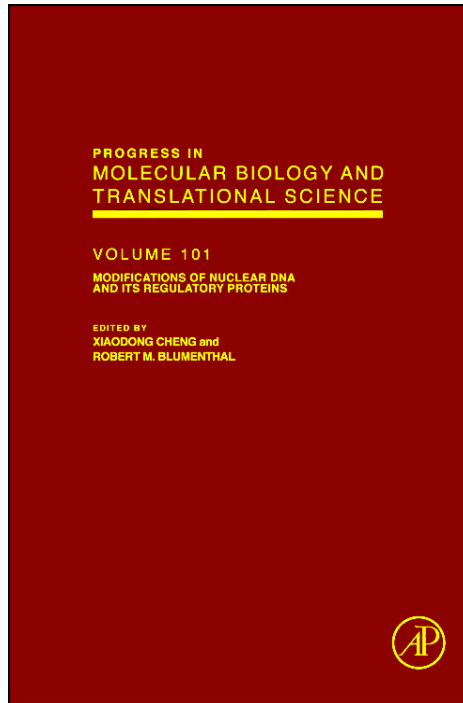


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Diseases Associated with Genomic Imprinting

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Genomic imprinting is the phenomenon where the expression of a locus differs between the maternally and paternally inherited alleles. Typically, this manifests as transcriptional silencing of one of the alleles, although many genes are imprinted in a tissue- or isoform-specific manner. Diseases associated with imprinted genes include various cancers, disorders of growth and metabolism, and disorders in neurodevelopment, cognition, and behavior, including certain major psychiatric disorders. In many cases, the disease phenotypes associated

with dysfunction at particular imprinted loci can be understood in terms of the evolutionary processes responsible for the origin of imprinting. Imprinted gene expression represents the outcome of an intragenomic evolutionary conflict, where natural selection favors different expression strategies for maternally and paternally inherited alleles. This conflict is reasonably well understood in the context of the early growth effects of imprinted genes, where paternally inherited alleles are selected to place a greater demand on maternal resources than are maternally inherited alleles. Less well understood are the origins of imprinted gene expression in the brain, and their effects on cognition and behavior.

This chapter reviews the genetic diseases that are associated with imprinted genes, framed in terms of the evolutionary pressures acting on gene expression at those loci. We begin by reviewing the phenomenon and evolutionary origins of genomic imprinting. We then discuss diseases that are associated with genetic or epigenetic defects at particular imprinted loci, many of which are associated with abnormalities in growth and/or feeding behaviors that can be understood in terms of the asymmetric pressures of natural selection on maternally and paternally inherited alleles. We next described the evidence for imprinted gene effects on adult cognition and behavior, and the possible role of imprinted genes in the etiology of certain major psychiatric disorders. Finally, we conclude with a discussion of how imprinting, and the evolutionary–genetic conflicts that underlie it, may enhance both the frequency and morbidity of certain types of diseases.

I. Overview of Genomic Imprinting

A. What Is an Imprinted Gene?

The term *genomic imprinting* is typically used to refer to the phenomenon where the pattern of expression of an allele depends on its parental origin.¹ In the simplest cases, one of the two alleles is transcriptionally silenced, while the other is expressed. Often, however, imprinted genes exhibit complex patterns of tissue- and isoform-specific imprinting.^{2–6} Some researchers will refer to a gene being “maternally imprinted” or “paternally imprinted.” However, these phrases are used inconsistently in the literature, leading to a degree of confusion. In some contexts, the phrase “maternally imprinted” is used to mean “maternally silenced,” while in other contexts it means “maternally modified,” where that modification could be either silencing or activating.

It is preferable to refer to a locus as being imprinted if maternally and paternally inherited alleles at the locus exhibit systematic expression differences, and to explicitly describe the pattern of silencing, expression, and modification at a given locus. For example, in the mouse, the imprinted gene *Grb10* is paternally expressed in brain, but maternally expressed in the

placenta and most embryonic tissues.⁷ In contexts such as this, use of phrases such as “maternally imprinted” and “paternally imprinted” leads to unnecessary confusion.

B. How Common Is Imprinting?

It is common to think of genomic imprinting as a specifically mammalian phenomenon. Consistent with this view, many of the key components and features of the imprinting system that we find in humans appear to have arisen before the split between marsupial and eutherian (placental) mammals.^{8–15} However, imprinted genes have also been identified in angiosperms (flowering plants), where imprinted gene expression has many similarities to what we observe in mammals, suggesting that an analogous phenomenon has evolved independently.¹⁶

There are also imprinting-like phenomena that have been described in various insects,¹⁷ where the term “imprinting” was originally coined.^{18,19} As for other taxa, such as birds and fish, it is at this point unclear whether any genes are imprinted. For several species, studies have looked at the expression of orthologs of certain genes known to be imprinted in mammals, typically the canonical pair of imprinted genes *Igf2* (insulin-like growth factor type 2) and *Igf2r* (insulin-like growth factor type 2 receptor). These studies have shown specific genes to be unimprinted in monotremes,^{9,10,20} amphibians,²¹ birds,^{12,13} and fish,^{22,23} leading some to conclude that imprinting does not exist in those species. However, there have been no systematic efforts to identify imprinted genes in most species, and it remains possible that other genes are imprinted in some or all of those species.

In humans, it is thought that somewhere between one and a few percent of the genome is subject to imprinting, although the exact number is unknown. The standard catalogs of imprinted genes,^{24,25} including only those loci for which there is strong, direct empirical evidence, typically include fewer than a hundred entries. However, computational studies have identified much larger numbers of “predicted” imprinted genes: 600 in mice²⁶ and more than 150 in humans.²⁷ Further, a pair of studies measuring the allele-specific expression levels in the mouse brain identified approximately 1300 genes with monoallelic or strongly biased gene expression, suggesting widespread imprinting in that tissue.^{28,29} Therefore, it seems likely that the total number of imprinted genes in humans will be greater than what is suggested by the current lists, but exactly how much greater remains to be determined.

C. How Does Imprinting Work?

Genomic imprinting relies on the existence of differential epigenetic modifications on the maternally and paternally derived alleles at a locus. This typically involves differential DNA methylation at CpG dinucleotides, as well

as differential modification of histones (acetylation, methylation, etc.). These epigenetic modifications are established during gametogenesis, with different marks being established in the male and female germ lines. After fertilization, these differential marks are propagated across cell divisions in an allele-specific manner, allowing different expression to be maintained throughout development. Epigenetic propagation involves the action of the maintenance methyltransferase Dnmt1, which specifically recognizes the hemimethylated form of CpG dinucleotides that results from DNA replication. (In the hemimethylated state, the cytosine on one strand is methylated, while the cytosine on the newly synthesized strand is unmethylated.)

Throughout development, particularly in the earliest stages, these epigenetic marks are also subject to various modifications and reprogramming. Most striking is the large-scale demethylation of the paternally derived genome that occurs after fertilization, but before fusion of the two pronuclei.^{30,31} Imprinted loci are also often subject to epigenetic spreading in *cis*, resulting in coordinated imprinted expression among clusters of loci. Thus, many of these clusters are defined by a suite of parent-of-origin-specific epigenetic modifications along an entire chromosomal region, but most of these modifications will derive from a single imprinting control region (ICR) that is differentially methylated during gametogenesis. Often, secondary epigenetic differences are not established until after fertilization.

D. Why Are There Imprinted Genes?

The discovery of genomic imprinting in mammals has triggered a proliferation of evolutionary theories.^{32,33} The theory that has received the greatest amount of attention, and which provides the best explanation for the phenotypic consequences, direction of silencing, and taxonomic distribution of imprinted genes is the kinship theory of imprinting.^{34–38} According to this theory, imprinting is the result of an intragenomic conflict, where natural selection acts differently on maternally and paternally derived alleles at the same locus. The asymmetric action of selection is often thought of in terms of inclusive-fitness effects: what matters in terms of natural selection is the total number of copies of an allele that are passed on to future generations, independent of whether those copies are passed on directly by the focal individual, or by a relative of the focal individual who is carrying identical copies of the allele.

This framework was developed initially in the context of imprinted gene effects on fetal growth, where natural selection acts differently on maternally and paternally inherited alleles at a locus that affects the magnitude of the fetal demand on maternal resources. From the perspective of an allele, the optimal level of resource demand is determined by a trade-off between the benefit derived from acquiring additional resources from the mother, and fitness cost

that results from reducing the quantity of resources available to the mother's other offspring. The magnitude of the fitness cost is determined by the relatedness of the focal allele to those other offspring, or the probability that those offspring inherit an identical copy of the allele. For a maternally inherited allele, that probability is 0.5, while for a paternally inherited allele, it is somewhat less, depending on the degree of polyandry in the population (the probability that the mother's other offspring have a different father).

Thus, at the margins, a paternally inherited allele will favor greater demand on maternal resources, while a maternally inherited allele will favor reduced demand, preserving more resources for the other offspring. At an unimprinted locus, alleles are constrained to exhibit a single pattern of expression, irrespective of whether they are inherited from a male or a female. In that circumstance, we expect natural selection to settle on a demand level somewhere between the maternal and paternal optima. However, at an imprinted locus, where alleles acquire the ability to take on two different conditional expression strategies, the evolutionary dynamics resulting from the intragenomic conflict lead to the transcriptional silencing of one of the two alleles. At a locus where increasing gene expression results in a greater demand on maternal resources (e.g., growth factor like *Igf2*), it is the maternally inherited allele that becomes silenced, while the paternally inherited allele is expressed at the level that maximizes its (inclusive) fitness. At a locus where higher gene expression reduces demand (e.g., a growth suppressor like *Igf2r*), the opposite pattern results, with paternal silencing and maternal expression.

In recent years, this theory has been extended to include other types of interactions among related individuals. In particular, the interaction between father and offspring within the nuclear family³⁹ and social interactions in a population with limited dispersal.^{40,41} The kinship theory of genomic imprinting was originally formulated within the context of mother–offspring interactions leaving the father outside of the picture. In mammals, fathers start contributing resources after weaning and even if the amount of resources contributed by the father might be less than the amount contributed by the mother, it can reverse the direction of the imprint.³⁹

Recent work takes the kinship theory beyond the nuclear family into a social context.^{40–43} These models no longer consider interactions between “mum, dad, and baby” for the allocation of parental resources, but interactions between brothers and cousins in a viscous population competing for resources at different developmental stages.^{40–43} The later models provide the theoretical foundation for the evolution of genomic imprinting the postinfant brain. Models for the evolution of imprinting through social interactions require that demographic patterns (migration, reproductive success, life expectancy) differ between males and females.^{40,41} When females tend to migrate more than males, a juvenile in the population is more related to her siblings, cousins, aunts, and uncles via her

paternally inherited copy than her maternally inherited copy. Thus the maternally inherited allele is selected to be more egoistic, while the paternally inherited copy is selected to be more altruistic. Similar conclusions can be derived when females show greater reproductive success and when the expected life of females is shorter than the expected life of males.^{40,41}

II. Disorders Associated with Particular Imprinted Genes and Regions

Much of our understanding of the phenotypic effects of imprinted genes in humans comes from the clinical manifestations of uniparental disomies (UPDs), where both copies of a chromosome are inherited from the same parent. These individuals are karyotypically normal, and, in the absence of genomic imprinting, we might expect UPDs to be without phenotypic effect. There are, however, two ways in which UPD can be associated with disease. First, uniparental isodisomy (where two copies of the same chromosome are inherited) can result in the unmasking of deleterious recessive mutations. Second, if a chromosome harbors one or more imprinted genes, a UPD will be associated with overexpression from imprinted loci, underexpression, or a combination of the two. Most imprinted genes occur in clusters, such that a UPD will typically encompass multiple imprinted genes. Thus, evidence linking disorders to a particular UPD may be suggestive of a role for imprinted genes, but this evidence becomes compelling only when systematic patterns emerge regarding the parental origin of the UPD, or when other evidence provides a direct link to one or more specific imprinted loci.

Imprinted genes are also subject to epigenetic dysregulation, such as hypomethylation or hypermethylation of regulatory elements. Clustered imprinted genes are often intricately coregulated, such that a single epimutation may alter expression of multiple imprinted genes. For imprinted loci where a complete loss of expression is lethal, certain epimutations may produce less severe phenotypes.

In this section, we describe the diseases that are associated with particular chromosomal regions.

A. Chromosome 20: Pseudohypoparathyroidism and Disorders of the *GNAS* Locus

1. FORMS OF PSEUDOHYPOPARATHYROIDISM

Pseudohypoparathyroidism (PHP) is associated with end-organ resistance to parathyroid hormone (PTH).^{44,45} That is, PTH levels are not reduced (as in hypoparathyroidism), but the response to PTH is diminished in a subset of its

target cells. In fact, PHP is associated with elevated serum levels of PTH, as well as elevated serum phosphate and reduced serum calcium. PTH normally regulates serum calcium through its action on bone and kidney, via the G_s -coupled receptor PTHR1, and secretion of PTH from the parathyroid gland is stimulated by low serum calcium.^{46,47} PTH acts on the renal proximal tubule to increase the level of 25-hydroxyvitamin D1- α -hydroxylase, which leads to elevated 1,25-dihydroxyvitamin D3, and thus to enhanced intestinal absorption of calcium and phosphate, and also mobilizes calcium and phosphate through its action on bone.

In patients with PHP, resistance to PTH appears to be limited to the renal proximal tubule, while the action of the hormone on bone and other tissues is unaffected.^{48–50} Clinically, PHP is divided into two types, based on urinary excretion following diagnostic administration of PTH. In PHP type I, excretion of both cAMP and phosphate are blunted, while in PHP type II, only phosphate excretion is blunted.⁵¹

PHP-II is relatively rare, and the molecular and genetic basis for this variant remains poorly understood. PHP-I is much more common and is associated with maternally inherited heterozygous defects at the *GNAS* locus, which encodes the α subunit of the stimulatory G-protein ($G_s\alpha$).^{52–55} The clinical manifestation of PHP-I and related disorders depends on both the nature of the genetic (or epigenetic) defect, and on the parental inheritance of the affected allele. PHP-I is further divided into two subclasses, PHP-Ia and PHP-Ib, based on the presence or absence of physical features that define Albright's hereditary osteodystrophy (AHO). PTH resistance coupled with AHO is categorized as PHP-Ia, whereas PTH resistance alone defines PHP-Ib. The physical features associated with AHO include short stature, mild mental retardation, obesity, and characteristic bone deformations, including shortening of the fourth and fifth metacarpals (brachydactyly).

2. TRANSCRIPTS AT THE *GNAS* LOCUS

The complexity of both the clinical manifestations and heritability of these disorders derives from the extreme transcriptional complexity of the *GNAS* locus. *GNAS* is located on chromosome 20q^{56,57} and is responsible for the production of numerous transcripts, the expression of which depends on both cell type and allelic parent of origin^{2–6} (see Fig. 1).

Several of the *GNAS* transcripts share a common set of downstream exons (2–13), but originate from different promoters, and incorporate alternate versions of exon 1.^{58–60} The furthest downstream promoter is responsible for production of the $G_s\alpha$ transcript and will be referred to here as the $G_s\alpha$ promoter. Through alternate splicing, this transcript produces long and short versions ($G_s\alpha$ -L and $G_s\alpha$ -S), which differ in the inclusion or exclusion of 45 nucleotides from exon 3.⁶¹ This transcript also produces the truncated $G_s\alpha$ -N1,

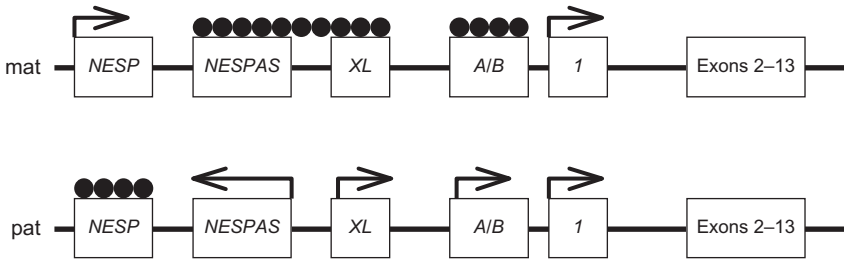


FIG. 1. Structure of the complex *GNAS* locus. This figure illustrates the methylation and expression patterns on the maternally (top) and paternally (bottom) inherited alleles. Arrows indicate expression, and filled circles indicate the three differentially methylated regions. Distances along the chromosome are not drawn to scale.

includes exons 1–3 and exon N1, which contains an in-frame stop codon. $G_s\alpha$ -L and $G_s\alpha$ -S perform similar functions but exhibit slight differences that remain incompletely understood.⁶² $G_s\alpha$ -N1 lacks many of $G_s\alpha$ functional domains, and its function is unknown, but its mouse homolog is highly expressed in the brain.⁶³

In most tissues, expression of $G_s\alpha$ is biallelic, although the paternal copy is partially or completely silenced in renal cortex,⁶⁴ thyroid, pituitary, and ovaries.^{65–67} This biallelic expression likely accounts for the fact that maternally inherited loss-of-function mutations are not lethal, as heterozygous expression of $G_s\alpha$ is sufficient to maintain normal function in those tissues. For instance, the fact that PHP does not affect the action of PTH on bone results from the biallelic expression of $G_s\alpha$ in that tissue.⁶⁸

Approximately 2.5 kb upstream from the $G_s\alpha$ promoter is a second promoter that is responsible for production of the A/B transcript (homologous to the 1A transcript in mice).^{69,70} The A/B transcript produces an alternate first exon, which is spliced to exon 2, but this first exon does not contain an in-frame translation-initiation codon, though transcription may start from within the shared exon 2, leading to a truncated $G_s\alpha$ variant.⁶⁹ Alternatively, the A/B transcript may be noncoding and may function primarily in a regulatory role *in cis*.

The A/B promoter lies within a differentially methylated region (DMR). The promoter is methylated and repressed on the maternally derived copy, and is unmethylated and active on the paternally derived copy.^{69–72} Loss of methylation from the maternally inherited allele acts not only to activate transcription of A/B from the allele but also to repress $G_s\alpha$ transcription *in cis*. Thus, the expression of these two transcripts is reciprocally regulated, but the mechanism of regulation is not understood.

The next promoter upstream from $G_s\alpha$ produces the extra-large $G_s\alpha$ variant ($G_s\alpha$ -XL), which shares a long C-terminal sequence with $G_s\alpha$, but differs in the large N-terminal region encoded by the XL alternate first exon.^{2,3,71,72} Like

$G_s\alpha$, $G_s\alpha$ -XL produces long and short variants through inclusion or exclusion of exon 3, as well as a truncated version that incorporates the N1 exon.^{2,3} Like the A/B promoter, the XL promoter lies within a DMR and is maternally silenced. Unlike A/B, which exhibits a complex pattern of tissue-specific and partial silencing, $G_s\alpha$ -XL is exclusively expressed from the paternal copy^{2,3,73,74} (but see Ref. 75).

The XL promoter is also responsible for a small protein produced from a second open-reading frame located entirely within the XL exon 1.^{76,77} The protein, ALEX, has been shown to interact with $G_s\alpha$ -XL *in vitro*, but the function of this gene product *in vivo* remains to be understood.

Furthest upstream is the *NESP* promoter. As with the other *GNAS* promoters, the *NESP* exon 1 is spliced to the shared exons 2–13. However, the entire protein-coding region for this transcript lies within the first exon so that this protein shares no sequence with the $G_s\alpha$ variants.^{2,3,74} The gene product (NESP55) is a neuroendocrine secretory protein expressed in neuroendocrine tissues and the peripheral and central nervous systems.⁷⁸ *Nesp* knockout mice appear phenotypically normal, but suffer from certain behavioral abnormalities.⁷⁹ The *NESP* promoter lies within a paternally methylated DMR, and expression of this transcript is exclusively from the maternally derived copy.^{2,3,74}

The *GNAS* locus is also host to a noncoding antisense RNA transcript known as *NESPAS* (or *GNASAS*). The *NESPAS* promoter lies within the XL DMR, and its transcript is produced only from the paternally derived allele.^{73,80,81} Elimination of the promoter results in derepression of *NESP* and demethylation of the *NESP* DMR, suggesting that transcription of *NESPAS* is the primary mechanism by which maternal expression of *NESP* is enforced.⁸²

Still further upstream is the *STX16* locus, encoding syntaxin 16. This locus is not imprinted, nor is it considered part of the *GNAS* complex locus. However, it appears that *STX16* may harbor a long-range *cis*-acting element that participates in regulation of the *GNAS* transcripts. Microdeletions within *STX16* have been associated with dysregulation of the A/B and $G_s\alpha$ transcripts, as these microdeletions cause PHP-Ib, but only when maternally inherited.⁸³ As *STX16* itself is not imprinted, this suggests that the cause is a *cis*-acting regulatory interaction with nearby imprinted genes.

3. ESTABLISHMENT OF EPIGENETIC MARKS AT *GNAS*

The *GNAS* locus contains three distinct DMRs, and in each case, methylation covering the promoter region is associated with transcriptional repression. The furthest downstream DMR covers the A/B promoter and is methylated on the maternally derived allele.^{71,72,84} Methylation of this DMR is responsible not only for the maternal silencing of the A/B transcript but also for the preferential paternal expression of the $G_s\alpha$ transcript in certain tissues.^{85–87}

Further upstream is a second maternally methylated DMR that covers the $G_s\alpha$ -*XL* and *NESPAS* promoters, driving paternal-specific expression of both transcripts.^{88–90} Furthest upstream is a DMR covering the *NESP* promoter that is paternally methylated, causing maternal expression of *NESP*.^{74,89,91}

The methylation patterns at these three DMRs are not independent, however. Methylation at the *NESP* DMR does not occur until after fertilization^{71,72} and depends on transcription from the paternally inherited *NESPAS*,⁸² as targeted deletion of *NESPAS* results in loss of methylation and biallelic expression of *NESP* when paternally inherited. Interestingly, this *NESPAS* deletion also leads to partial methylation of the paternal A/B promoter, which results in decreased A/B expression and increased $G_s\alpha$ expression.⁸² Thus, it appears that the *NESPAS* DMR is the element primarily responsible for control of imprinted gene expression in this cluster.

4. DISEASES AT THE LOCUS

PHP-Ia results from maternal inheritance of loss-of-function mutations at the $G_s\alpha$ locus, and the tissue-specific resistance patterns associated with PHP-Ia are explained by the tissue-specific patterns of imprinting at the locus.⁴⁴ Maternally inherited loss of function results in complete or nearly complete loss of transcription in cell types where the paternal allele is completely or partially silenced. In cell types with biallelic expression, the result is simply a 50% reduction in transcription, which does not appear to substantially affect the PTH response in those cells.⁶⁸

PHP-Ib is also inherited maternally, but is not due to inactivating mutations in $G_s\alpha$. Rather, this disease subtype is associated with broad epigenetic defects at the *GNAS* locus. A diverse set of genetic lesions have been associated with PHP-Ib, but in each case, the mutation causes loss of imprinting (derepression) of the A/B transcript.^{71,72,85,86} In cell types, where $G_s\alpha$ and A/B are reciprocally coregulated, the derepression of A/B reduces the expression of $G_s\alpha$, resulting in the PTH-resistant phenotype. However, the expression of these two transcripts does not appear to be coupled in all cell types, as A/B expression exists in some tissues in the absence of $G_s\alpha$ imprinting.^{85–87} Presumably, derepression in these tissues does not diminish $G_s\alpha$ expression, and it is PTH resistance in those tissues that are responsible for AHO, which is present in PHP-Ia, but absent in PHP-Ib.

In the related disorder of pseudopseudohypoparathyroidism (PPHP), the physical characteristics associated with AHO are present, but without the resistance to PTH and other hormones.⁹² Like PHP-Ia, PPHP results from $G_s\alpha$ -inactivating mutations, and, in fact, these two diseases can arise from the same genetic defect, and both are often found in the same families.^{55,93} Whereas PHP-Ia results from maternal inheritance of these defects, PPHP is paternally inherited.^{94,95} This pattern suggests that the hormone resistance

associated with PHP is attributable to the loss of maternal expression of $G_s\alpha$, whereas the AHO component of the disease is the result of haploinsufficiency of $G_s\alpha$ in tissues where it is normally biallelically expressed, but is independent of parental origin.

Mutations causing constitutive $G_s\alpha$ activity are also associated with various diseases, but are lethal if inherited, and are therefore typically of somatic origin. Activating mutations have been described in various tumors, including particularly endocrine adenomas.⁹⁶ Activating $G_s\alpha$ mutations occurring early in development (giving rise to mosaic constitutive activity) lead to McCune–Albright syndrome, which involves abnormalities of the skin, bone, and endocrine organs.^{97,98} To the best of our knowledge, the possibility of systematic phenotypic differences depending on the parental origin of the constitutively active allele has not been examined.

B. Chromosomes 7 and 11: Silver–Russell and Beckwith–Wiedemann Syndromes

1. SILVER–RUSSELL SYNDROME

Silver–Russell syndrome (SRS) is a growth disorder defined by intrauterine growth restriction (IUGR) in combination with a subset of other abnormalities that can include hypoglycemia, feeding problems, lack of subcutaneous fat, and early onset of puberty, among others. Individuals with SRS are typically small for gestational age, often weighing less than 3 kg at birth, and the average height for adults with SRS is less than 5 ft.^{99–101}

SRS does not have a single genetic basis, and genetic associations have been reported for chromosomes 1, 7, 8, 11, 15, 17, 18, and X.¹⁰² For most of these chromosomal associations, SRS has been observed in a small number of patients exhibiting either trisomy or a large-scale deletion or translocation, and the mechanism through which these defects lead to SRS remains poorly understood. The genetic (and epigenetic) defects on chromosomes 7 and 11 are most commonly associated with SRS, and have been most studied. Both of these chromosomes are host to clusters of imprinted genes that appear to play a role in the etiology of the disease, and it is these defects that are the focus of this section.

2. CHROMOSOME 7

Approximately 5–10% of SRS cases are associated with maternal UPD at chromosome 7 (MatUPD7), where the individual is karyotypically normal, but both copies of chromosome 7 have been inherited from the mother, and therefore exhibit the maternal-specific epigenetic modifications.^{102,103} Three regions of chromosome 7 contain clusters of imprinted genes, and any combination of these might contribute SRS. The three regions, 7p11.2–13, 7q21, and

7q32, all contain imprinted genes that are expected to contribute to growth restriction when maternally duplicated. In addition, there is some evidence from smaller genetic lesions that provides some insight as to how these different regions might contribute to other aspects of the SRS phenotype.

The 7p11.2–13 region includes the *GRB10* (growth factor receptor bound protein 10) locus, which may produce as many as 13 transcripts, most of which are thought to be noncoding, and which include maternal, paternal, and biallelic expression in different tissues.^{7,104–106} In particular, the maternally expressed $\gamma 1$ transcript has been identified in placental tissues, while other splice variants are paternally expressed in the brain.⁷ The genes neighboring *GRB10* are thought to be unimprinted in humans,¹⁰⁷ and *GRB10* has been shown to reduce the size and efficiency of the placenta.¹⁰⁸

These patterns suggest that the contribution of this chromosomal region to the growth-restriction aspects of the SRS phenotype in the MatUPD7 cases is likely mediated through increased expression of the $\gamma 1$ form in placental tissues. Loss of paternal expression of other forms in the brain may additionally contribute to the cognitive aspects of SRS. However, identification of a family in which maternal inheritance of a segmental duplication covering this region is associated with mental retardation¹⁰⁹ suggests that this loss of paternal expression may not be the only way in which this locus affects cognition in SRS patients, as these individuals possess a normal paternally inherited chromosome 7.

Four imprinted genes have been identified in the 7q21 region: the maternally expressed tissue factor pathway inhibitor 2 (*TFPI2*) locus and the paternally expressed epsilon-sarcoglycan (*SGCE*) and *PEG10* loci.^{110–112} The *CALCR* locus appears to be monoallelically expressed in the brain, but which allele is silenced has not yet been definitively established,¹¹⁰ though the mouse homolog *Calcr* is maternally expressed in brain.¹¹³ Other transcripts in the region are imprinted in the mouse, but are either unimprinted or have uncertain imprinting status in humans.

PEG10 is a retrotransposon-derived gene that plays an important role in placental development,¹¹⁴ and loss of *PEG10* expression is a likely contributor to growth restriction in SRS. *TFPI2* is a putative tumor suppressor,¹¹⁵ suggesting that it may interfere with cell proliferation. It is maternally expressed in extraembryonic tissues, and thus increased expression in MatUPD7 may also contribute to growth restriction. Mutations in *SGCE* are a major cause of myoclonus-dystonia syndrome (MDS).¹¹⁶ MDS is a movement disorder characterized by rapid muscle contractions and with twisting and repetitive movements producing abnormal postures. SRS patients often present with low muscle tone, but the connection between these phenotypes is not transparent.

The 7q32 chromosomal region contains the paternally expressed *MEST*, *MEST1T1* (antisense to *MEST*), and *COPG2IT1* (an intronic transcript found within the biallelically expressed *COPG2* gene) loci, as well as two maternally expressed loci, *CPA4* and *KLF14*.¹¹⁷ Knocking out the mouse ortholog of *MEST* (*Peg1/Mest*) results in IUGR, as well as a suite of behavioral abnormalities relating to maternal care for offspring, such as pup retrieval, nest building, and placentophagia.^{37,38,40,41,118} The absence of a functional *MEST* therefore seems a likely contributor to the undergrowth phenotype (but see Ref. 119). *KLF14* specifies a transcription factor, and has been undergoing accelerated evolution in the human lineage.¹²⁰ These features make it an interesting candidate, but do not suggest any specific mechanism through which over-expression in MatUPD7 might contribute to SRS.

Located nearby in the 7q31.2 region is the *FOXP2* locus, mutations of which are associated with developmental verbal dyspraxia (DVD).^{121–123} One study has suggested that this disorder may result specifically from the absence of a functional paternally inherited copy of the gene.¹²⁴ If *FOXP2* is, in fact, subject to parent-of-origin effects, the loss of a paternally inherited copy in MatUPD7 may contribute to the speech effects associated with SRS patients, many of whom exhibit DVD.

3. CHROMOSOME 11

Chromosome 11 contains two clusters of imprinted genes (see Fig. 2), both located in the 11p15.5 region, but regulated by separate imprinting control regions (ICRs). The more telomeric of the two ICRs, ICR1, controls expression of the reciprocally imprinted *IGF2* (insulin-like growth factor type 2) and *H19* loci. Normally, *IGF2* is paternally expressed,^{125,126} while *H19* is maternally

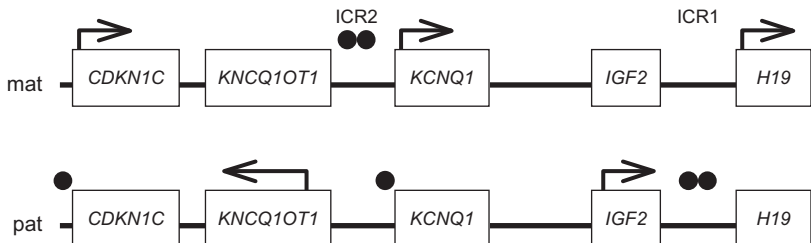


FIG. 2. Structure of the 11p15.5 imprinted gene clusters. This figure illustrates the methylation and expression patterns on the maternally (top) and paternally (bottom) inherited alleles. Arrows indicate expression, and filled circles indicate the ICR1 and ICR2 differentially methylated regions. Distances not to scale.

expressed.¹²⁷ This pattern is controlled by epigenetic differences between the two alleles at the *H19* DMR.^{128–130} When unmethylated (as on the maternally inherited copy), the *H19* DMR binds to CTCF, which serves as an insulator, isolating *IGF2* from a downstream enhancer element, which interacts instead with the *H19* promoter region. Methylation of the paternally inherited copy blocks CTCF binding, thereby eliminating the insulator activity and allowing the enhancer to interact instead with the *IGF2* promoter.

IGF2 is a major contributor to growth in early development, and approximately 50–60% of SRS patients exhibit epigenetic defects in the 11p15.5 region.^{102,131} Particularly common is hypomethylation at ICR1, which results in the epigenetic silencing of *IGF2* from both alleles.^{103,132} Further, the degree of hypomethylation correlates with the clinical severity of the SRS phenotype.¹³³ Thus, it appears that loss of *IGF2* expression is sufficient to generate all key aspects of the SRS phenotype, particularly those directly related to growth.

ICR2 controls a cluster of imprinted transcripts, most of which are maternally expressed and are associated with negative growth effects. Normally, maternal methylation of the KvDMR silences maternal expression of the *KCNQ1OT1* noncoding RNA transcript. Expression of *KCNQ1OT1* from the paternally inherited copy acts in *cis* to suppress expression of a number of nearby genes, including *SLC22A18*, *PHLDA2*, *CDKN1C*, and *KCNQ1*.^{134–136} Note that the imprinted region in mouse extends further, including the *Osbpl5*, *Tssc4*, and *Nap1l4* loci, which are biallelically expressed in humans.¹³⁷ At the moment, the potential contributions of genes in this region to the SRS phenotype remain unclear.

A prospective study identified a number of clinical features for which SRS patients with MatUPD7 and hypomethylation at ICR1 differ statistically, either in the likelihood of displaying that aspect of the disease phenotype, or in the clinical severity.¹³⁸ MatUPD7 patients were more likely to display developmental delays, to require speech therapy, and to exhibit certain craniofacial features, such as a triangular face and low-set ears. Patients with hypomethylation at ICR1 were more likely to exhibit developmental asymmetries and cognitive defects.

The remaining 30–40% of SRS cases have not been definitively associated with specific genetic or epigenetic defects, and it is possible that many of those cases are related to loci (imprinted or not) on chromosomes other than 7 and 11. This apparent causal heterogeneity, along with the subtle phenotypic differences among patients with different underlying causes, suggests that the bulk of the clinical features associated with SRS may be relatively generic consequences of undergrowth, particularly during prenatal development. It is also possible that in the future, SRS may be differentiated into subtypes based on genetic and epigenetic etiology.

4. BECKWITH–WIEDEMANN SYNDROME

Beckwith–Wiedemann syndrome (BWS) is associated with overgrowth and is in many ways genetically and phenotypically reciprocal to SRS¹³⁹. BWS is associated with macroglossia (enlargement of the tongue), large prenatal and childhood body mass (> 90th percentile), and defects in the abdominal wall. BWS also results in extreme placental overgrowth, with placentas that are approximately 2× normal weight.^{140–142}

Like SRS, BWS is associated with a heterogeneous genetic etiology but is most often associated with epigenetic defects covering the 11p15.5 imprinted region, which account for 60–70% of cases.^{143–147} Over half of BWS patients exhibit hypomethylation at ICR2, resulting in loss of expression of *SLC22A18*, *PHLDA2*, *CDKN1C*, and *KCNQ1* from the maternally inherited copy. In approximately 5% of cases, patients show hypermethylation at ICR1, which results in aberrant expression of *IGF2* from the normally silenced maternally inherited copy. Another ~15% of cases are accounted for by paternal UPD covering 11p15.5, eliminating maternal expression (and increasing paternal expression) from all imprinted genes in the region. A small fraction (5–10%) of cases are associated with mutations in *CDKN1C* (previously *p57(KIP2)*), which specifies a cyclin-dependent kinase, a tumor suppressor that exerts its negative effects on cell proliferation by inhibiting progression through the cell cycle.¹⁴⁸

The overall pattern observed in BWS is qualitatively analogous to what is seen in SRS. The syndrome can result from a heterogeneous collection of underlying genetic and epigenetic defects, but most cases are associated with dysregulation of one or both of two loci with broad effects on cell proliferation and growth: *IGF2* and *CDKN1C*. This pattern suggests that many of the features associated with BWS are generic consequences of an overgrowth phenotype. At the same time, certain patterns have emerged that point toward subtle clinical distinctions associated with different molecular etiologies. For example, certain features of BWS may be overrepresented in patients with *CDKN1C* mutations, including polydactyly, extra nipple, and cleft palate.¹⁴⁸ Eventually, patterns like this may make it possible to disentangle the contributions of various loci in the 11p15.5 region to this syndrome.

Given the reciprocal phenotypes associated with SRS and BWS, and the reciprocal epigenetic defects in the 11p15.5 imprinted region that are associated with the two syndromes, it seems reasonable to expect that BWS might also be associated with PatUPD7. In mice, PatUPD of chromosome 11, which is syntenic with human chromosome 7, results in offspring that are 30% larger than their littermates.¹⁴⁹ However, in humans, the consequences of paternal isodisomy in this region are unclear. In four reported cases of PatUPD7, three show normal growth,^{150–152} and one shows overgrowth.¹⁵³ Two of these patients (one of which showed overgrowth) were screened due to the fact that they had cystic fibrosis.

C. Chromosome 14: UPD14

UPDs of chromosome 14, first described in 1991,^{154,155} are thought to represent a relatively rare disorder. However, the frequency is not well estimated, particularly for the maternal UPD (MatUPD14), due to the facts that it has a relatively nonspecific phenotype and molecular testing is not routine. MatUPD14 syndrome is associated with growth retardation, hypotonia (muscle weakness), joint laxity, early onset of puberty, and mild dysmorphism of the hands, feet, and face.¹⁵⁶

Paternal UPD14 (PatUPD14) syndrome is substantially less common, and is associated with a much more extreme phenotype, including polyhydramnios, premature labor, skeletal abnormalities, respiratory and neurodevelopmental problems, and often early death.¹⁵⁶

Both UPD14 syndromes are thought to be associated with altered gene expression in the 14q32 region, which contains a cluster of imprinted genes, including the paternally expressed *DLK1*, *RTL1* (*PEG11*), and *DIO3* along with the maternally expressed *GTL2* (*MEG3*), *RTL1as*, *MEG8*, and *BEGAIN* (see Fig. 3). Imprinting in these regions is controlled by two different DMRs: the *DLK1-GTL2* intergenic DMR (IG-DMR) and the *GTL2-DMR*.^{157,158} The two DMRs appear to function hierarchically and in a tissue-specific fashion.^{159,160}

The centrality of this region is supported by patients displaying the MatUPD14 clinical phenotype in the absence of a chromosomal UPD. Loss of methylation at the paternal IG-DMR produces the MatUPD14 phenotype.^{161,162} Similarly, the PatUPD14 phenotype has been observed in a patient with a segmental paternal UPD spanning the 14q32–14q32.33 region.¹⁶³ In each case, however, the observed defects are associated with aberrant expression of the entire cluster of imprinted genes, and the relative contributions of individual genes to the disease phenotypes are not understood.

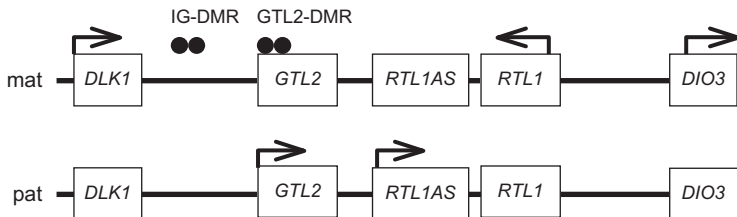


FIG. 3. Structure of the 14q32 imprinted gene cluster. This figure illustrates the methylation and expression patterns on the maternally (top) and paternally (bottom) inherited alleles. Arrows indicate expression, and filled circles indicate the intergenic and *GTL2* differentially methylated regions. Distances not to scale.

D. Chromosome 15: Prader–Willi and Angelman Syndromes

Prader–Willi syndrome (PWS) and Angelman syndrome (AS) were the first known examples of human diseases involving imprinted genes. They occur with a frequency of 1:15,000 and 1:25,000 live births, respectively, and are caused by alterations in region 15q11–13 of chromosome 15. This chromosomal region contains a cluster of imprinted genes that are expressed from the paternally inherited or the maternally inherited chromosome only (see Fig. 4). The parent-of-origin expression of genes in this cluster is regulated by an ICR.

The paternally expressed genes in region 15q11–13 are *MKRN3*, *MAGEL2*, *NDN*, *C15orf2*, *SNURF-SNRPN*, and a group of *snoRNA* genes. Expression of paternally inherited genes *MKRN3*, *NDN*, and *SNURF-SNRPN* is regulated by differential methylation of the promoter regions of each gene. *C15orf2* is paternally expressed in the fetal brain but biallelically expressed in other organs. The relative contribution of each of these genes to the PWS clinical phenotype is yet to be determined.

The maternally expressed genes in region 15q11–13 are *UBE3A* and *ATP10C*. Expression of maternally inherited genes *UBE3A* and *ATP10C* is not achieved through differential methylation of the promoter regions of each gene. Silencing of the paternally inherited copy of *UBE3A* is achieved through differential expression of the 3' end of the *SNURF-SNRPN* transcript acting as an antisense transcript.¹⁶⁴ The imprinted expression of gene *UBE3A*

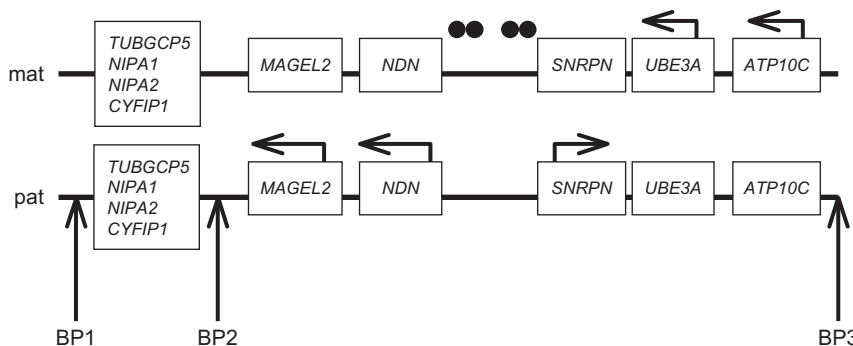


FIG. 4. Structure of the AS-PWS imprinted region. This figure illustrates the methylation and expression patterns on the maternally (top) and paternally (bottom) inherited alleles. Horizontal arrows indicate expression, and filled circles indicate the differentially methylated region. Distances not to scale. Vertical arrows indicate the relative locations of the three breakpoints described in the text. The genes lying between breakpoints one and two (at the far left side of the figure) are all unimprinted.

is tissue specific and restricted to some types of cells in the brain. *UBE3A* is the critical gene leading to the AS clinical phenotype. *ATPIOC* is maternally expressed in the brain but biallelically expressed in other organs.¹⁶⁵ The orthologous gene in mouse (*Atp10a*) is not imprinted.¹⁶⁶

The ICR regulates *in cis* imprint resetting and maintenance in the whole cluster of imprinted genes.¹⁶⁷ It consists of two critical elements the PWS-SRO and the AS-SRO.¹⁶⁸ PWS-SRO controls the maintenance of the paternal imprint during early embryonic development. AS-SRO controls the establishment of the maternal imprint in the female germ line.

PWS and AS result from complete or partial deletion of chromosomal region 15q11–13, UPD (inheritance of the two copies of a chromosomes from the same father) of chromosome 15. These are imprinting defects that may or may not be caused by deletions in the imprinting center of chromosomal region 15q11–13.

Seventy percent of all PWS cases are due to the paternal inheritance of a *de novo* interstitial deletion of a region of chromosome 15. This region includes the cluster of imprinted genes and several nonimprinted genes. Deletions are caused by nonhomologous recombination events and can be of two kinds: class I deletions affect the region comprised between break point 1 (BP1) and break point 3 (BP3), and class II deletions affect the region comprised between break point 2 (BP2) and BP3. Paternally inherited deletions result in the lack of expression of imprinted genes that are active when paternally inherited.

Between 25% and 30% of all PWS cases are due to maternal UPD. These UPDs are caused by maternal meiotic nondisjunction followed by mitotic loss of paternal chromosome 15 after fertilization. Maternal UPDs result in the lack of expression of imprinted genes that are active when paternally inherited and up to a twofold increment in expression of genes that are active when maternally inherited.

At most 3% of all PWS cases are due to imprinting defects that result in the paternal chromosome carrying a maternal imprint. Imprinting defects caused by deletions affecting the ICR are very rare, while imprinting defects caused by epimutations affecting the IR are more common. Epimutations can occur during imprint erasure in primordial germ cells, or during imprint establishment or maintenance after fertilization. If the epimutation occurs after fertilization, it may result in mosaicism. In PWS patients, the paternal chromosome that carries an incorrect maternal imprint is always derived from the paternal grandmother,¹⁶⁹ which suggests that the incorrect imprint in the PWS patients results from failure of the paternal germ line to erase the grandmaternal imprint. Supporting this observation, mosaicism in PWS patients due to an imprinting defect are very rare. Imprinting defects result in gene silencing of paternally expressed genes.

Seventy percent of all AS cases are due to the maternal inheritance of the same deletions described for PWS affecting the cluster of imprinted genes in region 15q11–13.

Ten percent of all AS cases are due to mutations in gene *UBE3A*.¹⁷⁰ Another 2–5% of AS cases are due to paternal UPD covering the 15q11–13 region. These UPDs are caused by maternal nondisjunction with postzygotic duplication of chromosome 15 inherited via sperm.

Between 2% and 4% of all AS cases are due to imprinting defects that result in the maternal chromosome carrying a paternal imprint. Imprinting defects caused by deletions affecting the ICR are very rare while imprinting defects caused by epimutations affecting the ICR are more common. In AS patients, the maternal chromosome carrying an incorrect paternal imprint is inherited either from the maternal grandfather or from the maternal grandmother.^{169,171} This finding suggests that the imprinting defect occurs after erasure of the parental imprints and results from an error in imprint establishment or imprint maintenance. Corroborating this observation, more than 40% of AS patients with an imprinting defect are found to have somatic mosaicism. The remaining approximately 15% of AS cases are caused by genetic defects of unknown nature.

Patients suffering from PWS present a clinical phenotype that affects feeding, weight, and growth among others. The clinical phenotype corresponding to these features is markedly biphasic with either weaning or menarche (which is still debated) separating both phases.¹⁷² Early infants present low birth weight, severe hypotonia, and feeding difficulties. Late infants show hyperphagia (insatiable and/or nondiscriminatory appetite) and obesity. Accompanying features are short stature, small hands and feet, almond-shaped eyes, triangular mouth, and hypogonadism in both sexes.

AS patients show distinctive behavior with temper tantrums, obsessive-compulsive behavior, and sometimes psychiatric disturbance. Mild to moderate mental retardation is also observed. Patients with class I deletion have generally more behavioral and psychological problems than individuals with class II deletion.¹⁷³

Patients suffering from AS also present clinical phenotype that affects feeding, and growth among others. They present prolonged sucking although poorly coordinated and microcephaly. In contrast with PWS, the clinical phenotype of AS patients is not biphasic. The behavior of AS patients is also affected showing sleep disorders, happy demeanor, that includes inappropriate laughter and excitability, and limited speech. Severe mental retardation is also observed.

E. X Chromosome: Turner and Klinefelter Syndromes

Turner syndrome (TS) results from the absence of all or part of one of the X chromosomes in females (45, XO females, with “45” referring to the total number of nuclear chromosomes, as opposed to the normal, 46-chromosome

karyotype). Individuals with TS typically display short stature with broad chests, low-set ears, and webbed necks and are often subject to cardiovascular and renal defects.^{174,175} Klinefelter syndrome (KS) is a condition in males in which they inherit two X chromosomes in addition to a Y chromosome (47, XXY males). Individuals with KS often have small testicles and reduced fertility, but the phenotypic manifestations are highly variable, with many individuals having few detectable symptoms.¹⁷⁶

Neither TS nor KS is an imprinting disorder per se, but both are potentially subject to influence by imprinted genes. A cluster of imprinted genes has been identified on the mouse X chromosome, and at least one of those genes is associated with effects on cognition and behavior.^{177,178} This raises the possibility of phenotypically relevant imprinted X-linked genes in humans.

In TS, individuals inherit a single X chromosome. Normally in mammals, males have one X chromosome, while females have two. The Y chromosome contains many fewer genes than the X, and dosage compensation is achieved through epigenetic silencing of one of the two X chromosomes in females.¹⁷⁹ In some contexts, X inactivation itself is imprinted, with the paternally inherited X undergoing inactivation in marsupials and in the extraembryonic tissues of some eutherians, including mice.¹⁸⁰

However, not all of the genes on the X chromosome are silenced, as approximately 15–20% escape inactivation,^{181,182} and many of the features associated with TS are likely due to haploinsufficiency at those loci. For example, the *SHOX* locus, located in the pseudoautosomal region, is thought to be the most significant contributor to the stature effects in TS.¹⁸³

The single X chromosome inherited by someone with TS will be either maternally or paternally inherited (X_mO or X_pO , respectively), and a number of studies have looked for phenotypic differences between these two subsets of TS patients. Some studies have failed to find any significant imprinting effects on the physical manifestations of TS, including stature, body mass index, cardiac, renal, skeletal, lymphatic, aural, or ocular systems,^{184,185} though one study has found that X_mO patients were more likely to have kidney malformations, had lower LDL cholesterol, and were less likely to have ocular abnormalities,¹⁸⁶ and there is some evidence for imprinting effects on the response to treatment with growth hormone.¹⁸⁷

While the effect of X-linked imprinted genes on the physical features in TS are at present unclear, there is strong evidence pointing toward cognitive differences between X_mO and X_pO females. The first study to focus on these differences found evidence that X_pO females had better verbal skills, less social-cognitive impairment, and better behavioral inhibition and planning skills.¹⁸⁸

More recent brain-imaging studies have identified systematic differences in brain structure that suggest a role for X-linked imprinted genes in neurodevelopment. X_pO females were found to have a larger volume of gray matter in the

caudate nuclei, and a larger volume of white matter bilaterally in the temporal lobes.¹⁸⁹ Another study has found that X_mO females have increased gray matter in the left superior temporal gyrus.¹⁹⁰ Other studies have failed to find significant imprinting effects on brain structure in TS patients.^{191–193}

Findings suggestive of functional differences have also been identified in subsequent studies, although the magnitude of the effects is often quite small. X_mO females appear to exhibit enhanced forgetting in verbal contexts, while forgetting is more pronounced for X_pO females in spatial contexts.¹⁹⁴ Other studies have suggested that X_mO females suffer greater impairment in verbal cognition¹⁹⁵ and arithmetic function.¹⁹⁶ The consequences of TS for brain structure and function, and the evidence for and against a significant effect of imprinted genes, have been the subject of two recent reviews.^{197,198}

Similarly, in KS, the supernumerary X chromosome can be either maternally or paternally inherited, such that there are two distinct groups of KS individuals: X_mX_mY males and X_mX_pY males. Studies on imprinting effects in KS have been more limited, but one study has found that X_mX_pY males had increased body size parameters for some measurements, consistent with a growth-enhancing effect of one or more imprinted genes on the X chromosome.¹⁹⁹ This study also found that X_mX_pY males were significantly more likely to have impaired speech and motor developmental problems. A second study reported an association between inheritance of a paternally derived X chromosome and later onset of puberty.²⁰⁰

F. Chromosome 6: Transient Neonatal Diabetes

The 6q24 region is associated with transient neonatal diabetes mellitus type 1 (TNDM1),²⁰¹ and contains two imprinted genes where a subset of transcripts is maternally silenced in at least some tissues,²⁰² *PLAGL1* (a.k.a. *ZAC1* or *LOT1*), a zinc-finger containing transcription factor involved in apoptosis and cell-cycle control,²⁰³ and *HYMAI*, which produces a noncoding RNA. Overexpression from these loci due to genetic or epigenetic abnormalities in the 6q24 region account for approximately 70% of cases of TNDM1,²⁰⁴ often accompanied by macroglossia. Sources of overexpression include PatUPD6, duplication of the paternal 6q24 region, and loss of methylation at the maternally inherited TND DMR.^{204,205}

The phenotype associated with paternalization of the 6q24 region is puzzling in two respects, both relating to the fact that the known imprinted genes in the region are maternally silenced. First, there are no reported phenotypic effects associated with maternalization of the locus (through, e.g., MatUPD6), despite the fact that this would result in a complete loss of function in cell types where these genes are maternally silenced. Second, based on theoretical analysis and the patterns observed with other imprinted loci, we expect maternal silencing to arise at loci with growth-enhancing effects.

Contrary to this expectation, *PLAGL1* appears to be a tumor suppressor,²⁰⁶ and paternalization of the locus results in IUGR in >95% of TNDM1 cases,²⁰⁷ rather than overgrowth.

III. Psychiatric Disorders and Other Behavioral Effects

Most of the disorders described in the previous section are characterized primarily by their effects on growth and metabolism, and in some cases effects on behaviors that relate directly to resource acquisition. The phenotypic effects associated with disruption or duplication of particular imprinted genes in these contexts are consistent with predictions from simple evolutionary models (with a few exceptions). However, many imprinted genes are also expressed in the adult brain and affect cognitive and behavioral traits in ways that are not as easily understood.

Nevertheless, it appears that there are certain systematic patterns in the phenotypic effects of imprinted gene expression in the brain, suggesting that the function of these genes has been shaped, in part, by intragenomic conflict. Further, many imprinted genes appear to contribute substantially to a number of common psychiatric disorders. Evidence for this contribution comes primarily from two sources: (1) psychiatric problems that are associated with known imprinting-related disorders and (2) genetic studies that have identified statistical associations of particular disorders with known imprinted genes, or have found parent-of-origin effects associated with particular genetic markers.

We begin this section with a brief summary of what is known regarding the roles of maternally and paternally expressed imprinted genes in the brain, and what these patterns suggest regarding the evolutionary pressures acting on these genes. We next discuss the evidence for the contribution of imprinted genes to the etiologies of schizophrenia and autism, and describe the oppositional model of these disorders that is suggested by this evidence. Finally, we briefly survey the evidence for imprinted gene effects in other psychiatric disorders.

A. Imprinting Effects on Brain Structure and Function

In previous sections, we have already encountered evidence, in the context of specific disorders, that imprinted genes play an important role in brain development and may have systematic effects on behavior and cognition. The behavioral phenotypes associated with AS and PWS have been interpreted in terms of intragenomic conflict over the distribution of parental resources,^{39,208} where paternally inherited alleles favor greater resource acquisition prior to weaning, when the resource demand falls primarily on the mother, but

maternally inherited alleles increasingly favor greater demand as the paternal resource contribution grows.³⁹ An alternative explanation has been made in terms of intragenomic conflict over egoistic and altruistic behaviors,^{40–42} where paternally inherited alleles favor greater egoistic behavior in interactions with nuclear family members, but maternally inherited alleles favor greater egoistic behavior in social interactions.^{40–42}

The patterns observed in some of the studies on TS are suggestive of an intragenomic conflict over the allocation of neural resources to different cognitive tasks, although the effects are small and have not been observed consistently. The patterns that have been observed are consistent with imprinted genes on the paternally inherited X favoring greater investment in verbal and social cognition, while those on the maternally inherited X favor greater investment in spatial cognition.^{188,194,195}

Evidence for intragenomic conflicts over brain structure has also been derived from parthenogenetic (PG) and androgenetic (AG) chimeras in mice. These chimeras consist of a mixture of normal, biparental cells, and cells that contain either two maternally derived (PG) or two paternally derived (AG) sets of chromosomes.²⁰⁹ The PG chimeras had an increased brain volume relative to body size, while the AG chimeras had a reduced brain to body size ratio. Further, cortical areas were particularly enlarged (relative to other brain structures) in PG chimeras, and the PG cells were particularly enriched in those areas. Conversely, AG chimeras showed relative enlargement of limbic structures, and enrichment of AG cells in those areas, including hypothalamic, septal, and preoptic structures.

The patterns of brain structure and cell deposition in the chimera experiment is suggestive of a conflict in which maternally derived alleles favor greater investment in cortical functions, while paternally inherited alleles favor relatively more investment in limbic functions, although it is worth noting that this interpretation is not necessarily consistent with the apparent patterns suggested by the TS comparisons. The recent genome-wide study of imprinted gene expression in the mouse brain found approximately 1300 imprinted transcripts, and found dynamic changes in the patterns of imprinted gene expression through development.^{28,29} For example, the majority of imprinted genes identified are maternally expressed early in development, while in the adult brain, the majority are paternally expressed.

One study on the inheritance of human cognitive abilities found a potential imprinting effect in normal cognition. The cognitive abilities of children were found to be highly correlated with their mothers' abilities for tasks associated with the frontal, parietal, and temporal lobes, while the effects of both parents were equally important for tasks associated with the occipital lobe.²¹⁰ This pattern is consistent with the distributions of PG and AG cells in the mouse chimeras.

Other behavioral effects associated with imprinted genes have been described in mice. Deletion of the paternally expressed *Peg1/Mest* and *Peg3* loci in adult females are each associated with deficits in specific maternal behaviors.^{118,211} Deletion of the maternally expressed *Ube3a* produces defects in context-dependent memory.²¹² Deletion of the maternally expressed *Rasgrfl* causes defects in memory consolidation,²¹³ and may contribute to depression.²¹⁴ Deletion of the paternally expressed *Ndn* actually results in enhanced spatial learning,²¹⁵ while deletion of the maternally expressed *Nesp* produces abnormal reactivity to novel environments.⁷⁹

What is clear at this point is that imprinted genes play a significant role in brain development and function, but that the influence of those genes is complex. Several of the empirical observations are suggestive of systematic patterns in the phenotypic effects of maternally and paternally expressed imprinted genes, but those patterns are often based on small effects observed for small numbers of loci. First steps have been taken to construct an overarching theoretical framework for understanding imprinted gene effects in the brain that would be analogous to the framework existing for growth effects.^{40,41} Significantly more research—both empirical and theoretical—is needed in this area.

B. Imprinted Gene Contributions to Schizophrenia and Autism

There has been a recent concerted effort to understand the role of imprinted genes in behavior and cognition, specifically in the context of schizophrenia and autism. A number of comprehensive reviews have collected the evidence for a role of imprinted genes in the etiology of both disorders.^{216–219} In fact, imprinted genes account for some of the most significant associations of these diseases with particular loci or chromosomal regions. For example, a recent meta-analysis of GWAS analyses of schizophrenia found only one locus that showed statistically significant association at the genome-wide level.²²⁰ This locus includes the imprinted gene *LRRTM1*, which is maternally silenced, and shows high expression during development throughout the cortical plate, as well as the septum caudate, putamen, dorsolateral thalamus, and lateral geniculate body.²²¹ Interestingly, *LRRTM1* is also associated with handedness,²²² suggesting that its effect on susceptibility to schizophrenia may be mediated through its effects on brain lateralization.

Many of these imprinted gene effects follow systematic patterns in which schizophrenia and autism correlate with imbalances in maternal and paternal genetic contributions to the individual. Schizophrenia is associated with excess

maternal contribution (e.g., loss of function of a paternally expressed gene, or duplication of a maternally expressed gene), while autism is associated with an excess of paternal expression.²¹⁷

This pattern suggests a model of cognitive/behavioral phenotypes in which schizophrenia and autism can productively be thought of as oppositional disorders. That is, it appears that they represent opposite extreme values along some phenotypic axis, and that there may be an intragenomic conflict between maternally and paternally derived genes with respect to the optimal cognitive/behavioral phenotype along that axis. While both optima are presumably well within the normal range (far from the extreme phenotype values associated with either of these two disorders), they differ such that the patrilineal optimum is slightly closer to the autism end of the spectrum, while the matrilineal optimum is slightly closer to the schizophrenia end.

Evolutionary theory predicts that psychotic-spectrum disorders will be linked to a clinical phenotype called the “hyper-egoistic brain,” while autistic-spectrum disorders will be linked to the “hyper-altruistic brain” clinical phenotype.^{40,41} The behavioral phenotypes associated with hyper-altruistic or hyper-egoistic brains need not (and generally will not) be functionally altruistic or egoistic, respectively. These disorders represent major disruptions at the level of the promiate mechanisms underlying social behavior and are not well-honed adaptations operating for the good of either the maternal or paternal gene copy.

TS is associated with elevated rates of autism, but, curiously, autism appears to be more common in X_mO patients than in X_pO patients,^{223,224} contrary to what might be expected based on extrapolation from the patterns observed with imprinted autosomal loci. One possibility is that imprinted genes on the X chromosome are under strong selection based on sex differences (since only females normally inherit a paternally derived X), and that this is confounding the other selective pressures on these loci. Recall that the apparent imprinting effects on certain aspects of cognition in TS also appear to be at odds with the general patterns of influence of imprinted genes. Unraveling the effects of imprinting and sex differences for X-linked and autosomal loci will require additional research.

C. Imprinted Gene Effects in Other Psychiatric Disorders

More limited evidence points toward a contribution of imprinted genes to the etiology of other specific psychopathologies,²²⁵ although in each case, the potential molecular and genetic mechanisms have yet to be fully elucidated, and attempts to understand the evolutionary origins are purely speculative at this point.

1. OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) is associated not only with obsessive and compulsive behaviors, but also with temper issues, externalizing behavior, and emotional problems.²²⁶ OCD is extremely common, estimated to affect as many as 5 million people in the United States,²²⁷ and shows a strong genetic component.²²⁸ OCD is comorbid with Prader–Willi syndrome and occurs in PWS-like patients.²²⁹ One hypothesis is that the absence of imprinted small nucleolar RNAs (SnoRNAs) that normally interact with Serotonin 2C receptor subtypes may contribute to the etiology of OCD.²³⁰

2. ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD)²³¹ is also extremely common and highly heritable and occurs at high frequency in conjunction with PWS.²³² Imprinting effects on hyperactivity have been reported in mice,¹⁴⁹ and parent-of-origin effects have been reported in disorders that are comorbid with ADHD, such as Tourette's syndrome,²³³ and a specific polymorphism in the gene encoding brain-derived neurotrophic factor (BDNF) has been specifically associated with susceptibility to ADHD.²³⁴

3. BIPOLAR AFFECTIVE DISORDER

Bipolar affective disorder (BPAD) and other mood disorders are highly comorbid with ADHD,^{235–237} and cyclical depression has been reported in conjunction with PWS.^{238,239} The severity of symptoms in BPAD in conjunction with ADHD shows dependence on parent of origin,²⁴⁰ and several genes that affect the dopaminergic and serotonergic systems that are common targets of therapeutic intervention show evidence for imprinting effects, including dopa decarboxylase (DDC),²⁴¹ tryptophan hydroxylase 2 (TPH2),²⁴² and BDNF.^{243,244}

IV. The Cost of Imprinting

In some ways, diseases associated with imprinted genes are no different from other diseases with a genetic basis. Mutations or epimutations occur in the germ line or the soma and produce the disease phenotype. One obvious difference is that, since imprinted genes are typically expressed from only one of the two alleles, only one loss-of-function mutation is required to effectively knock out the gene. Thus, at least for genes where loss-of-function mutations would normally be recessive, the monoallelic expression associated with imprinted genes adds a degree of penetrance to mutations. Further, imprinted genes are subject to certain mutations or epimutations that result in

transcriptional reactivation of the normally silenced allele, often referred to as “loss-of-imprinting” mutations. This reactivation results in an increase in the overall expression level, and is associated with a number of diseases.^{245–247}

Thus, there is a certain cost, in elevated penetrance of mutations and epimutations associated with imprinted genes, that is really associated with their monoallelic expression. However, there is a more subtle, but potentially much more significant, cost associated with genomic imprinting, that derives from how the imprinted genes alter the evolutionary dynamics of the systems in which they appear.

In general, the effect of natural selection is not identical for maternally and paternally inherited alleles. The magnitude of the selection asymmetry may be greatest in the context of fetal growth effects, decreasing significantly for postnatal behavioral effects, and may be quite subtle for many cognitive and behavioral phenotypes in adults. However, at loci where imprinted gene expression has been established, even subtle selective effects can have significant consequences over sufficiently long time scales.

In particular, consider a pair of oppositely imprinted loci (one maternally expressed and one paternally expressed), where the phenotypic effect of increasing gene expression at one locus is opposed to the effect of increasing expression from the other locus. If the matrilineal and patrilineal optima differ even slightly for this phenotype, these two loci will become engaged in an evolutionary arms race, with each under selection to increase its level of expression from the active allele.

In the simplest possible model, this escalation will go on forever, so that each locus is producing an infinite amount of gene product. Clearly, this is not realistic, and at some point, some other effect will limit the escalation. Among the possibilities for this limiting effect are metabolic cost associated with increased gene expression, mechanistic limitations on expression from one of the loci, and deleterious side effects associated with increased expression. The extent to which having imprinted genes is deleterious depends, in part, on which of these limiting factors dominates in practice. However, in each case, we expect to find pairs or groups of genes that have opposing phenotypic effects, and that are expressed at a level higher than what would be expected in the absence of imprinting. These elevated, oppositional patterns of expression have a number of potential consequences.

A. Mutational Effects

We have already noted that imprinted genes are more susceptible to loss-of-function mutations than their unimprinted counterparts, owing to their monoallelic expression. In addition, if the wild-type expression level is elevated

due to intragenomic conflict, the phenotypic consequences of a loss-of-function mutation will be more dramatic at an imprinted locus than it would have been in the absence of the conflict-driven escalation in gene expression.

B. Epimutations

In many cases, transcriptional inactivation of the silenced allele at an imprinted locus is achieved through the application of DNA methylation and/or histone modifications. At such a locus, the level of expression from the active allele will be determined largely by *cis*-acting regulatory elements encoded in the DNA itself. This arrangement produces a vulnerability to epimutations, where the silencing epigenetic marks are lost, resulting in a dramatic increase in the overall level of gene expression from the locus (as the normally silenced allele will have approximately the same *cis*-acting regulatory motifs, which become active in the absence of the epigenetic silencing).

The possibility of such reactivating epimutations imposes a twofold cost on systems of imprinted genes as compared to their unimprinted counterparts. Any locus may, in principle, be subjected to mutations that increase the gene dosage (e.g., a mutation that increases the copy number). Imprinted genes are susceptible to those mutation processes as well as to epimutations (which occur at substantially higher frequencies than other classes of mutation²⁴⁸). Further, due to the evolutionary escalation in expression level expected among imprinted genes, the effect of doubling the number of active gene copies in the cell may be more pronounced than would be the case for an unimprinted locus.

C. Imprinting and Cancer

We have noted that imprinted genes have an increased susceptibility to mutations and epimutations that increase or eliminate gene expression from the locus. In addition, the resulting change in the absolute gene expression level will tend to be greater at an imprinted locus than at an unimprinted one. Another feature of imprinted genes is that they are typically associated either with growth-enhancing or growth-suppressing functions in early development.

It is not surprising, then, that dysregulation of imprinted genes is found in many cancers. A locus with a growth-enhancing effect in early development will often maintain a mitogenic effect in adult somatic cells, and reactivation of the silenced allele can contribute to uncontrolled cell proliferation. At the same time, many (maternally expressed) imprinted genes have evolved a growth-suppressing function. Many of these genes may then act as *de facto* tumor suppressors in adult tissues. However, these genes will differ from many other tumor suppressors in the fact that there is only a single active copy, which reduces the number of somatic mutations required to eliminate the tumor-suppressing activity of the locus.

The contribution of epigenetic dysregulation to cancer is treated in detail elsewhere in this volume (Chapter 14), and will not be covered further here.

D. Pleiotropic Effects

In reality, pairs of antagonistically coevolving genes will not be perfectly aligned in terms of their phenotypic consequences. The space of possible phenotypes occupies a large number of dimensions, and the marginal effect of a small change in gene expression from a locus can be pictured as a vector in this high-dimensional space. In the previous sections, we have discussed the escalation among imprinted genes in terms of an evolutionary conflict over a single aspect of the phenotype (e.g., fetal growth rate). In general, changes in gene expression will affect not only the aspect of the phenotype that is the object of the evolutionary conflict, but other aspects of the phenotype as well, even if the maternally and paternally inherited alleles share a common phenotypic optimum for those other aspects. As a result of these pleiotropic effects, the escalation that is driven by a conflict over one aspect of the phenotype can force those other aspects of the phenotype away from their shared optima.

In a simple, linear model of the antagonistic coevolution of imprinted genes with pleiotropic effects, it is possible to quantify the magnitude of the phenotypic deviation at the evolutionarily stable state.²⁴⁹ In general, conflict will result in the fixation of suboptimal phenotypes. Except for a vanishingly small set of special cases, the equilibrium phenotype in the presence of imprinting will deviate from that which maximizes the overall fitness of the organism (or the average fitness of the alleles it is carrying), even for those aspects of the phenotype for which all of the alleles in the organism share a common optimum.

With respect to the particular aspect of the phenotype that is the basis of the conflict, we might naively expect that the evolutionarily stable phenotype value would lie somewhere between the matrilineal and patrilineal optima. However, in the presence of pleiotropic effects of the imprinted genes, this expectation does not necessarily hold. In a simple model, it is predicted that roughly half of the time the equilibrium phenotype value along the phenotypic axis of conflict will lie outside of the range defined by the matrilineal and patrilineal optima. Thus, the combination of intragenomic conflict and pleiotropic effects of imprinted genes create a situation where natural selection will often produce a phenotype that is more extreme than what is favored by either of the conflicting loci.

E. Decanalization

Another consequence of increasing the level of expression from a locus is that it will tend to generate an increase in the expression variance. Under widely differing circumstances, there seems to be a relatively simple

relationship, where the variance in gene expression scales roughly as the square of the mean. This relationship can be seen in yeast,²⁵⁰ where this variance represents stochastic variation among genetically identical cells, as well as in human lymphoblasts,²⁵¹ where it represents stochastic variation, as well as the consequences of interindividual genetic variation at other loci. In both cases, the scaling relationship is robust over multiple orders of magnitude of the absolute expression level.

Many biological processes are characterized by the phenomenon of canalization, which refers to mechanisms that reduce the phenotypic variation in the face of underlying genetic or environmental variation.^{252–254} The escalation that results from intragenomic, interlocus conflict among imprinted genes can, under some circumstances, lead to the undermining of these canalization mechanisms (conflict-induced decanalization), resulting in an increased frequency of extreme phenotypes, even if those phenotypes are associated with disease states.²⁵⁵

F. The Imprinting Load

The set of phenomena described here combines to produce the “imprinting load,” which can be thought of as the average fitness cost associated with imprinted gene expression. More formally, we consider the average fitness associated with a system that includes imprinted genes at its evolutionary equilibrium. This is compared to the average fitness of the same system, but in the absence of genomic imprinting. The imprinting load is simply the difference between the two average fitnesses.

The imprinting load is a quantity that is difficult to calculate for real systems. However, one can calculate the imprinting load for particular models, and this can provide insight into which factors are most important in determining the magnitude of the fitness reduction. For example, in the simple models of pleiotropy and decanalization described above, the imprinting load scales roughly as the square of the magnitude of the conflict between the matrilineal and patrilineal phenotypic optima.^{249,255} For example, assume imprinting load is ξ in a system where the matrilineal and patrilineal optimal phenotypes differ by a quantity α . In a system that was identical, but where the optima differed by 2α , the imprinting load would be approximately 4ξ .

Interestingly, in both models, the magnitude of the imprinting load is much more sensitive to other parameters of the model. In the pleiotropy model, the most important factor is the relationship between the pleiotropic effects of the two loci. In the decanalization model, the most important factor is the way in which the gene products interact to generate the phenotype.

In both cases, these other, dominant factors can be interpreted broadly as aspects of “mechanism.” Thus, the simple models suggest that the addition of genomic imprinting to a system generically results in a reduction in fitness.

However, there does not appear to be a general answer to the question of how large this effect is in the absence of consideration of certain details of how the system is constructed.

V. Conclusions

Genomic imprinting affects on the order of 1% of the genome and contributes to many parent-of-origin effects in heritable disease. The evolutionary forces responsible for the origin of imprinted gene expression help to explain many of the phenotypic consequences of imprinting-related disorders, including the growth effects and certain consequences for feeding behaviors and adult metabolism. In many cases, evolutionary reasoning also explains the direction of the parent-of-origin effects. Imprinting also plays an important role in neural development, and defects in imprinted genes are associated with numerous cognitive and behavioral consequences, including possible associations with major psychiatric disorders including autism and schizophrenia. Our evolutionary understanding of the cognitive and behavioral effects of imprinted genes is much less well developed than our understanding of the effects on growth and metabolism.

The existence of imprinted genes potentially increases the penetrance of genetic defects, as a single mutation is sufficient to induce complete loss of function at an imprinted locus. Similarly, the existence of the molecular machinery responsible for imprinting creates the opportunity for epimutations that result in dysregulation of expression, and may occur as orders of magnitude more frequently than mutations to the DNA sequence. Perhaps, more important than either of these effects, however, are the consequences of antagonistic coevolution among imprinted genes that can lead to the accumulation of maladaptive phenotypes, and may contribute to elevated frequencies of certain disease states.

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