–53.

McGuffin P, Asherson P, Owen M, Farmer A (1994): The strength of the genetic effect. Is there room for an environmental influence in the aetiology of schizophrenia? *Br J Psychiatry* 164:593–599.

Petronis A (2001): Human morbid genetics revisited: Relevance of epigenetics. *Trends Genet* 17:142–146.

Petronis A, Gottesman II, Kan PX, Kennedy JL, Basile VS, Paterson AD, Popendikyte V (2003): Monozygotic twins exhibit numerous epigenetic differences: Clues to twin discordance? *Schizophr Bull* 29:169–178.

Plomin R, Daniels D (1987): Why are children in the same family so different from one another? *Behav Brain Sci* 10:1–60.

Prescott CA, Kendler KS (1999): Age at first drink and risk for alcoholism: A noncausal association. *Alcohol Clin Exp Res* 23:101–107.

Rakyan VK, Blewitt ME, Druker R, Preis JI, Whitelaw E (2002): Metastable epialleles in mammals. *Trends Genet* 18:348–351.

Rakyan VK, Preis J, Morgan HD, Whitelaw E (2001): The marks, mechanisms and memory of epigenetic states in mammals. *Biochem J* 356:1–10.

Riggs A, Xiong Z, Wang L, LeBon J (1998): Methylation dynamics, epigenetic fidelity and X chromosome structure. *Novartis Found Symp* 214:214–227.

Robertson KD, Wolffe AP (2000): DNA methylation in health and disease. *Nat Rev Genet* 1:11–19.

Schulze TG, Chen YS, Badner JA, McInnis MG, DePaulo JR, McMahon FJ (2003): Additional, physically ordered markers increase linkage signal for bipolar disorder on chromosome 18q22. *Biol Psychiatry* 53:239–243.

Sutherland JE, Costa M (2003): Epigenetics and the environment. *Ann N Y Acad Sci* 983:151–160.

Terwilliger JD, Haghighi F, Hiekkalinna TS, Goring HH (2002): A biased assessment of the use of SNPs in human complex traits. *Curr Opin Genet Dev* 12:726–734.

Timofeeff-Ressovsky NW (1925) Uber den Einfluss des Genotyps auf das phanotypische Manifestieren eines einzelnen Gens. *J. Psychol. Neurol* 31:305–310

Torrey EF, Miller J, Rawlings R, Yolken RH (1997): Seasonality of births in schizophrenia and bipolar disorder: A review of the literature. *Schizophr Res* 28:1–38.

Tsuang MT, Stone WS, Faraone SV (2001): Genes, environment and schizophrenia. *Br J Psychiatry* 40(suppl):S18–S24.

Vogel F, Motulsky A (1997): *Human Genetics: Problems and Approaches*. 3rd ed. Berlin, New York: Springer-Verlag.

Weiss KM, Terwilliger JD (2000): How many diseases does it take to map a gene with SNPs? *Nat Genet* 26:151–157.

Weksberg R, Shuman C, Caluseriu O, Smith AC, Fei YL, Nishikawa J, et al (2002): Discordant KCNQ1OT1 imprinting in sets of monozygotic twins discordant for Beckwith-Wiedemann syndrome. *Hum Mol Genet* 11:1317–1325.