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Critical periods and the developmental origins of disease: an epigenetic perspective of schizophrenia

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Abstract

Epigenetics holds promise to explain some puzzles concerning the risk and course of psychiatric disorders. Epigenetic information is essential as a set of operating instructions for the genome, which is heritable with DNA. The epigenetic regulation of gene expression can plausibly be influenced by the environment of one's ancestors, prenatal exposures, and by early life events. Some epigenetic mechanisms may alter neurophysiology throughout life by programming gene expression, perhaps in anticipation of certain life experiences. These epigenetic signals are only meta-stable and may be perturbed by stochastic events, errors, or by environmental toxins. This introduction considers the possibility that epigenetic change that may occur as paternal age advances or during fetal adversity may be causally related to the susceptibility for schizophrenia.

Keywords

epigenetics; reproduction; genetics; paternal age; schizophrenia

Introduction

Following many decades in which the family environment and parental behavior were implicated as the major causes of severe mental illness, human genetic research promised to transform the theory and practice of psychiatry with a genetic perspective. While there have been some exciting discoveries about the genetic underpinnings of severe mental disorders, the vast proportion of population-wide genetic susceptibility factors is far more obscure today than we would have predicted a quarter century ago. We are still seeking to discover how the predisposition to mental illness is transmitted, the biological nature of the inherited factors, and how genes interact with the environment to produce the diseases.

These questions and approaches have been particularly well funded and thoroughly applied to the schizophrenia syndrome. This is a serious disorder characterized by “positive” (psychotic) symptoms, “negative” (deficit) symptoms and cognitive impairment. Most patients are initially affected in young adulthood; 50% go on to experience some disability throughout their lives, and an additional 25% never recover and require lifelong care. Family

studies provided strong epidemiological evidence for an inherited component to risk almost a century ago, which twin and adoption studies later confirmed. A substantially greater concordance for schizophrenia in monozygotic co-twins than for dizygotic co-twins particularly supported its high heritability, although the incomplete concordance in monozygotic twins also illuminated the fact that genes alone are an insufficient explanation for the illness (see¹).

Epidemiological models examined if environmental exposures influenced the risk for schizophrenia, acting alone or through gene-environment interactions. These studies were largely focused on the fetal and neonatal environment, based on the idea that schizophrenia was a neurodevelopmental disorder. Other epidemiological studies showed that postnatal life course exposures also elevated the risk for schizophrenia, including meningitis, severe early life trauma, traumatic brain injury and cannabis exposure;^{2,3} a common proposal was that these experiences increased the penetrance of schizophrenia susceptibility alleles. The genetic story of schizophrenia has become increasingly complicated. Although numerous loci, alleles, and copy number variations have now been associated with schizophrenia, these are by and large associated with only a small number of cases and they do not uniformly cause the illness in carriers.

A new paradigm shift may be in the offing to explain some risk for psychiatric diseases beyond the genetic code. The science behind epigenetics is maturing and may provide some answers. New research shows that more information is inherited from one's parents than just the DNA sequence and that this other information can influence the phenotype. An epigenetic perspective has the potential to throw new light on the etiology of complex diseases like schizophrenia. It encompasses not only genes, but the switches that shift their expression. Furthermore it appears that epigenetic processes can be modified by such influences as the environment of our ancestors, stochastic factors within and between generations, processes in germ cells, and over gametogenesis, fetal development and at critical life course epochs.⁴

The epigenetic perspective encompasses both the genetic and environmental discoveries about the nature of risk for schizophrenia, particularly emphasizing the influences of the early environment. Epigenetic mechanisms are a pathway through which these mechanisms may explain prior epidemiological findings linking such factors as later paternal age or prenatal adversity to the risk for schizophrenia.

Critical early life experiences can have a lasting influence on human behavior. The long debate on whether “nature versus nurture” plays the major role in explaining behavior can give way to cutting edge molecular research at the interface of genes and the environment. Epigenetic regulation occurs through such mechanisms as methylation of gene promoter regions, histone acetylation, and newly discovered RNA pathways.

Paternal age and schizophrenia

The maintenance of schizophrenia in the population despite the reduced fecundity of affected individuals is an enigmatic feature of the disease. For many familial diseases, later paternal age is associated with the *de novo* presentation of a “sporadic case.” In 2001, we

conducted an analysis of paternal age and schizophrenia in Jerusalem.⁵ This analysis revealed a robust association of paternal age and schizophrenia risk, with each decade of the father's age further multiplying the relative risk for schizophrenia by approximately 50% in controlled analyses, with no corresponding effect of maternal age; we immediately replicated these results in a second birth cohort in California.⁶ Other studies confirmed the association of advancing paternal age and an increasing risk for schizophrenia,^{7–12} although two case-based studies did not reach this conclusion.^{9,13} Taken together, these studies strengthened the conclusion that paternal age at birth is an important risk factor for schizophrenia. Collectively, they show a tripling of risk for schizophrenia for the offspring of the oldest group of fathers in comparison to younger fathers.

Research in our Jerusalem Perinatal Cohort Study permitted a careful control of confounding factors. It is the largest prospective population-based research data set with pre- and postnatal interviews, demographic data and obstetric complications, having a total cohort size of 92,500 births. Initially started as a case-control study of toxemia of pregnancy (1964–66), the study quickly grew to survey all reported live births and all stillbirths from 28 weeks gestation from 1964–1976. It includes data on antenatal maternal health, prenatal exposures, obstetric complications, parental health and history, as well as the offspring's pediatric health and a wealth of other measures. This study (and other reports) demonstrated that the paternal age effect is not explained by other factors, including family history, maternal age, parental education and social ability, family social integration, social class, birth order, birth weight or birth complications.

Putative gene mutation mechanisms

A leading explanation for the association of later paternal age and schizophrenia risk is the replenishment of schizophrenia genes through new mutations. Paternal age is reported to be the major source of *de novo* mutations in humans and other mammals, likely due to the constant cell replication cycles that occur in spermatogenesis that lead to “copy errors.”¹⁴ Following puberty spermatogonia undergo some 23 divisions per year. At ages 20 and 40, a man's germ cell precursors will have undergone about 200 and 660 such divisions, respectively. In contrast with the continuing cell replication cycles of spermatogenesis, the female's germ cells (ova) are fully developed at birth as terminally differentiated oocytes. These cells undergo approximately 24 divisions in fetal life and then remain quiescent until ovulation and fertilization.¹⁵ As a result of these differences between male and female reproductive personalities, spermatogenesis and oogenesis are prone to different types and timing of mutations.

During a man's life, the spermatogonia are vulnerable to DNA damage, and mutations may accumulate in clones of spermatogonia as men age.¹⁶ The number of mutations introduced with each cell division increases exponentially in later years, presumably because of reduced levels of DNA proofreading and repair enzymes. The integrity of spermatogenesis is further compromised by physiological changes that accompany aging, including declining testosterone, reduced antioxidant enzyme activity, and the limitations in vascular supply that also impact on the efficiency of other organs (reviewed in¹⁷). In addition to point mutations, the mechanism that accompanies advancing paternal age could be *de novo* copy number

variants, which are more common in sporadic cases,¹⁸ or result from progressive DNA trinucleotide expansions, as demonstrated in neuropsychiatric disorders, including myotonic dystrophy, fragile X syndrome, spinocerebellar ataxias.¹⁹

Putative epigenetic mechanisms

Another compelling explanation for paternal age-related schizophrenia would be though changes in epigenetic regulation of paternal genes. A particular set of epigenetic mechanisms are very intriguing explanations; these are genes that undergo parent-of-origin dependent expression in the offspring, known as imprinted genes. Imprinting is an epigenetic form of gene regulation in which gene expression depends on whether the allele was inherited from the male or female parent in the prior generation. Imprinted genes that are only expressed if paternally inherited are reciprocally silenced at the maternal allele, and the contrary is true for maternally expressed genes. Genes are silenced by DNA methylation, which may preclude transcription factor binding, and by alterations in chromatin structure. The inherited methylation pattern is maintained in somatic cell divisions, but it is erased in the primordial germ cells and re-established late in gametogenesis. The monoallelic pattern of gene expression is maintained in offspring of the same sex and is reversed when genes are transmitted through individuals of the opposite sex. Imprinted genes do not conform to Mendelian principles since only one allele from the prior generation is expressed, even though an equivalent amount of genetic material, other than sex chromosomes, are inherited from both parents.

There are several characteristics of imprinted genes that make them reasonable candidates for schizophrenia vulnerability. First, imprinted genes play a key role in brain development, leading to lasting changes in cognition and behavior.²⁰ Paternal and maternal genes are both necessary for embryogenesis,²¹ playing greater parts, respectively, in placental and embryo development.²² The influence of paternal genes in the placenta may represent a mechanism for the father to assure that his offspring derive adequate resources from the maternal *in utero* environment, even if it may be in the best interest of the mother to limit these resources (see²³). Second, there appears to be a neuroanatomic localization pattern for the expression of certain paternally imprinted genes in mice in which the paternal or maternal allele expression patterns correspond, respectively, to limbic and neocortical regions.^{24,25} The conceptualization of schizophrenia symptoms as derived from an imbalance or modulatory disturbance between these regions²⁶ might be pertinent to these expression differences. In addition, genes for several neurotransmitters implicated in schizophrenia may be imprinted, including those for the GABA A receptor.²⁷

Third, both imprinted genes and schizophrenia are associated with language development and social functioning. The sexual dimorphism in the expression of schizophrenia, with males showing an earlier onset, more severe course, and a greater disability, could also involve imprinting of the X chromosome. Only normal female offspring receive a paternal X-chromosome and normal male offspring only receive a maternal X-chromosome. Because the paternal X-chromosome genes are associated with superior social communication skills, their absence in male offspring may account for their increased vulnerability for developmental disorders involving social behavior and language such as schizophrenia.

A role for imprinted genes in determining language and social capacity was shown in an elegant set of studies by Skuse et al.²⁸ in patients with Turner's syndrome. Many genes related to cognition and sociality are thought to be on the X-chromosome. Among women with Turner's syndrome it has been reported in some (but not all) studies that there are differences between women whose X-chromosome was transmitted through the maternal line (Xm) versus women whose X-chromosome was transmitted through the paternal line (Xp). Some studies have noted differences in social skills, executive function, and arithmetic ability between 45, Xp and 45, Xm women.^{28,29} Others have noted that a strong correlation with cardiovascular disease in Xm but not Xp women.³⁰ Another more recent study reported that Xm and Xp women differed in superior temporal gyrus gray matter but not in white matter.³¹ Based on these and other studies, imprinted genes are expected to be identified on the X-chromosome. The association between advancing paternal age and schizophrenia among women may be a result of imprinting errors in the paternal X-chromosome of older fathers. Finally, parent of origin effects have been linked with several other neuropsychiatric disorders, including schizophrenia.³²

Fetal adversity and schizophrenia

Schizophrenia has purported developmental origins and the risk for disease has been associated with a multitude of intra-uterine adversities. A large body of evidence points to an increased incidence of schizophrenia after complications of pregnancy and labor, and after maternal stress, famine or infections in pregnancy, including influenza or rubella.³³ Leading models previously considered the teratogenic effects of fetal adversity on the proliferation, migration and connectivity of neurons. In these models, the environment was seen to damage neurodevelopment.

In the epigenetic perspective, however, the fetal milieu may communicate information about the pregnancy and postnatal environment; the fetus responds to optimize its survival and reproductive outcomes based on this information. If so, then the common experience of increased maternal and fetal glucocorticoid signaling across many adversities may unite several pathways to schizophrenia in a parsimonious model.

Developmental disruption

It is of interest that many of these effects may be explained by maternal psychological stress alone, without invoking toxic effects on cellular proliferation and migration by extrinsic agents. Maternal psychosocial stress can moderately decrease fetal growth and gestational length and lead to preterm birth. Maternal cortisol is correlated with fetal derived maternal plasma corticotropin-releasing hormone (CRH) since maternal glucocorticoids increase CRH gene expression in the placenta. Animal models show maternal stress during critical fetal periods may modify opioid, GABA, serotonin and dopamine systems. These mechanisms may augment stress sensitivity and/or increase the risk for a number of psychiatric disorders, based on the presence of underlying disease susceptibility alleles. Our study linking the data from the Jerusalem Perinatal birth cohort to the Israel Psychiatric Registry³⁴ revealed that exposure to the severe but time-limited stress of the six-day Arab-Israeli war was associated with a two-fold excess of schizophrenia overall. Consistent with

this being a psychosocial stressor, the risk was elevated 3.68 fold in those with the lowest socioeconomic status. These findings are consistent with the idea that maternal stress can alone increase risk for schizophrenia in offspring, and that it does so during critical developmental epochs.

Fetal programming

Fetal programming refers to epigenetic changes that occur during fetal development and that alter the offspring's phenotype. These may arise in response to maternal health, nutrition, and the emotional environment during the pregnancy, leading to alterations in the lifelong expression or silencing of genes. Elevation of maternal cortisol and placental CRH during critical developmental periods initiates a cascade that can reprogram the offspring's hypothalamic-pituitary axis (HPA), selectively diminishing type I and type II glucocorticoid receptors in the hippocampus.⁴ A lifelong reduced capacity to inhibit stress-induced glucocorticoid secretion can ensue, which enhances stress responsivity to intrinsic and extrinsic perturbations.

While CRH is well known as the central regulator of the stress response, it plays additional roles in human pregnancy with large amounts being synthesized by the placenta and secreted into the maternal and fetal circulatory systems. CRH is the primary determinant of gestation length and is an important mediator of fetal growth and development. In the setting of a threatened pregnancy, whether from maternal or fetal factors, increased secretion of maternal cortisol and CRH can ramp up the placental CRH production to accelerate parturition and restrict fetal growth, independent of other effects of any medical complications. Thus, risks for low birthweight and preterm birth are increased by severe pregnancy stress, and these are furthermore associated with the risk for schizophrenia; the epigenetic perspective is a compelling explanation for these observations.

Conclusions

Research in epigenetics offers new insight on how the disposition to mental illness is transmitted, the biological nature of the inherited factors, and the ways in which these genetic factors interact with environmental determinants. Recent advances in epidemiology have created a new and more promising context for epigenetic discovery. Epigenetic influences on behavior may extend from the exposures of earlier generations to those in the womb and perhaps lifelong, continuing to the tomb, in light of new information on neuroplasticity.

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