Aberrant Epigenetic Regulation Could Explain the Relationship of Paternal Age to Schizophrenia

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The causal mechanism underlying the well-established relation between advancing paternal age and schizophrenia is hypothesized to involve mutational errors during spermatogenesis that occur with increasing frequency as males age. Point mutations are well known to increase with advancing paternal age while other errors such as altered copy number in repeat DNA and chromosome breakage have in some cases also been associated with advancing paternal age. Dysregulation of epigenetic processes may also be an important mechanism underlying the association between paternal age and schizophrenia. Evidence suggests that advancing age as well as environmental exposures alter epigenetic regulation. Errors in epigenetic processes, such as parental imprinting can have serious effects on the offspring both pre- and postnatally and into adulthood. This article will discuss parental imprinting on the autosomal and X chromosomes and the alterations in epigenetic regulation that may lead to such errors.

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Advancing Paternal Age and Schizophrenia

Although a relationship between paternal age and schizophrenia has been investigated intermittently since the 1950s,1 only in the past decade has a clear link between the 2 been established and sources of confounding ruled out. In 2001, Malaspina et al2 showed that the incidence of schizophrenia increased progressively with increasing paternal age, the risk being 2-fold and 3-fold for offspring of fathers aged 45–49 and 50 or more years, compared with those of fathers aged less than 25 years. That seminal work was based on a study in a large prospective cohort. Nine of 10 investigations, published in 8 articles3–10 as well as a meta-analysis,11 have confirmed the original finding. Together, these studies demonstrated that the effect of paternal age on risk of schizophrenia was not explained by a variety of factors such as family history, maternal age, parental education and social ability, family social integration, social class, birth order, birth weight, and birth complications. Other evidence points to a role for paternal age in learning and cognition. Offspring of older rodents showed deficits in learning compared with those of younger fathers.12 In humans, the incidence of autism was increased nearly 6-fold in offspring of fathers in their 40s and 50s compared with those of fathers aged up to 30 years.13 IQ was reduced in the offspring of older fathers, independently of effects of maternal age.14 In another study, paternal age greater than 40 years was associated with an increased likelihood that the offspring would be placed in special education tracks in school.15

A question arose as to whether effects of paternal age on schizophrenia might be explained by psychiatric problems that might delay childbearing in the parents and be inherited by their offspring. For this to be true, we would anticipate paternal age effects to be stronger in familial cases than in sporadic ones. In studies that examined whether the relation between paternal age and schizophrenia was modified by family history,6–9 one actually observed the reverse effect while the others did not observe any modification of the relation by family history.6,8,9

The Effects of Advancing Paternal Age on Spermatogenesis

Spermatogonial stem cells are constantly dividing and undergo hundreds of replications during the lifetime.16 Crow17 proposed that there is a higher frequency of point mutations in males, the frequency of which increases with age. In fact, paternal age has been associated with birth defects in several studies.18–20 Other forms of mutation, eg, altered copy number in repeat DNA, and chromosome breakage, also occur in the male germline and in some cases have been related to male aging.21–23 Paternal
age may then be, in part, a marker for genetic alterations that occur during spermatogenesis in older men underlying the association between paternal age and schizophrenia. In addition to genetic changes, aberrant epigenetic regulation, the subject of this article, may also underlie the association between advancing paternal age and schizophrenia.

**Aberrant Epigenetic Regulation**

Epigenetic processes lead to heritable changes in gene expression through DNA methylation and demethylation and changes in chromatin structure, rather than changes in DNA sequence; methylation of genes silences them preventing transcription while demethylation allows transcription. An epigenetic process of interest in schizophrenia and other neuropsychiatric disorders is parental imprinting.

There are approximately 70 autosomal loci known to be parentally imprinted, and others are suspected on the sex chromosomes. Imprinted genes play a critical role in growth of the placenta and fetus and central nervous system. Genes are differentially marked during gametogenesis after the methylation patterns of the previous generation are “erased” and the new parent of origin-specific methylation and additional changes in chromatin are established. This differential marking silences or imprints the maternal or paternal allele. Imprinted genes generally occur in large clusters containing both maternally and paternally imprinted genes. A gene that is imprinted in some tissues may not be imprinted in other tissues; in the brain, it is thought that imprinting may even be cell specific and differ according to the stage of development.

Errors associated with imprinting can occur during imprint erasure, establishment, and maintenance. Loss of imprinting whereby the epigenetic mark is not established or erased can result in partial or complete biallelic expression of a gene. For instance, loss of imprinting of the insulin-like growth factor 2 (IGF2) gene has been linked to both Beckwith-Wiedeman syndrome and colorectal neoplasia. In Angelman syndrome and Prader-Willi syndrome (PWS) there are errors in imprinting the correct parental chromosome. This failure to correctly imprint in some cases has been attributed to a microdeletion in the imprinting center of 15q11–13, while in other cases, it has been attributed to a primary epimutation which can occur during erasure, establishment, or maintenance of the imprint. Though both these syndromes are associated with behavioral, cognitive, and neurologic impairment, in the case of PWS, 5%–10% of cases experience schizophrenia-like psychotic symptoms. Interestingly, the chromosomal region involved in these syndromes lies adjacent to a region, 15q13–14, which has been linked to schizophrenia in many but not all studies. Imprinting errors could increase the risk of schizophrenia through multiple pathways including direct effects on the expression of genes involved in neuropsychiatric pathology or indirectly through imprinting errors in genes related to the normal functioning of the placenta.

**X-chromosome Inactivation**

X-chromosome inactivation is a special form of epigenetic silencing. Females receive the X chromosome of both parents while males receive only the maternal X chromosome. To maintain dosage compensation in females, 1 X chromosome is randomly silenced by a nontranslating RNA called the X inactive–specific transcript and other changes resulting in a 50:50 mosaic of cells with the paternal or maternal X chromosome inactivated. Deviations from this norm are common and more than 15% of genes on the inactivated X chromosome escape silencing.

Parent of origin effects suggested the presence of imprinted genes on the X chromosome in a study of the sporadic disorder, Turner syndrome. Turner syndrome is characterized by complete or partial loss of the paternal or maternal X chromosome. Skuse et al reported that females who had only the paternal X chromosome had better verbal skills and higher executive functioning than females who had only the maternal X chromosome. In addition to providing support for the presence of imprinted genes on the X chromosome, these results also supported the hypothesis that imprinted genes reside on the X chromosome related to cognition and behavior. Kesler et al found that there were differences in brain morphology between Turner syndrome patients who inherit the paternal versus a maternal X chromosome. Imprinted genes on the X chromosome have been posited as one of several explanations for sex differences in neuropsychiatric disorders.

**Effects of Aging and Environmental Exposures on Epigenetic Processes**

Though epigenetic traits are generally stably inherited through numerous cell divisions, over time, epigenetic errors do occur in somatic cells. The frequency appears to increase with age and thought to be more frequent than mutations. In mice, epigenetic loss of repression of a gene was reported in older mice compared with younger mice. In humans, a study observed that young monozygotic twins were virtually identical on measures of 5-methylcytosine DNA and histone acetylation, whereas in older twins, the differences in these measures were often fairly striking. These differences in older twins might have occurred independently of or in concert with exogenous exposures. These findings suggest that epigenetic regulation in the rapidly dividing spermatogonia cells may also be disrupted as a consequence of aging or as an accumulation of exogenous or endogenous exposures over time. In fact, it was recently reported that there
were changes in chromatin packaging and integrity in spermatozoal cells in older rats compared with younger rats, while investigators from China reported that older paternal age was associated with a loss of imprinting of IGF2, a maternally imprinted gene, in cord blood.48

DNA Methyltransferases

There are a number of different DNA methyltransferases (DNMTs) that differ in whether they initiate or sustain methylation and are more active at certain times in development but less during others.49 In aging fibroblast cell lines, there is a progressive loss of a maintenance DNMT1 and an increase in one of the de novo DNMTs.50 It has been observed in mouse testis that DNMTs levels peak postnatally and decrease to steady adult levels about a month later.51 It is possible that some DNMTs levels could decrease and others could increase with aging. Altered levels of the DNMTs in older men could contribute to the disruption of epigenetic processes affecting the era- sure, establishment, and maintenance of paternal imprints during spermatogenesis and after fertilization. Environmental exposures over the course of males’ lifetime may also cause defective epigenetic regulation. Several environmental exposures, eg, arsenic and nickel are associated with epigenetic changes, and exposure to these and other toxins may affect spermatogenesis. One study reported that early embryos of male rats chronically exposed to a chemotherapy drug, cyclophosphamide, had defects in epigenetic programming.54

Conclusion

Advancing paternal age may be a marker of epigenetic dysregulation leading to errors in imprinting and other epigenetic processes, the consequence of which may be a susceptibility to schizophrenia and other neuropsychiatric disorders in the offspring. Interest in the epigenetic origins of neuropsychiatric disease has concomitantly increased with the mounting evidence of the importance of paternal age as a risk factor in schizophrenia and other disease outcomes. Currently, there are more questions than answers, providing opportunities for translational research across many disciplines.

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