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The influence of genomic imprinting on brain development and behavior

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Abstract

Genomic imprinting, a newly discovered and significant form of gene regulation, refers to the differential expression of a gene depending on whether it is inherited from the male or female parent. The genetic conflict theory of genomic imprinting postulates that conflicts between the genetic interests of mothers, fathers, and their offspring, as well as asymmetric genetic relationships with maternal and paternal kin, led to an evolutionary ''arms race'' within the genome, which resulted in the expression of these conflicts at the phenotypic level. This paper provides background and evidence regarding genomic imprinting and its role in brain development, describes the cognitive and behavioral phenomena that have been interpreted in terms of the genetic conflict model, and points to potential avenues of further research. © 2001 Elsevier Science Inc. All rights reserved.

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1. Genomic imprinting

With the exception of the sex chromosomes, the sets of chromosomes inherited from each parent have traditionally been regarded as functionally equivalent, and the source of genetic material was not considered a crucial factor in ontogeny. More recent observations, however, have uncovered the phenomenon of genomic imprinting, whereby the expression of a gene differs depending on whether it is inherited from the male or female parent (Hall, 1997). Imprinted genes show expression from one allele only, while the other allele is silent.

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Like other mammalian genes, imprinted genes are transmitted in accordance with Mendelian Laws of Inheritance (Solter, 1988). As with unimprinted genes, pairs of alleles at imprinted genes are separated randomly into gametes during meiosis. However, the imprinted gene is altered to reflect the type of gamete, egg or sperm, in which it is incorporated. Therefore, imprinted genes are not the constant entities envisioned by Mendel, but may have variable properties depending on their parental source. This contravention of Mendel's Laws has led some researchers to conclude that imprinting represents a paradigm shift in genetics comparable to the Einsteinian revolution in physics (Goshen et al., 1994). Others are more circumspect (Solter, 1988). All agree, however, that genomic imprinting represents a unique and significant type of gene regulation.

1.1. Gene regulation and expression

The modification of gene expression by sex is not new in itself. The particular significance of genomic imprinting lies in the timing of its regulatory mechanism. Genomic imprinting is trans-generational: The modification of a gene in one generation regulates its expression in the next.

There are also important differences between genomic imprinting and other types of allelic interactions. Genomic imprinting is a stable feature of a locus — the same genes are imprinted in all members of a species. The imprinting status of each allele, however, is not: The imprint is added or removed based on the sex of the individual passing on the allele. As a result, an allele silenced in one generation may be active in the next. In contrast, the dominant or recessive nature of an allele is a property of that allele, and is not changed by local environmental conditions such as the sex of the individual. Similarly, mutations may silence the expression of an allele in one individual and not others, but the mutation is not reversible in subsequent generations.

The influence of parental sex on the transmission of imprinted genes is reminiscent of sex-linked inheritance. Sex-linked traits seem to have similar parental origin effects, and the phenotypic expression of a sex-linked trait is partially determined by the sex of the offspring; that is, traits may be limited to, or more common in, male or female offspring. As a result, the phenotype associated with a sex-linked trait often appears variable across generations. However, the genes on the sex chromosomes are not actually altered from one generation to the next. In contrast, the phenotype produced by an imprinted gene occurs in offspring of both sexes equally, but the nature of the phenotype is determined by the sex of the transmitting parent (Solter, 1988). As a result, the phenotype associated with an imprinted gene may also appear to "skip" generations. However, in each generation, the imprint on a gene is erased and reestablished. Pedigrees comparing maternal and paternal imprinting are shown in Hall (1997).

1.2. How a gene is imprinted

Although the specific mechanism by which genes are imprinted is not known, the prevailing hypothesis is the methylation of cytosine nucleotides in the promotor region of