

# 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

genes (Bartolomei & Tilghman, 1997), a mechanism known to function in other types of gene regulation. For example, genes expressed only in certain tissues are unmethylated in those tissues, but methylated in tissues where they are not expressed (Strachan & Read, 1996). X-chromosome inactivation also appears to be achieved by this means (Tycko, 1994). Hypermethylation is thought to prevent the transcription of DNA by repelling transcription factors, or by attracting proteins that block access to the transcription start site (Strachan & Read, 1996). Significantly, methylation patterns are inherited from the male and female parent intact, are erased in primordial germ cells, and then reemerge during germ cell maturation (Iwasa, 1998).

Imprinted genes usually show allelic differences in methylation, with silenced alleles hypermethylated and active alleles hypomethylated (Strachan & Read, 1996; Tycko, 1994), but occasionally the reverse pattern is reported (Bartolomei & Tilghman, 1997; Feinberg, 1993). Clarification of this issue will likely facilitate the search for imprinted genes.

### *1.3. Evidence for genomic imprinting*

Though the importance of genomic imprinting is acknowledged by researchers worldwide, relatively few genes are imprinted. In 1997, 19 imprinted genes had been identified in humans or mice (Bartolomei & Tilghman, 1997). By 1999, more than 25 imprinted genes had been identified in humans, and estimates based on the mouse genome suggest that 100–200 imprinted genes may exist (see Table 1 in Falls, Pulford, Wylie, & Jirtle, 1999; Morison & Reeve, 1998).

Imprinting has also been found to vary over space and time: A gene may be imprinted in some tissues but not others, or only at certain stages of development (Spencer, Clark, & Feldman, 1999). Functional analyses of imprinted genes have revealed that most are involved in development, specifically the regulation of fetal and placental growth (Bartolomei & Tilghman, 1997). Imprinted genes involved in cell proliferation and cancer, human genetic disease and adult behavior have also been identified (Falls et al., 1999; Hall, 1997).

## **2. The genetic conflict hypothesis of the evolution of genomic imprinting**

Conflict replaced functionalism as the dominant force in evolutionary theory when Darwin published *On the Origin of Species* in 1859 (Hurst, Atlan, & Bengtsson, 1996). What Darwin made clear was that conflict between individuals in the struggle for survival was the force that propelled entire species through evolutionary time. This view was made even more explicit after the modern synthesis gave us a “gene’s eye view” of evolution and brought the conflict between individuals to the level of the genome.

The genetic conflict model of genomic imprinting, proposed by Haig and Westoby (1989), postulates that conflicts between the fitness interests of mothers, fathers and their offspring led to an evolutionary “arms race” within the genome (Hurst & McVean, 1997). According to Haig and Westoby (1989, see also Haig & Graham, 1991) genomic imprinting is likely to evolve when females carry offspring by more than one male during their life span, and also

provide most of the postfertilization nutrition. In these conditions, the probability that the identical paternally derived allele will be found in multiple offspring of the same female is low ( $<0.5$ ), compared to the probability for a maternally derived allele ( $=0.5$ ) (Hurst & McVean, 1997). Thus, the male parent's genetic interest in any future offspring of the female is decreased, as is the coefficient of relatedness between offspring of the same female (Haig, 2000; Haig & Westoby, 1989; Moore & Haig, 1991). This genetic imbalance might be inconsequential were it not for the second condition: intense uniparental care. A female's reproductive resources are limited such that resources invested in parental care decrease the amount available for future reproductive events. In addition, maternal provisioning has a significant impact on offspring survival and reproductive success (Hinde, 1987). Therefore, maternal provisioning is a limited resource for which the various genetic stakeholders in a reproductive event can be expected to compete.

Based on this conflict model, Haig and Westoby (1989) predicted increased expression of paternal alleles at loci directly involved in resource acquisition, such as those involved in placental growth, suckling, neonatal behavior, appetite, nutrient metabolism, and postnatal growth rate. They also predicted increased expression of maternal alleles at a second set of loci, important in tissue functioning but not resource acquisition, that would function to decrease the costs associated with the hypothesized paternally expressed alleles (Haig & Westoby, 1989). As an illustration, if the genes involved in suckling are paternally expressed and maternally silent, genes influencing the infant's satiety might be maternally expressed and paternally silent.

Numerous hypotheses have been proposed to explain the evolution of the genetic imprint itself, as distinct from the phenotypic effects of imprinted genes described by Haig and Westoby (1989). These include the avoidance of parthenogenesis and chromosome loss, control of cellular differentiation and expression rates, and bacterial host defence extensions (Bartolomei & Tilghman, 1997; Hurst, 1997). Discussions of various theories of the evolutionary origin of genomic imprinting, including the match of each theory to observed data, can be found in Haig and Trivers (1995) and Hurst (1997). The issue of emergence aside, the genetic conflict model is most widely discussed and used by evolutionary theorists due to its explanatory and predictive power with respect to the phenotypic outcome of selection on paternally vs. maternally expressed genes (Hurst, 1997).

### *2.1. Relatedness asymmetries, inclusive fitness, and parent–offspring conflict*

Hamilton's kin selection theory and Trivers's theory of parent–offspring conflict, two major conceptual expansions of Darwin's theory, broadened our understanding of the range of evolutionary forces and the possibilities for explicit predictions about behavior. The genetic conflict model of the evolution of genomic imprinting requires revisions within these theories regarding the means by which the degrees of relatedness between kin are assessed, and also "molecularizes" them. In their revised form, the theories may make predictions about the form and function of particular genes, prompting Trivers (1997, p. 394) to describe the genetic conflict model as the "most important advance in understanding kinship since Hamilton's work."

Each unit of maternal investment obtained by an offspring provides a fitness benefit to a number of individuals: the offspring, the mother and father whose genes are in that offspring, and maternal and paternal genetic relatives who may carry the same genes. The fitness benefit is proportional to the coefficient of relatedness between them. Offspring who are likely to have different fathers can be expected to garner as many resources as possible for themselves, at the expense of current and future siblings (Haig, 2000). Furthermore, through paternal alleles in the offspring a male parent competes with other male parents to acquire as many maternal resources as possible for the offspring carrying his genes, to the benefit of his kin as well as himself. Since the mother provides the resources, the father and his kin incur no costs as a result of the investment. In contrast, the fitness costs incurred by maternal investment in each offspring are borne by the mother, as well as her genetic relatives, whose genes are now less likely to be transmitted through future reproductive events. Thus, asymmetrical degrees of relatedness between parents and offspring suggest that the action of maternal and paternal genes within an offspring may have very different consequences in terms of maternal and paternal fitness. By the same token, the actions of maternal and paternal kin may have different effects on the fitness of maternal and paternal genes in an individual offspring (Haig, 1997). Genetic conflicts such as these will tend to escalate, with each move matched by a countermove (Haig, 1993).

Trivers's original theory of parent–offspring conflict predicted that prenatal conflict between parent and child would be biochemical in nature, whereas conflict postnatally would be behavioral (Haig, 1993; Trivers, 1974). In fact, many imprinted genes have been found to regulate fetal and placental growth biochemically (Haig, 1993), much in the manner predicted by Haig and Westoby (1989). Postnatally, mother–offspring behavioral conflict can be expected at weaning, the change to a more autonomous (and arduous) method of feeding for the offspring. In primates, this major transition is accompanied or closely followed by fewer and shorter bouts of offspring carrying and defence, as the infant makes the transition to locomotor and then social independence as well (Nicolson, 1987). Behavioral conflict between offspring and parents has been observed in primates, including humans, at all of these junctures (Buss, 1999; Nicolson, 1987).

The extended postnatal development period characteristic of humans and our complex social structure suggests that opportunities for resource conflict after birth will be manifold. Accordingly, imprinting of the genes underlying many postnatal behaviors may be expected. The genetic conflict hypothesis suggests that offspring genes involved in the acquisition of maternal resources should be paternally expressed. Thus, as occurs prenatally, offspring genes involved in postnatal resource acquisition behavior should also be inherited from the paternal genome. These would include the behaviors required to physically obtain the resource, such as suckling and grasping abilities in early ontogenetic stages, as well as the behavioral dispositions and capacities instrumental for maximizing resource acquisition during later childhood and adolescence. The genetic conflict hypothesis also suggests that maternally expressed genes would likely be involved in the control of resource availability. This may be manifested behaviorally in the infants readiness for weaning or locomotor autonomy or any developmental advance which reduces dependence on maternal resources.

These propositions may provide fruitful questions for evolutionarily and genetically oriented researchers in all areas of behavioral development and family dynamics.

## *2.2. The genetic conflict hypothesis and imprinting in fetal growth and development*

Occasionally, a conception occurs in humans in which an extra set of chromosomes from one parent is retained, in addition to the normal complement. Even more rare are conceptions carrying genes from only one parent. While neither of these situations results in viable offspring, they provide insight concerning the role of each parental genome in human fetal development.

Trophoblast proliferation in the human placenta appears directly related to the relative proportions of the maternal and paternal genome in the developing offspring. Overcontribution of the paternal genome leads to enlarged, invasive placentas, and overcontribution of the maternal genome leads to significantly reduced or absent placentas (Goshen et al., 1994, Table 1, pp. 904; Lindor et al., 1992). Where a fetus is present, an extra set of maternal chromosomes results in a stunted fetus with a relatively large head (McFadden & Kalousek, 1991). In contrast, an extra set of paternal chromosomes results in a nearly normal sized fetus with a relatively small head (McFadden & Kalousek, 1991).

The production of chimeras is a useful laboratory method to study the differential effect of the paternal and maternal genome on development in mice. Zygote formation can be experimentally induced from the union of two sperm pronuclei (androgenetic zygotes), the union of two egg pronuclei (gynogenetic zygotes), or from a single diploid egg cell progenitor (parthenogenetic zygotes). The entire genome in these zygotes carries a uniparental imprint, which explains why these zygotes fail to develop to term (Barton, Surani, & Norris, 1984; McGrath & Solter, 1984; Solter, 1988). Cells in the androgenetic zygote carry only the paternal genome, with the characteristic paternal pattern of imprinting. There are no active maternal alleles to take the place of silenced paternal alleles. Similarly, gynogenetic and parthenogenetic cells carry only the maternal genome, with the characteristic maternal pattern of imprinting. Chimeras are produced by inserting androgenetic (Ag), gynogenetic (Gg), or parthenogenetic (Pg) cells from these induced zygotes into a normal blastocyst (Barton, Ferguson-Smith, Fundele, & Surani, 1991). As long as the contribution of Ag, Gg, or Pg cells is less than 50%, the embryo will survive, and the developmental trajectory of the cells with the uniparental genome can be traced via cellular or genetic markers (Keverne, 1997; Keverne, Fundele, Narasimha, Barton, & Surani, 1996).

Experiments with androgenetic chimeras confirm the importance of the paternal genome in the development of the extraembryonic tissues such as the placenta: Androgenetic cells are the only cell type found in these tissues (Thomson & Solter, 1988). The growth of the embryo is also disproportionately influenced by the paternal genome: The introduction of Ag cells into normal mouse blastocysts results in an increase in embryonic growth of up to 50% (Barton et al., 1991). It has also been demonstrated that androgenetic cells, and, thus, the paternal genome, make a significantly greater contribution to the mesoderm than normal cells (Barton et al., 1991). The greatest dimorphic contribution in Ag chimeras is seen in cartilage and skeletal muscle tissues, which are comprised almost solely of Ag cells (Fundele, Barton,

Christ, Krause, & Surani, 1995; Keverne et al., 1996; Mann, Gadi, Harbison, Abbondanzo, & Stewart, 1990). On the other hand, these cells are virtually absent from the brain (Barton et al., 1991; Keverne et al., 1996).

The reciprocal pattern of uniparental cell distribution is observed in gynogenetic or parthenogenetic chimeras: Pg/Gg chimeras are significantly reduced in weight and size compared to normal offspring, with birth weight negatively correlated to the proportion of Pg cells (Fundele et al., 1990; Paldi, Nagy, Markkula, Barna, & Dezso, 1989). Pg/Gg cells are significantly decreased in the extraembryonic membranes, skeletal muscle, liver and pancreas (Fundele et al., 1990; Thomson & Solter, 1988), whereas they contribute more to the ectoderm than normal cells (Keverne et al., 1996). The ectoderm gives rise to the nervous system, in which Pg/Gg cells are significantly overrepresented (30–40% more than normal cells) (Keverne et al., 1996), with even greater percentages (up to 90%) in specific brain locations such as the frontal lobes (Allen et al., 1995).

This is but a brief summary of empirical findings regarding differential cell deposition patterns in chimeric mice. Interested readers are referred to Barton et al. (1991), Fundele et al. (1995), Paldi et al. (1989), and Thomson and Solter (1988).

The importance of female mating patterns in maintaining the phenotypic differences characteristic of genomic imprinting has been demonstrated by crosses between the monogamous rodent species *Peromyscus polionotus* and the related polyandrous species *Peromyscus maniculatis* conducted by Vrana et al. (2000) and Vrana, Guan, Ingram, and Tilghman (1998). If imprinting was absent in the monogamous *P. polionotus*, the resultant offspring of crosses between these two species would have growth phenotypes characteristic of the *P. maniculatis* parental imprint alone. That is, fetal and placental overgrowth should result with *P. maniculatis* fathers, and fetal and placental undergrowth should result with *P. maniculatis* mothers. In fact, *P. maniculatis* males crossed with *P. polionotus* females produce offspring that are oversized to the point of inviability (Vrana et al., 1998). *P. maniculatis* females crossed with *P. polionotus* males result in offspring 40% smaller than normal offspring of either species (Dawson, 1965). A sixfold difference in the placental weight is also observed between these two crosses (Vrana et al., 1998). Vrana et al. evaluated the imprinting status of a number of genes in *P. polionotus*, and found, contrary to expectation, that imprinting is retained within this species. However, *P. polionotus* parental imprints are severely disrupted and/or lost in the F1 hybrids, resulting in the observed phenotypes (Vrana et al., 1998, 2000).

Vrana et al. (1998) suggest the maintenance of imprinting in the monogamous species is contrary to the predictions of the conflict hypothesis. However, if *P. polionotus* became monogamous after genomic imprinting was established in the genus, there would actually be selection against the loss of the imprint, since the immediate effect of such a loss would be to double the resource transfer demands on the mother (Moore & Mills, 1999). A more reasonable outcome following a change to monogamy would be the mediation of the strength of the effect of maternally and paternally imprinted alleles through some means other than the loss of the imprint itself (Moore & Mills, 1999). In this way, a new equilibrium of maternal resource transfer could be achieved to maximize parental fitness in the context of the new mating pattern. This type of mediation could explain the results observed in these studies.

### 3. Genomic imprinting and the brain

Genes that are directly involved in brain development are estimated to number in the tens of thousands (Keverne, 1994). The first clue that imprinting plays a significant role in brain development was the dimorphic contribution of Pg/Gg and Ag cells to brain development in mouse chimeras. Not only do paternally and maternally derived cells contribute differentially to the overall size of the brain, they are found in very specific and reciprocal locations (Keverne et al., 1996). These patterns are consistently observed experimentally despite variations in the degree of chimerism (Keverne et al., 1996).

#### 3.1. *Brain size, cell proliferation, and death*

While Ag chimeras are usually large in size, the brains of these chimeras are smaller than those of normal mice, regardless of body weight (Keverne, 1997). In fact, the relationship between brain weight and body weight seems to be inversely proportional: The brain weight of Ag chimeras is lowest when body weight, and proportion of Ag cells, is highest (Keverne et al., 1996). Conversely, Pg and Gg chimeras show enhanced brain growth relative to body size (Keverne et al., 1996) despite significant reductions in body weight relative to normal mice (Keverne, 1997).

Differential parental influences on cell growth may be the mechanism by which selective cell proliferation and programmed cell death, two extremely important processes observed during brain development, are controlled (Keverne, 1997). Detailed analysis has indicated consistent and reciprocal differences in the location of uniparental (Ag and Pg/Gg) cell deposition within the brains of chimeric mice (Keverne et al., 1996). Early in gestation, uniparental cells in chimeras are found throughout the brain, mixed with normal, biparental cells. However, the number of uniparental cells in particular areas of the brain changes over time relative to normal cells (Keverne et al., 1996) due to enhanced proliferation in some regions and negative selection in others, on the basis of parental origin (Fundele et al., 1990). Uniparental cells that contain genes active in the development of a particular brain region remain viable and increase in number over time. Uniparental cells that do not contain genes active in the development of a particular brain structure or region fail to produce a lineage and are eliminated (Keverne et al., 1996). Thus, it can be inferred from differences in cell deposition patterns by parental origin that the maternal and paternal genomes contribute unequally to the development of certain brain structures. According to the genetic conflict hypothesis, paternally active genes should contribute to the development of brain structures involved in the acquisition of resources from the mother and her kin, particularly in the neonatal period when offspring growth is at a premium. Maternally active genes should contribute to the development of brain structures able to temper these resource-acquiring motivations.

#### 3.2. *Brain organization*

Androgenetic cells make their largest contribution in the brains of chimeric mice to the mediobasal forebrain and the hypothalamus, especially the septal nuclei, the bed nucleus of

the stria terminalis, and the medial preoptic area (MPOA) (Keverne et al., 1996). The number of Ag cells in the hypothalamus and MPOA is three times higher than control cells in the same region by Day 13 of gestation (Keverne et al., 1996). By Day 17 of gestation, the number of Ag cells in the hypothalamus is six times higher than control cells (Keverne et al., 1996). These values are six times and twenty times higher, respectively, than the number of Pg cells in chimeras at the same stages of development (Keverne et al., 1996). This localized pattern is preserved until birth. At the same time, Ag cells are virtually undetectable in the striatum and neocortex (Keverne, 1997; Keverne et al., 1996).

The hypothalamus regulates the autonomic maintenance of homeostasis including body temperature, osmoregulation, food intake, the sexual cycles, emotional expression, circadian rhythms, and the biological clock (Hole, 1984; Kandel, Schwartz, & Jessell, 1995). The hypothalamus secretes two important hormones itself: oxytocin, which controls milk letdown during lactation, uterine contractions during delivery, and stimulates maternal behavior; and vasopressin, a powerful vasoconstrictor and antidiuretic. Through a variety of releasing hormones, the hypothalamus exerts control over the release of all the major endocrine hormones of the pituitary gland, such as growth hormone, adrenal corticotropic hormone, thyroid-stimulating hormone, follicle stimulating hormone and leuteinizing hormone. Therefore, the parts of the brain to which the paternal genome makes a substantial contribution exert significant control over important motivated behaviors such as feeding, sex and mothering (Keverne et al., 1996). They also influence the mechanisms involved in growth and metabolism. The action of the hypothalamus can be moderated by information from higher cortical areas and the outside world, which is transferred from the higher limbic structures (e.g. hippocampus and amygdala) to the hypothalamus via the septum (Kandel et al., 1995). The paternal genome also makes a disproportionately large contribution to the septum in the brains of mouse chimeras (Keverne et al., 1996).

Unlike Ag cells, Pg cells are virtually undetectable in the hypothalamus of mouse chimeras (Keverne et al., 1996). Most Pg cells are found in the striatum and neocortex (Keverne et al., 1996), with increasing concentrations from the occipital area to the frontal lobes (Allen et al., 1995). Just over half-way through gestation (Day 10.5), Pg cells are present in greater numbers than control cells in the basal ganglia and cerebral cortex, but are already virtually absent from the diencephalic areas that give rise to the thalamus and hypothalamus (Allen et al., 1995; Kandel et al., 1995). The number of Pg cells in the cortex and striatum at Day 12 of gestation is three times higher than control cells, and six times higher than the comparative proportion in Ag chimeras (Keverne et al., 1996). In the adult, the fetal pattern is maintained, with the smallest contribution of Pg cells in the hypothalamus and the largest in the striatum, hippocampus, and cortex, especially the frontal cortex (Allen et al., 1995). Outside the brain, Pg cells also accumulate in the retina, olfactory mucosa and vomeronasal organ (Allen et al., 1995).

The striatum (caudate nucleus and putamen) processes sensorimotor information destined for the supplementary motor area (SMA) of the frontal cortex, as well as the association areas of the prefrontal cortex (Burt, 1993). These areas are critical in the planning, programming and execution of complex motor behavior, as well as responses related to emotion, affect and problem solving (Burt, 1993). The SMA is active during the planning and execution of

complex motor sequences, and coordinates bilateral movements (Kandel et al., 1995). The prefrontal association areas influence strategic planning and the ability to choose appropriate motor responses on the basis of internal and external sensory information, emotional/motivational state, and memory (Kandel et al., 1995). To facilitate this, the prefrontal association cortex also has connections with other somatosensory cortices, as well as limbic structures such as the amygdala and the hippocampus (Kandel et al., 1995).

### 3.3. *Neural connections*

Interestingly, there appear to be unique neural connections between the areas of the brain to which the paternal genome contributes most, and those in which the maternal contribution is primary. For example, the prefrontal area of the neocortex (almost exclusively composed of Pg cells in mouse chimeras) is the only cortical area known to have direct downward projections to the hypothalamus (Burt, 1993). Most afferent projections between lower brain structures and the cortex are relayed through the thalamus. There are, however, six projections to the cortex that bypass the thalamus (Burt, 1993), all of which originate in structures to which the paternal genome makes a disproportionate contribution: the hypothalamus, the basal forebrain (septal structures) and the reticular formation (Keverne et al., 1996). Unlike projections through the thalamus, which are extremely narrow in their cortical influence, these neurons project to and modulate large, functionally unrelated areas of the cortex (Burt, 1993). The exact purpose of these reciprocal neural pathways and the question of whether paternal and maternal genes differentially influence the development of these pathways both remain unresolved. Current speculation (Haig, 2000; Keverne, 1997) is based on the contention that competition for the regulation of motivated behavior may have been crucial in the evolutionary development of these pathways.

## 4. Genomic imprinting, brain, and behavior

### 4.1. *Behavioral disorders and differential parental influences on brain development*

If a disorder is more frequently or exclusively transmitted from a parent of a particular sex, genomic imprinting may be implicated (Hall, 1997). A number of human neurological disorders have such an inheritance pattern. Based on the cell deposition patterns discussed above, it can be expected that a disorder transmitted from the mother would involve the cortex or striatum, whereas a disorder transmitted from the father would involve the hypothalamus or septum. The behavioral phenotypes of a number of human neurological disorders support the hypothesis that the parental genomes play differential roles in human brain development.

#### 4.1.1. *Prader–Willi and Angelman Syndromes*

Differential expression of maternal and paternal alleles influencing adult behavior is most clearly demonstrated by Angelman Syndrome (AS) and Prader–Willi Syndrome (PWS).

PWS is characterized by mental handicap, hypotonia (lack of muscle tone and response to stretch), hypogonadism, poor temperature regulation, and obesity (Butler, 1990; Friend, 1995). Infants with PWS show poor suck reflexes following birth, and often show failure to thrive as a result (Moore & Haig, 1991). In the older child, food-related behavioral problems continue to occur, specifically insatiable appetite, food stealing, gorging, and pica (Friend, 1995). The hyperphagia may be very extreme, with weight gains of more than 200% above normal body weight (Butler, 1990; Flint, 1992). These individuals may also demonstrate rage, depression and lethargy (Friend, 1995).

AS is characterized by mental retardation, seizures, and repetitive, uncoordinated but symmetrical movements. Patients may also have fits of inappropriate laughter (Friend, 1995). As neonates, AS patients show uncoordinated tongue movements, and have difficulty sucking and swallowing (Moore & Haig, 1991).

There are no consistent genetic differences between PWS and AS: Both are caused by mutations or deletions on the long arm of chromosome 15 at 15q11–q13 (Flint, 1992). However, the phenotype of the disorder varies significantly according to the parent from whom the mutation was inherited: PWS is inherited via the paternal chromosome, whereas AS is inherited via the maternal chromosome.

There are a multitude of imprinted genes in the 15q11–q13 region, some of which are paternally expressed, some of which are maternally expressed, and some where the imprinting status shows conflicting experimental results (Jiang, Tsai, Bressler, & Beaudet, 1998). All, however, appear to be brain specific in expression or imprinting (Nicholls, Saitoh, & Horsthemke, 1998).

The characteristic physical and behavioral abnormalities associated with PWS suggest hypothalamic dysfunction (Butler, 1990), though the symptoms are sufficiently limited to suggest that hypothalamic failure is incomplete (Nicholls et al., 1998). Recent research has implicated dysfunction of one subtype in a family of receptors for the neurotransmitter serotonin.

Serotonin 2C receptor subtypes (designated 5-HT<sub>2C</sub>R) are found widely distributed throughout the brain and spinal cord (Kandel et al., 1995), including the paraventricular nucleus (PVN) of the hypothalamus (Hoffman & Mezey, 1989). Lesions of the PVN lead to a behavioral obesity syndrome in mice (Parkinson & Weingarten, 1990). Mice with mutation of the 5-HT<sub>2C</sub>R gene show a similar propensity, overeating to the point of obesity despite no associated metabolic change (Tecott et al., 1995). Hypothalamic serotonin receptors normally inhibit neuropeptide Y, a potent stimulator of hunger and food intake (Halford & Blundell, 2000).

The 5-HT<sub>2C</sub>R gene is located on the X chromosome in humans (Cavaillé et al., 2000), making it seem an unlikely candidate in the etiology of PWS. However, Cavaillé et al. have identified a unique subset of small nucleolar RNA, or snoRNA, that link 5-HT<sub>2C</sub>R dysfunction to PWS. SnoRNA normally function throughout the body in the modification of ribosomal RNA (rRNA) during ribosome synthesis. These particular snoRNAs, however, show no association with rRNA. Instead, they are found only in brain tissue and appear to function in the modification of the 5-HT<sub>2C</sub>R mRNA prior to synthesis of the functional receptor. The genes encoding three of these snoRNAs are paternally expressed and map to

within 1.5 megabases of the region on chromosome 15 most closely linked to PWS (Cavaillé et al., 2000; Filipowicz, 2000). Furthermore, the genes encoding these three snoRNAs are not expressed in brain tissue from PWS patients or in mouse models of the disease (Cavaillé et al., 2000).

Genes coding for three subunits of the A-type GABA receptor (*GABRB3*, *GABRA5*, and *GABRG3*) have also been mapped to the PWS/AS critical area (Friend, 1995; Wagstaff et al., 1991). GABA is an important inhibitory neurotransmitter used in the brain. There have been conflicting reports about the imprinting status of these receptor genes, with studies of the B3 subunit gene providing the most paradoxical results (Jiang et al., 1998). The most recent study suggests paternal expression/maternal silence in humans (Meguro et al., 1997).

The GABA<sub>A</sub> receptor subunit genes are implicated in AS. Loss of the maternal genes could lead to dysfunctional GABA<sub>A</sub> receptors in the neocortex and striatum, to which the maternal genome makes the largest contribution. The basal ganglia, of which the striatum is a part, modulate information from parts of the cortex involved in movement (e.g. the motor, premotor and somatosensory cortices, and the supplemental motor area), and feed it back to the supplemental motor area and premotor cortex (Kandel et al., 1995). GABA plays an important role in the modulation of this information within the basal ganglia (Kandel et al., 1995), since impulses from the basal ganglia normally inhibit motor functions (Hole, 1984). If inhibitory GABA neurons from the basal ganglia synapse with dysfunctional GABA<sub>A</sub> receptors in the SMA, the inhibitory impulses would be ineffective. Based on the function of the SMA, this type of disinhibition could lead to the symmetrical involuntary movements characteristic of AS.

The *GABRB3* gene is deleted in most AS patients (Lalande, Minassian, DeLorey, & Olsen, 1999), but conclusions regarding the functional significance of this deletion must await clarification of its imprinting status. If the gene is found to be maternally silenced in brain tissue, its hypothesized role in the etiology of AS is unlikely, since the deletion of a silent allele would have no phenotypic effect. However, imprinting of the GABA<sub>A</sub> receptor subunit genes will have important implications for our understanding of other disorders mediated by GABA, such as anxiety and seizure disorders (Durcan & Goldman, 1993).

A more likely candidate in the genetic etiology of AS is *UBE3A*, the product of which (the enzyme *ubiquitin protein ligase*, or E6-AP) is involved in protein degradation and processing (Lalande et al., 1999). Protein degradation plays an important role in a variety of basic cellular processes, including the regulation of cell cycles and division, certain aspects of differentiation and development, morphogenesis of neuronal networks, and DNA repair, among others (Ciechanover, Orian, & Schwartz, 2000b). The enzyme product E6-AP is expressed in very specific regions of the human and mouse brains, namely the hippocampus and cerebellum (Nicholls et al., 1998). The fact that *UBE3A* is maternally expressed/paternally silent in these tissues (and these tissues alone—it is biallelically expressed elsewhere; Jiang et al., 1998; Meguro et al., 1997), has led most researchers to conclude that "... maternal deficiency for *UBE3A* is the primary biochemical and molecular defect leading to AS" (Jiang et al., 1998, pp. 339). *UBE3A* is mutated in many, but not all AS patients (Lalande et al., 1999). It is also the gene most closely linked to

*GABRB3* (Jiang et al., 1998), which may partially explain the confusing experimental results obtained in studies of that gene.

The ubiquitin protein degradation system, of which the *UBE3A* product E6-AP is a part, is responsible for targeting and marking protein substrates to be degraded (Attaix, Combaret, Pouch, & Taillandier, 2001). Proteins within the cell are targeted for destruction through the attachment of a ubiquitin chain (Ciechanover, Orian, & Schwartz, 2000a). Hundreds of cellular proteins are targeted for degradation in this way, including abnormal and denatured or misfolded proteins. Several families of enzymes, comprising hundreds of members, control this process (Attaix et al., 2001). However, each enzyme in the system, including E6-AP, recognizes only a small subset of target proteins (Ciechanover et al., 2000b; Yamamoto, Huibregtse, & Howley, 1997). It is hypothesized that the substrate normally marked for degradation by E6-AP remains unmarked in AS patients, thereby accumulating to toxic levels in the developing brain. This substrate has not yet been identified.

This discussion highlights the fact that the action of imprinted genes may involve complex biochemical interactions with other genes, some of which are also imprinted. Nevertheless, knowledge of the differing contributions of the maternal and paternal genome to brain development can help explain behavioral phenotypic effects before the precise biochemical pathway is known.

#### 4.1.2. Autism

The 15q region has also been implicated in the genetic etiology of autism. While a specific cause has been documented in fewer than 20% of autistic cases, there is significant evidence for a genetic basis to the disorder. Autism tends to occur together with other heritable disorders, siblings are at increased risk of developing the disorder, and there is increased concordance in monozygotic twins (Cook et al., 1997; Schroer et al., 1998). In addition, cognitive, language, and behavioral disorders occur more frequently in close relatives than in the population at large (Schroer et al., 1998).

Duplications and deletions of 15q have been found in a number of patients with autism, and in all cases the abnormal chromosome was maternal in origin (Cook et al., 1997; Schroer et al., 1998). In one large study, abnormalities of chromosome 15q emerged as the single most common identifiable cause of the disorder (Schroer et al., 1998). In two reported cases, a paternally inherited duplication in the mother caused no abnormal phenotypic effects until it was passed from her to her children (Cook et al., 1997; Schroer et al., 1998), thereby implicating maternally expressed imprinted genes.

Duplication and deletion of maternally expressed genes in the 15q region both lead to divergence from the normal monosomic gene dosage (Schroer et al., 1998). The same genetic alteration inherited from the father would have no effect. Significantly, autism is frequent in AS patients, but rarely occurs with PWS (Schroer et al., 1998). Candidate genes in the area include those implicated in AS: *UBE3A* and the three GABA<sub>A</sub> receptor subunit genes, *GABRB3*, *GABRA5*, and *GABRG3*. Perturbations of the normal maternal complement would have the greatest effect in the cortex, to which the maternal genome makes a primary contribution. Indeed, widespread cortical dysfunction is clearly indicated by the abnormal social, language and cognitive development characteristic of autism.

#### 4.1.3. Turner's Syndrome

Nondisjunction of the sex chromosomes during meiosis occasionally results in the formation of an egg or sperm with no sex chromosomes. If this gamete combines with a normal gamete during reproduction, the only viable offspring possible will be a female with the genotype  $X_0$ , and the phenotype will be Turner's syndrome. Turner's syndrome is characterized by hypogonadism, infertility, and short stature (Hole, 1984). This syndrome provides a unique opportunity to investigate the differential effects of the paternal and maternal genome, since approximately 70% of individuals with Turner's syndrome inherit their X chromosome from their mother (labelled  $X_{m0}$ ), whereas the remainder inherit the paternal chromosome ( $X_{p0}$ ) (Isles & Wilkinson, 2000; Skuse et al., 1997). Recent research, using familial questionnaires and direct psychological assessment, has indicated that these individuals are also differentiable on the basis of cognitive and social skills, possibly due to the functional inequivalence of the maternal and paternal X chromosome.

Parents were administered a social cognition questionnaire to assess such things as the child's awareness of others' feelings or the effect of their behavior on the family and others, the ability to follow commands, the frequency and type of offensive, demanding, or disruptive behavior, and their understanding of body language (Skuse et al., 1997). According to their parents,  $X_m$  females had difficulties in all of these areas, but they particularly seemed to lack flexibility and responsiveness in social interactions (Skuse et al., 1997). Parents also indicated that  $X_m$  females had more difficulty suppressing inappropriate behaviors in social situations than did  $X_p$  females (Scourfield, McGuffin, & Thapar, 1997). Taken together, the results of the parental questionnaires indicate impaired social cognition in  $X_m$  females.

The results of direct psychological testing support the conclusions drawn from the questionnaire studies.  $X_m$  females score significantly lower than  $X_p$  females on tests of verbal IQ, a measure that correlates negatively with measures of social dysfunction (Scourfield et al., 1997). Direct tests of behavioral inhibition, such as the "same–other world" test, also favour  $X_p$  females (Skuse et al., 1997). These results are also consistent with health and scholastic records showing 72% of  $X_m$  females have clinically significant social difficulties relative to  $X_p$  females, and special education needs (Keverne, 1997; Scourfield et al., 1997).

The results of these studies suggest that genes involved in social cognition and verbal ability may be preferentially paternally expressed/maternally silenced in humans (Skuse et al., 1997). If this can be confirmed by further research, it may improve our understanding of why males, who only receive the maternal X chromosome, are more susceptible to developmental disorders of language and social cognition, including autism (Skuse et al., 1997). In fact, while autism is rare in females (approximately 1 in 10000 normal females), 3 of 80  $X_{m0}$  females in the population studied by Skuse and colleagues (1997) had been diagnosed with the disorder.

The asymmetrical influence of the parental genomes with respect to social cognition and language may provide further support for the conflict model of genomic imprinting. Human social interactions are crucial in acquiring a wide variety of material and nonmaterial resources, and resource acquisition is more common among kin than nonkin. Both are consistent with the proposition of the model that paternally active genes are primarily involved in resource acquisition from the mother and her kin.

#### 4.1.4. Other neurological disorders where imprinting is implicated

If a disorder is more frequently or exclusively transmitted from a parent of a particular sex, genomic imprinting is implicated (Hall, 1997). A number of disorders have inheritance patterns implicating genomic imprinting in brain development. Based on the cell deposition patterns discussed above, it can be expected that a neurological disorder transmitted from the mother would involve the cortex or striatum, whereas a disorder transmitted from the father would involve the hypothalamus or septum.

For example, the bulk of empirical evidence suggests that women with bipolar affective disorder (BPAD) are more likely to have children with the condition than are men with the disorder (Keverne, 1997; McMahon, Stinc, Meyers, Simpson, & DePaulo, 1995). In addition to their mothers, individuals affected with BPAD often have numerous affected female relatives as well (McMahon et al., 1995). MRI studies of BPAD have implicated the prefrontal cortex, a finding consistent with maternal transmission (Keverne, 1997).

Similarly, the risk of an individual having seizures is higher if the mother has epilepsy than if the father is affected (Ottman, Annegers, Hauser, & Kurland, 1988). This was found to be true regardless of seizure type (generalized vs. partial), etiology, drug use, or management during pregnancy (Ottman et al., 1988). The transmission is not totally maternal, since the children of males with epilepsy still have a higher risk than the general population (Ottman et al., 1988). Nevertheless, support for the hypothesis of maternally transmitted seizure susceptibility appears to be growing (Ottman et al., 1988). Epileptic seizures most often have their focus in the cerebral cortex, where the maternal genetic contribution is primary.

Numerous other neurological disorders, including Tourette's syndrome, schizophrenia, and Huntington's disease (Isles & Wilkinson, 2000; Lichter, Jackson, & Schachter, 1995) also show parent-of-origin influences on inheritance. However, the diagnostic and etiological complexity of these disorders and the lack of nonhuman homologues make more detailed genetic investigation difficult.

#### 4.2. Imprinted genes and normal maternal behavior in the mouse

Significant effects of imprinted genes on complex behavior are perhaps most explicitly shown by studies involving mice with knockout mutations of particular imprinted genes. Both of the genes that have been studied in this way are paternally expressed/maternally silenced in normal mice, and show a large degree of expression in the hypothalamus.

The first of these genes, *Mest* (also called *Peg1*), is paternally expressed during development, especially in the mesoderm (Lefebvre et al., 1998). Loss of *Mest* decreases body size and birthweight to less than 85% of normal, with weight continually decreasing with time after birth (Lefebvre et al., 1998). By Day 28 postpartum, 50% of *Mest*-deficient pups are dead (Lefebvre et al., 1998). Lacking a clear causal explanation in the offspring, researchers looked to the behavior of *Mest*-deficient mothers to explain this significantly increased mortality. These mothers had 88% of their offspring die, regardless of the genotype of the offspring (*Mest*-deficient vs. *Mest*-positive) (Lefebvre et al., 1998). These same pups could be successfully fostered with normal wild-type females (Lefebvre et al., 1998), suggesting that deficiencies in the maternal behavior of the mothers were the cause of mortality. Analyses of

maternal behavior in *Mest*-less females showed that while they approached and sniffed their pups just like normal mothers, they were severely impaired in other aspects of the maternal behavioral repertoire. They did not remove and ingest the placenta and extraembryonic membranes from around the pups, they left the pups unattended for long periods, they did not retrieve them, and their nest building skills were impaired (Lefebvre et al., 1998).

*Mest* is highly expressed in areas of the brain where the paternal genome makes a substantial contribution, such as the hypothalamus (Lefebvre et al., 1998). Specific regions of the hypothalamus (namely the MPOA and the lateral hypothalamic nuclei) have been shown to be involved in the control of maternal and ingestive behavior, including placentophagia (Lefebvre et al., 1998). *Mest* is also highly expressed in the olfactory bulb (Lefebvre et al., 1998). Given the crucial role of olfaction in the stimulation of maternal behavior in mice (Fleming & Rosenblatt, 1974a, 1974b), one might assume that a generalized impairment in olfactory ability could underlie the deficiencies in maternal behavior seen in these mice. However, *Mest*-deficient mice were as proficient as wild-type mice in finding food when hungry (Lefebvre et al., 1998), suggesting that the olfactory impairment was offspring specific.

The second gene implicated in maternal behavior in the mouse is *Peg3*. *Peg3* is paternally expressed in mesoderm and endodermal tissues during development, and in the hypothalamus in adult brains (Li et al., 1999). *Peg3*-deficient mice had similar behavioral abnormalities to *Mest*-deficient mothers: They approached and sniffed their pups quickly, but failed to gather, nest, and care for their pups as normal mothers would (Li et al., 1999). Lactational ability was also impaired in *Peg3*-deficient mothers (Li et al., 1999). Not only did they take longer to assume the required crouching position, but their offspring gained less weight than offspring of normal mothers, despite equal time spent suckling (Li et al., 1999). After weaning, however, their offspring caught up to wild-type weights (Li et al., 1999), suggesting a nutritional or quantitative deficit in milk from *Peg3*-deficient mothers.

Histological analyses revealed normal mammary glands, but a striking lack of oxytocin-producing neurons in the hypothalamus (Li et al., 1999). Oxytocin stimulates maternal behavior, uterine contractions, and the secretion of milk during lactation. Infant suckling causes the release of oxytocin from the hypothalamus, which stimulates the contraction of muscles surrounding the mammary glands and the ejection of milk (Hole, 1984; Li et al., 1999). A decrease in the amount of this hormone would result in lower quantities of milk being delivered to suckling offspring, despite normal mammary gland function. It could also lead to the placentophagia and nest-building deficiencies observed. While this finding appears to explain much of the observed deficiencies in *Peg3*-deficient mothers, they still had normal conceptions, pregnancies, births, and mammary development (Li et al., 1999). Thus, endocrine dysfunction is only one piece of this complex puzzle.

The paternal expression of genes involved in mothering behaviors, namely *Mest* and *Peg3*, provides a significant interpretive challenge for the genetic conflict hypothesis. Li et al. (1999) suggest that asymmetrical parental interests resulted in maternal imprinting/paternal expression of these genes. They propose that paternal regulation of maternal behavior evolved to enhance paternal fitness, through the prolonged care and feeding of offspring bearing his genes (Li et al., 1999). However, it is the maternal grandfather of the offspring

that would be contributing these genes to the mother, as opposed to the father of the offspring. There is an equal chance that an offspring will receive from his or her mother a grandpaternal or a grandmaternal allele. Therefore, grandpaternal alleles that promote maternal behavior would benefit grandfathers and grandmothers equally (Smits, Parma, & Vassart, 2000). It has been suggested that the imprint on these genes, especially *Peg3*, evolved primarily in response to their influence on offspring size, since both of these genes have been shown to have growth promoting effects *in vivo* (Lefebvre et al., 1998; Li et al., 2000; Smits et al., 2000; Vrana et al., 2000). The advantage conferred by imprinting in the regulation of offspring growth may have been significant enough to lead to fixation, independent of any other phenotypic effects, including maternal behavior (Haig, 1999; Lefebvre et al., 1998; Li et al., 2000).

#### 4.3. *In vivo* changes to imprinting

Evidence for environmental influences on imprinting has emerged from drug and alcohol research, suggesting that changes to the parental imprint may have adverse effects on neural development in offspring. In mammals, chemicals ingested by the mother have numerous ways in which to alter development in her offspring. However, drug and alcohol consumption by fathers has also been shown to affect offspring behavior in rats, possibly through alterations to genomic imprinting. The offspring of male rats fed alcohol have decreased body weight, increased susceptibility to stress, poor avoidance learning, and impaired spatial learning (Abel, 1989; Abel & Lee, 1988; Wozniak, Cicero, Kettinger, & Meyer, 1991). They show no difference, however, on activity levels, exploration, object recognition, developmental trajectory, or sensorimotor development (Wozniak et al., 1991).

A number of mutagens, including alcohol, have been shown to alter the methylation of DNA in a variety of tissues (Kirkness & Durcan, 1992). Although this has not yet been demonstrated in sperm, a single dose of alcohol has been shown to change the methylation of DNA in rat liver (Durcan & Goldman, 1993). It is possible that alcohol consumption could alter the normal male pattern of imprinting, resulting in overexpression of these genes in the brain and subsequent behavioral abnormalities.

In addition to effects on the brain, individual or environmental factors that alter the imprint on a gene and the timing of these factors could play a large role in a person's genetic susceptibility to cancer (Reik, 1989). Changes in DNA methylation consistent with the reactivation of an imprinted allele are observed in all premalignant or malignant tumours, and represent "... the earliest and most ubiquitous ... DNA alteration in cancer" (Feinberg, 1993, pp. 113). These examples illustrate how the biological imprint on a gene is one point at which factors in the environment may influence development and health.

### 5. Intrafamilial correlations: A potential new approach to imprinting research

Behavior geneticists have compared correlational patterns among pairs of immediate family members by various methods to establish the influences of sex-linked recessive genes

(e.g. Ashton & Borecki, 1987; Yen, 1975), and this approach may be applied to genomic imprinting as well. If a maternally expressed, paternally silenced gene is expressed in the offspring of either sex, the probability is 100% that it is carried by the mother. The probability that it is carried as well by the father will correspond to the frequency of the allele in the population and will be less than 100%. The reverse conditions apply for paternally expressed maternally silenced genes. Thus, significantly larger correlations for a given trait between offspring and parents of either sex are suggestive of genomic imprinting. These methods, as they are used to explore sex-linked recessive effects, may be applied to traits with high heritability quotients or other indications of a notable genetic factor. Alternatively, with the benefits of brain scanning techniques, intrafamilial correlations may be used adjunctively with brain and behavior studies; that is, correlational patterns may be assessed for traits which appear to be mediated by areas of the brain showing differential contributions of the maternal and paternal genomes.

## **6. Conclusions**

Genomic imprinting has important implications for our understanding of the genetic regulation of development, disease, and behavior. Knowledge of imprinting adds a new facet to risk assessment and genetic counseling, as well as to the study of genes themselves in biochemistry, genomics, and gene mapping. While many imprinted genes appear to influence fetal development and growth, the expression of imprinted genes also varies over space and time within an individual. Genes may be imprinted in some tissues and not others, or only at certain times during development, making imprinting an important regulatory process over the entire life span.

Numerous human genetic diseases are being reevaluated to determine if there are parent-of-origin effects. The risk of transmitting or inheriting a disease can be calculated with more accuracy if the imprinting status of the gene is known. Studies of the role played by genomic imprinting in disease states may be particularly enlightening in the case of cancer. Identifying the cancerous consequences of losing the imprint on a gene furthers our understanding of the etiology of cancer, and improves our understanding of how environmental factors can influence genetic events. Normal development can no longer be viewed as a stable linear trajectory with one set of “plans” and a backup copy. It is, at least in part, a balance between the contrasting forces of the parental genomes. When this balance is disturbed, the resultant phenotypic effects may be more predictable given an understanding of genomic imprinting. Such disturbances also provide information about the role of each contributing genome in normal development.

The genetic conflict hypothesis of genomic imprinting predicts greater paternal contribution to parts of the brain involved in resource acquisition behavior from the mother and her kin. It also suggests that the maternal contribution to the brain would be more likely to control and suppress these behaviors. This view is consistent with knowledge of the functions of the tissues for which highly dimorphic contributions are observed (Iwasa, 1998). The areas of the brain showing the highest degree of uniparental cell deposition in

chimeras, namely the frontal cortex and the hypothalamus, are both involved in motivation. Motivational states generated in each of these areas may diverge, resulting in internal conflicts (Haig, 1998). Where the goal most beneficial to an individual's fitness requires interaction with kin, internal conflicts in motivation may be particularly acute due to the asymmetric genetic relationships between an individual and their maternal and paternal kin (Haig, 1997, 2000).

The theoretical implications of genomic imprinting will require a paradigm shift as our view of particulate inheritance is altered to accommodate local but predictable changes in gene expression in each generation. The conflict theory of genomic imprinting is a powerful yet elegant predictive tool that may be fruitfully applied by all evolutionary scientists interested in the interrelationships of brain, cognition, and behavior.

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