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Perspective

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Perspective

SERIES
on epigenetic regulation

Benjamin Tycko, Editor

The majority of genes are inherited in 2 copies, 1 from each parent (the exceptions being sex-linked genes in males and mitochondrial genes). Whereas most such genes have identical functions, imprinted genes usually function only when inherited from either the mother or the father. Imprinted genes are marked in the male and female germline and retain molecular memory of their parental origin, resulting in allelic expression differences during development. Over 35 imprinted genes have been identified to date in the combined human and mouse genomes, representing perhaps 5–20% of those predicted to be imprinted (1, 2). Abnormalities in imprinted inheritance occur in several well-known developmental and neurobehavioral disorders, including Albright's hereditary osteodystrophy and Angelman, Beckwith-Wiedemann, and Prader-Willi syndromes. Each of these diseases involves complex genetic loci and gene regulation and will be compared in this article. Recent studies have also demonstrated directly a role for imprinted genes in determining brain development and for 2 paternally expressed genes in regulating maternal behavior in mice. Here I will review evidence that imprinted mammalian genes influence complex neurobehavioral phenotypes, including psychiatric disorders. Such observations have significant implications for genetic approaches to identifying the etiological genes involved in these and other similar complex traits.

Prader-Willi and Angelman syndromes. Clinical features of Prader-Willi syndrome (PWS) include postnatal failure to thrive with childhood onset of hyperphagia and severe obesity, and short stature with neurosecretory growth hormone deficiency (3). Other neurobehavioral attributes of PWS include developmental delay, mild to moderate mental retardation, learning disabilities (with strengths in reading, speech, and long-term memory and weaknesses in arithmetic and short-term memory), obsessive-compulsive disorder, temper tantrums and stubbornness, poor social interactions, abnormal sleep, hypogonadotropic hypogonadism, temperature instability, and, in 5 to 10% of patients, psychosis. In contrast, the Angelman syndrome (AS) clinical phenotype is characterized by severe neurological features, including developmental delay, ataxia, severe mental retardation, lack of speech, paroxysms of laughter, seizures, hyperactivity, attention deficit (with poor social interactions), sleeping difficulty, aggressive behavior, and tongue protrusion.

The genetic aberrations in PWS and AS include a common 4-Mb 15q11-q13 deletion of paternal or maternal origin, respectively, or maternal uniparental disomy

(UPD) in PWS and paternal UPD in AS (Table 1) (4, 5). These 2 genetic classes indicate that the PWS gene(s) are normally expressed only from the paternal allele and are silent on the maternal chromosome, with the opposite pattern and a maternally expressed gene causing AS. The latter has been identified as the *UBE3A* gene, because specific mutations occur in familial and sporadic patients (Table 1) (5). Intriguingly, *UBE3A* typifies a growing number of mammalian imprinted genes, in that it only displays imprinting in a tissue-restricted manner. Thus, maternal-only expression of *UBE3A* occurs only in certain regions of the human and mouse brain, such as cerebellar Purkinje's cells and hippocampal neurons (5), with biparental expression in all other tissues. These observations explain the neurological-specific phenotype of AS.

In contrast to AS patients, individuals with PWS of the classic type always have chromosomal abnormalities — large deletions, UPD, or an imprinting mutation (the latter discussed below) — affecting multiple genes. As seen in Table 1, no patient has inheritance consistent with a single gene mutation, suggesting that PWS requires the loss of function of 2 or more paternally expressed genes (3, 4). Indeed, multiple genes have been identified across a 1.5–2-Mb region of human chromosome 15q11-q13 that are expressed only from the paternally inherited allele (Figure 1a) (3, 4). The deletion interval associated with PWS also includes the maternally expressed *UBE3A* gene and several nonimprinted genes (Figure 1a). The finding of many paternally expressed genes presents a major obstacle to identifying the critical imprinted genes involved in PWS, because each of these, or others not yet identified, may play some phenotypic role in PWS. As the 15q11-q13 genes are identified from the human genome sequence and allele-specific expression assays, it becomes possible to test their contribution to the PWS phenotype, either by generating mouse models or by studying people with specific components of PWS for evidence of mutations in the gene of interest. Of the PWS candidate genes, one intriguing locus (*SNURF-SNRPN*) is polycistronic and encodes 2 functional proteins (3). This complex locus is of considerable interest because it specifically shows microdeletions (7–200 kb) in patients with mutations in the imprinting process, indicating an involvement in the regulation of imprinting in 15q11-q13 (see below).

Although a few balanced translocations occur in PWS (Table 1), the molecular basis is not understood (3). Two patients with classical PWS have a translocation break-

Table 1

Complex molecular basis of 3 imprinted, developmental disorders

Molecular class	PWS ^A	AS ^A	BWS ^A
Deletion or duplication	Paternal deletion (75%)	Maternal deletion (75%)	Paternal duplication (< 1%)
UPD	Maternal (meiotic) (22%)	Paternal (meiotic) (2%)	Paternal (somatic) (10%)
IM	IC microdeletions (1%)	IC microdeletions (1%)	None
inherited	+ ^B (2%)	+ ^B (2%)	LOI at <i>IGF2</i> (20%) or <i>LIT1</i> (50%) ^D
sporadic			
Translocation, chromatin effects ^C	Paternal inheritance (< 1%)	None	Maternal inheritance (< 1%)
Gene mutation	None	Maternal <i>UBE3A</i> (7%)	Maternal <i>CDKN1C</i> (<i>p57^{KIP2}</i>) (10%)
Unknown	None	+ ^B (13%)	None/+ ^B (0–8%)

^AParentheses indicate overall percentage of patients showing this molecular class. See also Maher and Reik (this series). ^{B+}, molecular class present. ^CTranslocations are postulated to cause disease as a consequence of disrupting chromatin or long-range epigenetic regulation. In contrast to PWS and BWS, translocations in AS fall into the gene mutation class. ^DThe imprinting mutations, or LOI, in BWS include at least 2 classes. One class of patients has biallelic *IGF2*, is also null for *H19* expression, and shows abnormal methylation at *H19*. The second class shows biallelic *LIT1* (*K,LQT1-AS*) expression coupled with hypomethylation at an associated CpG-island, with or without LOI at *IGF2* (7, 8; Maher and Reik, this series).

ing within the bicistronic *SNURF-SNRPN* gene and express all tested paternally expressed genes in 15q11-q13, implicating the disrupted locus in PWS. However, the translocations in 2 patients with atypical “PWS-like” phenotypes lay distal of *SNURF-SNRPN* but proximal to the *IPW* gene (Figure 1a), which may indicate a role for genes at or on the distal side of the translocation. A unifying hypothesis is that the translocations affect neuronal chromatin structure, disrupting the function of multiple genes within 15q11-q13 through some form of position effect. Whereas it is also possible that the germline imprinting process (see below) is affected, the imprint may already have been set before the chromosome rearrangement, and this hypothesis is not fully compatible with the expression and methylation data.

Several mouse models have recently been developed for PWS or AS. These include animals with UPD and strains that carry a 4-Mb deletion affecting the region of the mouse genome that corresponds to human 15q11-q13. Interestingly, the deletion model segregates mouse phenotypes that mimic both PWS and AS, depending on the inheritance of the mutation. In addition, an imprinting mutation, discussed below, causes features of PWS, and targeted mutations of the murine *Ube3a* gene have been used to study AS (reviewed in ref. 6). The AS models display a mild neurobehavioral phenotype, observable only on careful testing, whereas the PWS mouse models all fail to thrive and often die shortly after birth. Failure to thrive is also seen in infants with PWS, and recent

Table 2

Selected developmental and neurobehavioral disorders and genes with evidence for an imprinting effect

Disorder	Chromosome Location	Genes	Expressed allele	Comments	References
Mouse, maternal behavior	7q32	<i>Mest</i> (<i>Peg1</i>)	Pat	Human equivalent not clear	(15)
Russell-Silver syndrome (growth retardation)	7	Unknown	Pat	Mat UPD	(1)
BWS; embryonal tumors	11p15	<i>IGF2</i> , <i>LIT1</i> , <i>H19</i> <i>CDKN1C</i>	Pat, Pat, Mat, Mat	See Table 1, Figure 1b	(*)
Hereditary paraganglioma	11q13 & 11q23	Unknown	Pat	Paternal inheritance	(19)
Retinoblastoma; (affective disorder, schizophrenia?)	13	<i>HTR2A</i>	Mat	Polymorphic imprinting in brain	(18), (20)
Endocrine and developmental abnormalities (Mat); 14 MR, multiple congenital abnormalities (Pat)		Unknown	Pat; Mat	Mat UPD; Pat UPD	(1)
PWS	15q11.2	Unknown	Pat	see Table 1, Figure 1a	(4)
AS	15q12	<i>UBE3A</i>	Mat	see Table 1, Figure 1a	(5)
Autism	15q11-q13	Unknown	Mat	duplications	(1)
Mouse, alcohol preference	17q21	<i>Alcp2</i> (unknown)	Mat	Acts on females after mat inheritance	(21)
Bipolar disorder	18p11.2	Unknown	Pat	Linkage with male relatives	(22), (23), (24)
Mouse, maternal behavior	19q13.4	<i>Peg 3</i>	Pat	Human equivalent not clear	(16)
AHO; PHP-1a	20q13	<i>GNAS1</i>	Pat, Mat	See Figure 1c	(10), (11)
Turner's syndrome	X	Unknown	Pat	Enhanced social skills with a Pat X	(25)
Catatonic schizophrenia	-	Unknown	Pat	Lower age of onset	(26)
Bipolar affective disorder	-	Unknown	Mat	Increased incidence of affected mothers	(27)
Tourette's syndrome	-	Unknown	Mat	Lower age of onset	(28)
Late-onset Alzheimer's disease	-	Unknown	Pat	Increased incidence born to younger fathers	(29)
Neural tube defects	-	Unknown	Mat	Increased incidence	(30)
Audiogenic seizures	mouse 7A-C	<i>Asp3</i> (unknown)	Pat	Susceptibility	(31)

Mat, maternal; MR, mental retardation; Pat, paternal. *See other Perspectives in this series (Maher and Reik; Tycko).

mouse studies involving gene-specific knockouts suggest that this phenotype involves the additive contribution of several genes (6), including the *NDN* gene, *SNURF-SNRPN*, and/or an unknown gene between the latter locus and *IPW* (see Figure 1a) (6). By restoring these genes individually into PWS mouse models it may be possible to identify their contributions to the various phenotypic components of PWS. Ultimately, therapeutic intervention in PWS or AS will require a fuller understanding of the biochemistry and physiological roles of the products of these genes.

Developmental disorders involving imprinted genes. Molecular analysis of 2 disorders, Beckwith-Wiedemann syndrome (BWS) and Albright hereditary osteodystrophy (AHO), provides the clearest examples of imprinted genes that regulate growth and development, although Table 2 indicates other developmental disorders that show similar, but less well-understood, effects. As for PWS and AS, the molecular basis of BWS is extraordinarily complex. The genetic mechanisms underlying BWS include paternally derived duplications, UPD, and loss of imprinting (LOI) at *IGF2*, implicating a role for a paternally expressed gene, and maternally derived

translocations and specific *CDKN1C* (*p57^{KIP2}*) mutations, implicating a role for a maternally expressed gene (Table 1) (7, 8; Maher and Reik in this Perspective series). Mouse model studies suggest that in some tissues, where both are expressed, *IGF2* and *CDKN1C* antagonize each other's effects on cell cycle progression (9). Nevertheless, these 2 oppositely imprinted candidate genes are located over 500 kb apart and may be located in independently regulated imprinted domains (Figure 1b). Detailed mutational studies in the mouse have clearly shown that the 5' *H19* region is able to regulate the imprinting of *H19*, *Igf2*, and *Ins2*, but that this domain is independent of the other imprinted genes in chromosome 11p15 (Figure 1b) (2). It is unclear whether, or to what extent, the imprinting of these other genes is coordinately regulated. Evidence for long-range chromatin effects is provided by the occurrence of translocations in BWS patients within *K_vLQT1* (Table 1), which, though imprinted in most tissues, is clearly not the target gene, because recessive and dominant cardiac diseases occur as a consequence of the lack of imprinting in this tissue. Furthermore, recent studies have identified a paternally expressed antisense

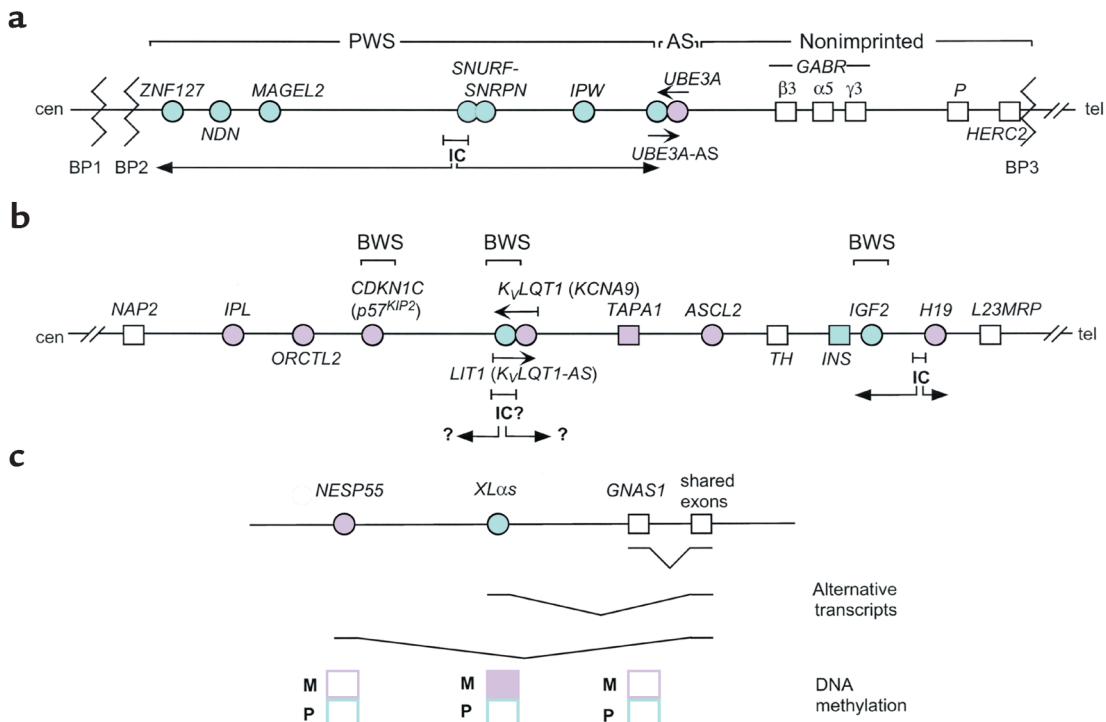


Figure 1

Complex structures of imprinted gene loci. (a) Genetic map of the 2-Mb imprinted domain in chromosome 15q11-q13 associated with PWS and AS. An IC is associated with the 5' end of the bicistronic *SNURF-SNRPN* locus. Blue or pink circles, imprinted genes showing expression of only the paternal or maternal allele, respectively; open squares, nonimprinted genes; small arrows, overlapping and antisense transcription; large arrows, regional imprint control through an IC; zigzag lines, common breakpoint (BP) regions for deletions. (b) Genetic map of the 1-Mb imprinted domain in chromosome 11p15 associated with BWS. Symbols are the same as in a; colored squares represent genes imprinted in some tissues in mice, but not yet shown in humans. Three loci have been specifically implicated in the pathogenesis of BWS. The 5' *H19* region appears to act as a local IC regulating imprinting at *IGF2*, whereas a 5' CpG-island for *LIT1* (*K_vLQT1-AS*) has been proposed to perhaps (denoted by ?) act as an IC for either *CDKN1C*, *IGF2*, and/or other genes in the 11p15 domain. (c) Genetic map of the 75-kb *GNAS1* locus in chromosome 20q13. Three alternative promoters of transcription all lead to splicing to a common set of 12 downstream exons. Each exon 1 region has a different pattern of parental origin-specific allelic methylation and transcription, and each leads to a different encoded protein product.

transcript (*K_vLQT1-AS* or *LIT1*) associated with a differentially methylated CpG-island and shown that LOI at this locus is the most common abnormal epigenetic alteration in BWS (Table 1 and Figure 1b) (7, 8; Maher and Reik, this series). In some, but not all, of these translocation and *LIT1* LOI cases, there is also LOI at *IGF2*. Hence, it is not clear if this genetic element acts as a general imprint regulator (Figure 1b) or if these BWS epimutations specifically interfere with gene regulation of *CDKN1C* (7, 8).

AHO is associated with short stature and skeletal defects and arises due to dominant inactivating mutations in the *GNAS1* gene encoding the α -subunit of the heterotrimeric G protein G_s , as does a more severe disorder with AHO and the hormone-resistant syndrome termed pseudohypoparathyroidism type 1a (PHP-1a; Table 2) (10). Isolated parathyroid hormone resistance (PHP-1b) is also linked to the same locus, although $G_s\alpha$ levels are normal. PHP-1a and PHP-1b arise from exclusive maternal inheritance, whereas AHO alone occurs within PHP-1a pedigrees after paternal inheritance. Oppositely imprinted endocrine, behavioral, and morphological phenotypes also arise from UPD at this locus or from the targeted disruption of exon 2 of the mouse *Gnas* gene (see ref. 11 for review). The disease complexity at this locus may be explained by its remarkable genetic structure (Figure 1c) (10, 11). Although $G_s\alpha$ is encoded by the nonimprinted exons 1-13 of *GNAS1*, 2 upstream alternative promoters are found in this locus, and, as seen in Figure 1c, these sequences are oppositely imprinted. Thus, the first exon under control of each of these promoters is spliced with exons 2-13 of *GNAS1* to generate the maternally expressed NESP55 or the paternally expressed XL α s. The latter 2 proteins appear to be coexpressed, and both are involved in formation of neuroendocrine secretory granules (10). The inheritance patterns produced by mutations at this locus in the mouse or in human PHP-1a could be explained by interference with transcriptional or splicing regulation at *GNAS1* (10, 11) or by antagonistic roles of the 3 proteins translated from this bizarre locus. AHO may arise solely from 50% reduction in $G_s\alpha$, with or without an effect on XL α s, whereas PHP-1b mutations may occur in *NESP55*. Further mutational studies in both species will be needed to clarify these issues.

Molecular basis of genomic imprinting. It is clear from the preceding discussion that imprinted genetic disease is associated with complex inheritance patterns and elaborate gene loci often comprising large clusters of imprinted genes (Figure 1). Other than allelic transcription differences, the epigenetic modification most clearly demonstrated for imprinted genes is the differential patterns of allele-specific DNA methylation in somatic tissues, dependent on the parent of origin (2, 12). Differential and specific DNA methylation imprints have been identified within several imprinted genes in sperm and oocytes, and in several cases, experimental studies in the mouse have shown that these represent the gametic

imprints (molecular memory of parental origin) transmitted to the next generation. However, recent studies have implicated a wide range of gene-specific and chromatin-domain features in the regulation of imprinted gene expression in somatic cells (2, 7, 8, 12, 13). These include differential histone H4 and H3 acetylation, nucleosome sensitivity, and nuclear matrix association, as well as the presence of G-rich direct-repeat sequences in or near CpG-islands, oppositely imprinted antisense RNA transcripts (see above), and asynchronous DNA replication and homologous chromosome association. Nevertheless, whereas many of these factors may help maintain imprinted domains in somatic cells or be secondary events consequent to differential packaging of chromatin on the 2 alleles, the respective roles in establishing the imprint in germ cells or after maternal and paternal pronuclei fusion after fertilization remain unknown.

Imprinting is a reversible process requiring the previous parental imprint to switch in the germline of progeny of the opposite sex. Mutations in this process occur in approximately 3% of AS and PWS patients, and particular insight into the molecular mechanism has come from study of those patients with heritable microdeletions in 15q11-q13 (Table 1) (4). Although the genotype of such imprinting mutation (IM) patients appears normal, their pattern of DNA methylation and gene expression — that is, their epigenotype — is abnormal, with maternal-only imprints in PWS and paternal-only imprints in AS.

Familial transmission of such epigenetic defects results from specific microdeletions in this region, but many IM patients are sporadic and have no detectable mutation; stochastic events during parental gametogenesis probably account for this class of imprinting defects (Table 1) (4). Inherited microdeletions in familial PWS and AS IM patients occur at the 5' end of the *SNURF-SNRPN* gene, defining a region termed the imprinting center (IC; Figure 1a). The IC is thought to regulate initiation of the parental imprint switch in the male and female germline (4, 13), leading to the establishment of heterochromatic-like DNA at the IC in oocytes and euchromatic-like DNA at the IC during spermatogenesis. Subsequently, these chromatin states may propagate bidirectionally and consequently regulate imprint switching for all genes over the 2-Mb imprinted domain (Figure 1a) (13). Both the familial and sporadic forms of IM effects are remarkable among human genetic diseases in that the IM acts, not in the affected patient, but rather in the parental germline, where it blocks the switch of the grandparental imprint. Clinical manifestations occur only because the offspring has inherited the incorrect grandparental imprint.

An understanding of the molecular events underlying these cases may also lead to insight into the basis of imprinting mutations at the *H19*, *IGF2*, and *LIT1* (*K_vLQT1-AS*) genes in chromosome 11p15 in BWS and in human embryonal tumors (Table 1) (7, 8; Maher and Reik, this series; Tycko, this series). In these diseases, the epigenetic changes usually occur sporadically

cally and hence are probably somatic in origin. At present, the primary genetic or epigenetic events causing these changes are unknown, and this is paralleled by our ignorance of the primary events causing sporadic IM in PWS and AS. Identification of these events will have a significant impact on our understanding of how imprinting occurs and whether it may one day be feasible to manipulate the epigenetic state of a normally silent imprinted allele as a therapeutic approach in imprinted disorders.

Imprinted genes play important roles in brain function and behavior. Imprinted genes have been indirectly implicated in brain function and behavior as a consequence of the genetic defects in well-studied syndromes such as PWS, AS, and AHO, although the roles of such genes in growth processes have received greater attention. However, recent experimental studies in the mouse have more directly indicated an important role for imprinting in regulating brain development and behavior. The first evidence for imprinting in mice came from nuclear transfer experiments that generated parthenogenetic and androgenetic embryos, the former containing a diploid maternal genome and the latter containing a diploid paternal genome. This work established that the 2 parental genomes play complementary developmental roles, and subsequent experiments revealed that tissues are differentially affected by uniparental development. Using chimeras between normal and uniparental cells to overcome the lethality seen in parthenogenetic and androgenetic embryos, it has been found that androgenetic cells contribute to, or survive in, specific tissues, including placenta, muscle, and certain brain structures, but that the maternal genome contributes to other brain structures and to a greater extent to brain growth (2, 14). A high proportion of parthenogenetic cells in the brain was also associated with male aggression. The paternal genome contributed primarily to regions important for primary motivated behavior, such as the hypothalamus, but androgenetic cells were excluded from the neocortex and striatum, areas that showed selective accumulation of parthenogenetic cells (14).

Two recent studies are of particular relevance to understanding the roles imprinted genes have in growth and behavior. Mutations were targeted into the mouse *Mest* and *Peg3* genes, resulting in both instances in a moderate postnatal growth retardation up until weaning at 4 weeks of age and an intriguing effect on maternal behavior following grandpaternal transmission of the mutation (15, 16). Thus, most offspring of such females do not survive, because the mother fails to retrieve, feed, or warm the pups; these females also lack such typical maternal behaviors as nest building and consuming the placenta after pups are born. In the case of *Peg3* mutations, a maternal lactation defect with a reduced number of oxytocin-positive hypothalamic neurons may contribute to this phenotype (16). Both paternally expressed genes therefore appear to play roles in controlling postnatal growth and nurturing

behavior in mothers.

Evolution of imprinting in growth and behavioral pathways. Perhaps the best supported theory for evolution of imprinting is that a parent-offspring "conflict" results in enhancers of prenatal and postnatal growth being of paternal origin, whereas those of maternal origin should be growth suppressors (2, 17). Parent-offspring conflict arises from the dependence of mammalian offspring on maternal resources from conception through weaning and the potential involvement of multiple paternity. This model fits well with the proposed antagonistic roles of paternal IGF2 and maternal CDKN1C expression in promoting and inhibiting growth, respectively, and for several other imprinted genes (2). Similarly, we have proposed that selection for imprinting in the PWS region arose for a postnatal growth advantage to a paternally derived gene, given the failure-to-thrive phenotype of PWS neonates and PWS mouse model pups (3). However, this selection pressure need only operate on a single gene within a large, coordinately regulated imprinted domain, and most genes within the domain may display imprinting simply as a consequence of recent evolutionary acquisition by the domain or as a consequence of the spreading effect of the imprinting mechanism.

The parent-offspring conflict hypothesis has been expanded to explain the grandpaternal role of *Mest* and *Peg3* in controlling maternal behavior for the survival and care of offspring to ensure growth enhancement postnatally (15, 16). More generally, this hypothesis can also be related to evolutionary changes in mammalian brain growth, in which the expansion of the neocortex and striatum associated with social behavior can explain the role of the maternal genome in contributing to these structures (14). Similarly, the predominant contribution of the paternal genome to the hypothalamus and other structures involved in reproduction, feeding, and growth, may account for the relative contraction of these regions in the brain during the evolution of primates and humans. These changes provide a genetic explanation for complex neural development and behavior.

Psychiatric disorders and behavioral phenotypes that may involve imprinted genes. Recent studies provide additional genetic clues implicating imprinted genes in complex neurobehavioral phenotypes, including susceptibility genes involved in alcohol preference and audiogenic seizures (Table 2). In addition, evidence for linkage of candidate loci to bipolar affective disorder is, in some cases, sensitive to the parent of origin of the putative disease allele. Similarly, a lower age of onset of one subtype of schizophrenia after paternal inheritance and of Tourette's syndrome after maternal inheritance, or an increased incidence of familial neural tube defects maternally transmitted and late onset Alzheimer's disease paternally transmitted, may indicate underlying imprinted genes (Table 2). In one intriguing example, social cognitive skills were better for Turner's syndrome patients inheriting the paternal, rather than the mater-

nal, X chromosome (Table 2). Until the relevant imprinted genes associated with these disorders are isolated it will not be possible to prove the imprinting hypothesis in such cases, and the occurrence of tissue-specific and mRNA isoform-specific imprinting (discussed above) or polymorphic imprinting (18) will potentially complicate the identification of these genes. However, the insight from the cited studies that imprinting allows susceptibility alleles to be transmitted silently from parents of one sex within a pedigree may account for some of the difficulties in psychiatric genetics that are otherwise ascribed to environmental modification of the phenotype, variable expressivity, incomplete penetrance, or genetic modifiers.

The work discussed here clearly indicates the complementary requirement for normal development and neurobehavioral function of inheritance deriving from the mother and the father. These studies also highlight the potential for significant advancement in multidisciplinary fields ranging from genetics and epigenetic regulation to behavioral sciences, development, and pathology, which will further aid development of therapeutic approaches to developmental and neurobehavioral disorders.

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