Genomic Imprinting and Physiological Processes in Mammals

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Review

Genomic Imprinting and Physiological Processes in Mammals

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Complex multicellular organisms, such as mammals, express two complete sets of chromosomes per nucleus, combining the genetic material of both parents. However, epigenetic studies have demonstrated violations to this rule that are necessary for mammalian physiology; the most notable parental allele expression phenomenon is genomic imprinting. With the identification of endogenous imprinted genes, genomic imprinting became well-established as an epigenetic mechanism in which the expression pattern of a parental allele influences phenotypic expression. The expanding study of genomic imprinting is revealing a significant impact on brain functions and associated diseases. Here, we review key milestones in the field of imprinting and discuss mechanisms and systems in which imprinted genes exert a significant role.

Genomic Imprinting: A Historical Overview

The term "imprinting" was first used by the cytogeneticist Helen Crouse in the 1960s to describe the elimination of paternally derived X chromosomes in flies (Crouse, 1960). However, during the early 1980s, we witnessed the renaissance of genomic imprinting due to fundamental studies in mice. Pronuclear transfer experiments conducted in newly fertilized mouse eggs (McGrath and Solter, 1983a, 1983b, 1984; Surani and Barton, 1983; Surani et al., 1984) allowed the creation of diploid gynogenetic (two maternal copies) or androgenetic (two paternal copies) conceptuses (Figure 1A). The embryos were not viable, proving that the two parental sets of chromosomes are not functionally equivalent and that both a maternal set and a paternal set are required for early development. Interestingly, these experiments also showed that conceptuses developed from gynogenetic pronuclei failed in part due to compromised extra-embryonic lineages, while the androgenetic conceptuses presented underdeveloped embryos. These data suggested that maternal and paternal genomes contain indispensable components for both embryonic and extraembryonic development, and that they also play complementary roles in sustaining these lineages.

While the experiments by Surani and Solter showed that the parental genomes were nonequivalent, whether this was a whole-genome effect or whether specific genes were involved was not known at that time and raised considerable debate. Studies by Cattanach and Kirk (Cattanach and Kirk, 1985) and colleagues provided fundamental evidence for gene-specific imprinting. Using reciprocal and Robertsonian translocations, they took advantage of chromosome "non-complementation" analysis, identifying regions of the genome for which the presence of two maternal or two paternal chromosomal copies resulted in abnormalities in growth, behavior and/or viability (Figure 1B). This systematic approach showed that imprinting was restricted to some regions of the genome, implied that some genes were expressed or repressed according to their parental origin and provided a comprehensive genome-wide genetic map of imprinted regions (https://www.mousebook.org/mousebook-catalogs/imprinting-resource). The finding that mice with particular uniparental disomies and abnormal phenotypes could survive to birth and beyond implied that imprinting defects could also be a significant cause of human diseases. Consistent with findings in mice, at the same time, human syndromes were being described that exhibited parent-of-origin effects in their patterns of inheritance. The genomic regions involved shared syntenic homology with some of those identified by Cattanach and colleagues in the mouse.

Earlier, in 1974, Johnson (Johnson, 1974) reported the unusual phenomenon of parent-of-origin effects on the viability of mice with deletions within a small region of chromosome 17 in mice, the *T-maternal effect* (*Tme*) locus. This observation paved the way for the discovery of the first imprinted gene. Using the *Tme* deletion and systematic molecular genetic mapping approaches, Barlow and colleagues uncovered the imprinted insulin-like growth factor 2 receptor (*Igf2r*) locus on mouse chromosome 17, which is expressed from the maternally inherited chromosome but repressed on the paternally inherited chromosome (Barlow et al., 1991). That same year, *Igf2* on mouse chromosome 7 (DeChiara et al., 1991; Ferguson-Smith et al., 1991) was demonstrated to be expressed specifically from the paternally inherited chromosome. Adjacent to but downstream of *Igf2*, the non-coding RNA *H19* gene was found to be reciprocally imprinted to *Igf2*, expressed from the maternally inherited chromosome (Bartolomei et al., 1991). In normal embryos, co-expression of these three genes regulates growth, with the

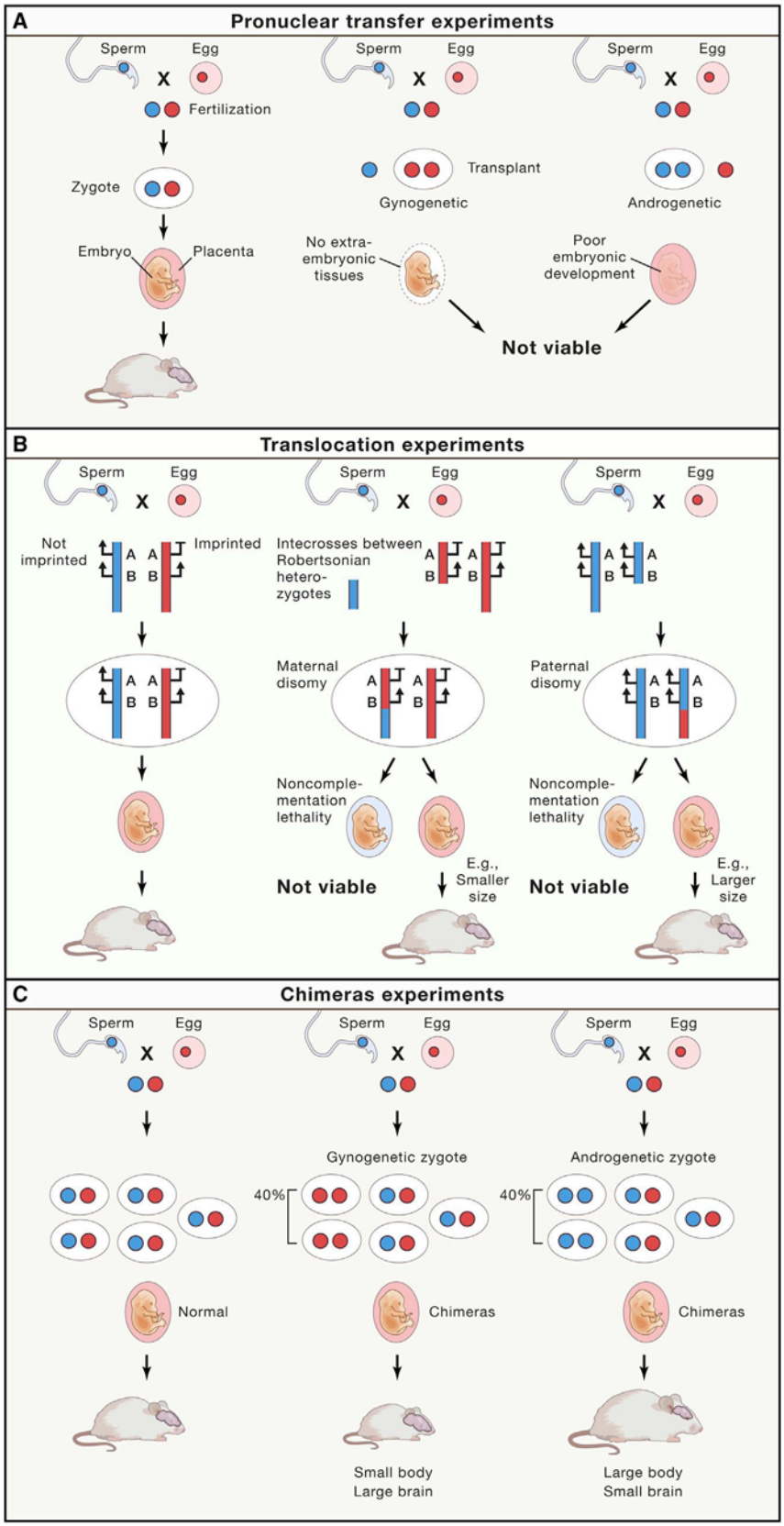

Figure 1. Parental Genomic Imprinting Expression of Maternal and Paternal Alleles Is Pivotal in Embryogenesis

(A) *Pronuclear transfer experiments*: representation of enucleated experiments as evidence for genomic imprinting in mice. Gynogenetic (two maternal pronuclei) transplants resulted in a lack of extra-embryonic tissue development, while androgenetic (two paternal copies) transplants retarded embryo development but maintained the development of trophoblast.

(B) *Translocation experiments*: representation of uniparental balanced disomy derived from intercrosses of heterozygous Robertsonian fusions showed that maternal disomy produced offspring with reduced size, while paternal disomy produced mice with the opposite (increased) phenotype.

(C) *Chimeras experiments*: representation of gynogenetic/androgenetic + wild-type chimeras and the effects on viable offspring.

paternally expressed gene (*Igf2*) being growth promoting and the maternally expressed imprinted genes (*Igf2r* and *H19*) being negative regulators of growth.

Since the parent-of-origin specific expression was not genetically determined, genomic imprinting was recognized to be an epigenetic phenomenon. At the simplest imprinted locus, parental alleles are mono-allelically expressed, with either the maternally inherited or paternally inherited allele being transcriptionally repressed by differential epigenetic modifications initiated in the male and female germlines. Shortly after the discovery of the first imprinted genes, parental-allele-specific DNA methylation was shown at imprinted loci (Bartolomei et al., 1993; Ferguson-Smith et al., 1993; Li et al., 1993; Stöger et al., 1993), suggesting that it may play a key role in imprinting control.

In addition to its now well-known roles in placental biology, fetal growth, and homeostasis (Peters, 2014; Plasschaert and Bartolomei, 2014), genomic imprinting is being increasingly appreciated for its role in the nervous system, and almost half of all the known imprinted genes show imprinted expression in the brain. The most fascinating evidence for a key function of genomic imprinting in the brain first came in the late 1990s. At that time, it was known that mouse chimeras containing gynogenetic or androgenetic cells mixed with wild-type (WT) cells provided a promising experimental model with reciprocal distributions of the androgenetic and gynogenetic cells within these chimeras, which suggested that genomic imprinting was important for particular embryonic lineages, including the brain (Barton et al., 1991; Fundele et al., 1990). Subsequently, Keverne et al. (1996) demonstrated that gynogenetic-WT chimeras developed as abnormal embryos with large brains, while embryos developed from androgenetic-WT chimeras presented abnormally small brains (Figure 1C). Furthermore, androgenetic and gynogenetic cells showed biased regional distributions throughout the brain: specifically, gynogenetic cells were distributed throughout the cortex, striatum, and hippocampus, while androgenetic cells were enriched in the hypothalamus, raising interest in the various physiological functions ascribed to such distinct brain areas and the potential functions of paternally and maternally expressed imprinted genes in those locations.

The field of genomic imprinting is continually expanding and has gradually spread to disciplines other than embryology, such as cell physiology, behavior, and neuroscience. In this Review, we highlight the more recent investigations, addressing the current mechanistic understanding of the epigenetics governing genomic imprinting and reviewing the latest genomic map of imprinted genes. Moreover, we provide an overview of the roles of imprinted genes in the wide-range of physiological functions throughout the life course. We discuss examples of imprinting-related diseases and recent discoveries in the sleep and circadian clock field. The Review concludes with a theoretical overview of evolutionary aspects of imprinting and an exploration of new avenues on how genomic imprinting may highlight epigenetic regulatory mechanisms affecting genome-function more widely.

Epigenetic Control of Imprints

Cells with identical genes, histories, and environments can display a repertoire of different functions that are regulated both transcriptionally and post-transcriptionally. Much of this transcriptional variability is governed by epigenetic mechanisms. Epigenetic processes, such as DNA methylation and histone modifications, are fundamental to the establishment, maintenance, and dynamic changes in gene expression; such epigenetic states contribute to cell-type-specific genome functions throughout the life course, providing critical memories of earlier decisions. Epigenetic states are most dynamic during germ cell specification and early embryogenesis. Some epigenetic information, including that determining genomic imprinting, is inherited. Therefore, genomic imprinting is an important paradigm for understanding non-genetic inheritance.

DNA methylation—the addition of a methyl (CH_3) group to cytosines—is a heritable epigenetic mark that is associated with transcriptional repression when occurring on regulatory sequences, such as promoters. The parent-of-origin-specific acquisition of DNA methylation marks at imprinting control regions (ICRs) in the germline is essential for the mono-allelic expression of imprinted genes in embryos and are retained as the memory of parental origin after fertilization (Kelsey and Feil, 2013). Imprinted genes reside mostly, but not exclusively, in clusters throughout the mammalian genome; a cluster typically contains a single ICR, which harbors germline-derived parental-allele-specific methylation and governs imprinted expression of multiple genes within the entire domain. In addition, some imprinted genes exhibit complex patterns of tissue-specific and promoter-isoform-specific imprinted gene expression, with maternal, paternal, and biallelic expression observed in different cell lineages and for different transcripts.

How are DNA methylation and other epigenetic marks patterned during gametogenesis and embryogenesis? DNA methylation is controlled by a family of DNA methyltransferases (DNMTs), wherein DNMT3A and DNMT3B establish DNA methylation patterns *de novo*, while DNMT1 maintains methylation after DNA replication (Smallwood and Kelsey, 2012a, 2012b). Embryonic development is characterized by periods of loss and gain of DNA methylation. After fertilization, there is a demethylation phase in which gametic DNA methylation patterns are erased on both parental genomes except for certain genomic regions, including ICRs that robustly retain parent-specific DNA methylation. From implantation, there is a phase of *de novo* methylation after which the overall genomic levels of DNA methylation remain relatively stable except for cells allocated to the germ cell lineage. Indeed, primordial germ cells undergo a second wave of genome-wide demethylation. DNA methylation modifications at imprinted loci are also erased in the germline allowing removal of parental epigenetic ''memory'' so that it can then be re-established subsequently at ICRs in an oocyte- or sperm-specific manner as germ cell development proceeds. Germline ICR methylation is mostly established by DNMT3A in combination with DNMT3L, a cofactor with no methyltransferase activity (Bourc'his et al., 2001; Kaneda et al., 2004). These ICRs are considered ''primary'' or ''germline'' differentially methylated regions (DMRs). There are only three known paternally derived germline methylation imprints, and these are all intergenic; in contrast, over twenty ICRs acquire methylation in the maternal germline and these comprise all promoters (Bartolomei and Ferguson-Smith, 2011). After fertilization, ''secondary'' DMRs

Box 1. The Persistence of Imprinted Memory: The Role of ZFP57 and ZFP445

Many regions of the genome acquire germline differences in DNA methylation, but unlike imprints, these parent-specific differences become equivalent during post-fertilization epigenetic reprogramming. Hence, this retention of epigenetic memory during the preimplantation stage is the event critical for imprinting control. Therefore, how this memory is retained in an environment when methylation marks elsewhere are in such dynamic phases remains an important question.

One mechanism potentially regulating this phenomenon acts via sequence-specific binding factors that can recruit epigenetic modifiers. One such binding factor is the KRAB-zinc finger protein ZFP57 (Quenneville et al., 2011). For the correct maintenance of imprints, maternal ZFP57 stores must be present in the oocyte upon fertilization, and ZFP57 must also be expressed zygotically during the preimplantation period. Importantly, this DNA-binding protein binds in a sequence-specific and methylation-dependent manner. Mice that are maternal-zygotic mutants lose many of their imprints and die during gestation; those without embryonic expression have a variably penetrant phenotype and reduced viability (Li et al., 2008). In humans, recessive *ZFP57* mutations result in multi-locus imprinting disorders, with most patients exhibiting transient neonatal diabetes alongside other imprinting-associated phenotypes, such as growth defects. Unlike in mice, in humans, ZFP57 is not expressed in oocytes and is thus not a maternal factor (Mackay et al., 2008).

The incomplete penetrance of *ZFP57* mutations in human and mouse suggests additional effectors. Most recently ZFP445, which traces to the origins of mammalian imprinting, also has been shown to bind ICRs in mouse and human. In ZFP57/445 mouse double mutants, methylation at all ICRs (except one) is lost indicating that these two proteins together are necessary and sufficient for imprint maintenance. The earlier embryonic expression of ZNF445 in humans and its intolerance to loss of function mutations indicate its greater importance in the maintenance of human imprints (Takahashi et al., 2019).

may arise at imprinted gene clusters, often as a consequence of the imprinted expression of non-coding transcripts or passively following transcriptional repression (Nowak et al., 2011; Sasaki et al., 1995).

Maternal and paternal ICRs are not subject to a specific targeting process of DNA methylation during gametogenesis. Genome-wide, DNA methylation is preferentially established at intergenic sequences and transposons during spermatogenesis, while oocyte DNA methylation acquisition is coupled to transcriptional elongation and mostly found in gene bodies, including at intragenic CpG islands (Kobayashi et al., 2012). What distinguishes ICRs from the rest of gametically methylated regions is their ability to be retained during post-fertilization epigenetic reprogramming. This has been linked to the presence of several binding sites for ZFP57, which recruits the KAP1 heterochromatic complex (Quenneville et al., 2011) (Box 1). Hundreds of ZFP57-containing regions still exhibit parent-specific DNA methylation at the blastocyst stage, but very few survive post-implantation except the canonical twenty or so ICRs. Interestingly, in the human placenta, there is a high retention of oocyte-derived methylation, and this placenta-specific imprinting is highly polymorphic among individuals (Hanna et al., 2016; Sanchez-Delgado et al., 2016). This suggests that epigenetic differences among embryonic cells that establish extra-embryonic lineages at the time of implantation become fixed in the placenta (Hanna et al., 2016).

Recent studies indicate additional complexities in the regulation of DNA methylation patterns in oocytes and cleavage embryos. The protein Ubiquitin-like, containing PHD and RING finger domains 1 (UHRF1), recruits the maintenance-type DNA methyltransferase DNMT1 to hemi-methylated CpG sites on newly replicated DNA to restore pre-existing CpG methylation patterns after replication (Sharif et al., 2007; Unoki et al., 2004). Accordingly, UHRF1 is required for imprint maintenance in post-implantation embryos (Sharif et al., 2007). Paradoxically however, UHRF1, together with DNMT1, is mainly localized in the cytoplasm of oocytes and preimplantation embryos, with only a small fraction in the nucleus (Maenohara et al., 2017). Oocyte-specific ablation of *Uhrf1* decreases CpG methylation in fully grown oocytes (FGOs) to levels below those of *Dnmt1* knockout (KO) FGOs (Maenohara et al., 2017). Because no DNA replication occurs in growing oocytes and this stage corresponds to the *de novo* methylation phase, this evidence suggests that both DNMT1 and UHRF1 have a role in *de novo* CpG methylation. The exclusion of UHRF1 and DNMT1 from the nucleus is mediated by the protein Stella. In the absence of Stella, UHRF1 and DNMT1 ectopically methylates intergenic regions that ordinarily escape *de novo* methylation, indicating an unanticipated active mechanism to protect large parts of the oocyte genome from methylation by these factors (Li et al., 2018). Such protection may be important to ensure proper zygotic genome activation. CpG methylation levels in blastocysts derived from *Uhrf1* KO oocytes (*Uhrf1* maternal-KO blastocysts) are decreased throughout the genome, including at ICRs. This indicates that maternally derived UHRF1 plays a central role in maintaining CpG methylation in preimplantation embryos, perhaps by contributing to the recruitment of maternally derived and/or zygotically produced DNMT1 (Hirasawa et al., 2008; Howell et al., 2001). This activity protects the ICRs against genome-wide demethylation occurring at this stage. Interestingly, *Uhrf1* maternal-KO embryos die before implantation, which is a much more severe phenotype than that observed in any DNA methyltransferase KO embryos (maternal KO or zygotic KO), which suggests that preimplantation lethality may arise independent of methylation defects (Maenohara et al., 2017).

While "canonical" imprinting is stably maintained throughout life, a less-studied form of gamete-determined DNA methylation survives only for a few days after fertilization. Regions subjected to this "transient" form of imprinting carry ZFP57 binding sites but lose their parental specificity at the time of embryo implantation, as they become either fully methylated or fully unmethylated (Kobayashi et al., 2012; Proudhon et al., 2012). Most of these regions are methylated from the oocyte (Duffié et al., 2014). Hundreds of germline-derived DMRs have been described in mice and human blastocysts, although the overlap between the two

species appears rather limited (Sanchez-Delgado et al., 2016). Whether transient imprinting could impact the early embryonic transcriptome and even have long-lasting consequences is an intriguing question. However, because this is a recently described phenomenon, its developmental and physiological importance has not yet been fully described. Of the newly described transiently imprinted loci, the *zinc finger, DBF-type containing 2* (*Zdbf2*) locus is the most characterized so far. Importantly, this locus shares the same regulatory properties in mice and humans. The transcription start site (TSS) of an alternative transcript of *Zdbf2*, *Liz* (*long isoform of Zdbf2*), coincides with a maternal germline DMR, which disappears at implantation by gaining DNA methylation on the paternal allele. Consequently, *Liz* expression is restricted to the pluripotent embryo and occurs in a mono-allelic, paternal-specific manner before ceasing expression at implantation for the rest of somatic life (Duffié et al., 2014). Very brief *Liz* expression in the embryo is required for initiating a long-lasting epigenetic switch; it disrupts a repressive block of histone 3 lysine 27 trimethylation (H3K27me3)-enriched chromatin via the deposition of antagonistic DNA methylation marks and thus consequentially allows *Zdbf2* activation from the same allele from which *Liz* was expressed, i.e., the paternal allele. Importantly, the consequences of imprinted *Liz* expression are manifested at much later stages: *Liz*-deficient embryos develop normally and are healthy and fertile but show a growth defect right after birth. This culminates with a 20% body weight reduction at two weeks of age, and this systemic growth defect persists throughout life (Greenberg et al., 2017). Indeed, without *Liz*, *Zdbf2* is not released from polycomb repression and fails to activate in postnatal brain derivatives, especially in the hypothalamus-pituitary axis. Thus, evidence exists that transient preimplantation imprinting can have autonomous and life-long effects on adult phenotypes (Greenberg et al., 2017). *Zdbf2* appears to be a new paternally expressed growth-promoting gene, but besides the fact that this protein contains a zinc finger motif, nothing else is known about its molecular function. Its major sites of expression –the hypothalamus and pituitary gland– may imply a role in the production or secretion of endocrine hormones, including the growth hormone.

Recently, Inoue and colleagues (Inoue et al., 2017a, 2017b) provided evidence for a form of genomic imprinting independent of gametic DNA methylation. Specifically, they determined that H3K27me3 marks can mediate imprinted mono-allelic expression in the early embryo. H3K27me3 is deposited over large genomic blocks early in oocyte development, and these can persist to some extent after fertilization, at least until the blastocyst stage. This form of imprinting is generally transient, however, as it disappears in the post-implantation embryo; nonetheless, it can persist at a few genes in extra-embryonic lineages, including at the *Xist* gene. Accordingly, lack of maternally inherited H3K27me3 affects imprinted X chromosome inactivation in extra-embryonic tissues (Inoue et al., 2018). The mechanisms for this very selective persistence in extra-embryonic tissues remain to be elucidated.

Genome-wide Allelic Expression

Nearly three decades of classical genetic, molecular, and embryological investigations in this field have produced a catalog of approximately 200 confirmed imprinted genes (less than 1% of all genes), some of which play pivotal roles in growth, viability, and various physiological functions. Functional screening based on genetics in mice is a costly and time-consuming approach but has been the most robust methodology for mapping imprinted transcription in mammals to date. Over the past few years, next-generation sequencing technologies combined with mouse strain-specific polymorphisms have offered a promising strategy to quantify genome-wide parental-origin specific allelic transcription. Although simple in its conceptual framework, this large-scale approach has been more insidious than expected (DeVeale et al., 2012). The basic idea underlying this approach is that the expression of heterozygous single-nucleotide polymorphisms (SNPs), measured in RNA-sequencing (RNA-seq) reads, can be further divided into allele-specific expression based on the parental origin of the allele. Moreover, the use of reciprocal hybrids allows the discrimination of parent-of-origin dependent transcriptional effects from those caused by strain differences (Babak et al., 2008; Wang et al., 2008). This approach can narrow the investigation of imprinted transcription to the tissue and/or cell level and has been applied to imprinted studies on brain (Gregg et al., 2010a, 2010b; Wang et al., 2008) and placental (Okae et al., 2012) tissues. Early rounds of studies that used the transcriptomic sequencing of reciprocal F1 mouse hybrids extended the list of imprinted genes by only a few dozen (Figure 2; Table S1) but have suggested the presence of many genes that appear to exhibit parent-of-origin allelic biases in their expression. Importantly, these approaches have highlighted the many methodological challenges that exist when using RNA-seq datasets for this particular purpose (DeVeale et al., 2012; Kelsey and Bartolomei, 2012). Furthermore, bias leading to misinterpretation of placental imprinted gene status can also derive from maternal decidual contamination of placental samples (Okae et al., 2012). The solutions suggested to overcome issues are based on the establishment of restrictive and experimentally dictated thresholds to prevent false positives, the development of sophisticated statistical models, and the mandatory validation of individual candidates using independent methods (Perez et al., 2015). This, along with improvements in strain-specific reference genomes and in bioinformatic approaches to more precisely quantify allele-specific transcript isoforms accompanied by higher-resolution cell purification methodologies, should also contribute to our understanding of the extent of parental-origin-specific allelic bias and the relationship of this with the more canonical imprinting process both functionally and mechanistically (Perez et al., 2015; Gregg, 2017). In parallel, studies in humans on the genetically well-characterized Icelandic population are yielding new information on the genome-wide extent of imprinted expression and methylation (Zink et al., 2018).

The effort of searching for imprinting-like effects across tissues has initiated an important debate on the definition of genomic imprinting since these more sensitive RNA-seq based methods identify genes exhibiting less extreme parental-origin specific allelic bias rather than a clear monoallelic expression pattern. In mice, several examples of established imprinted clusters contain genes displaying parental bias rather than the monoallelic expression of one allele have been shown (e.g., *Gnas*,

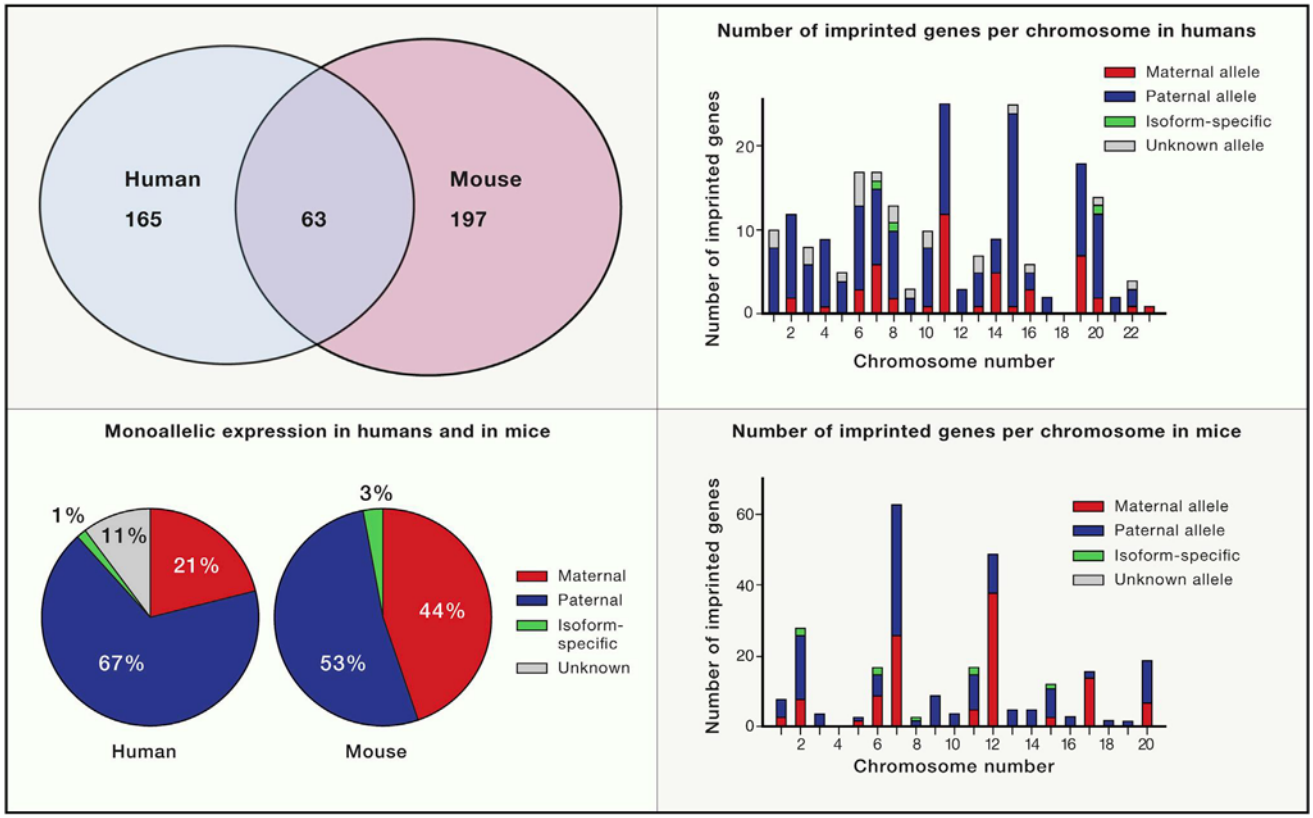

Figure 2. Imprinted Genes in Mouse and Humans

(A) Number of imprinted genes annotated in the mouse and in humans. The number is updated to December 2018. A complete list of the genes is also reported in Table S1.

(B) For both humans and mice, we report the distribution of imprinted genes across chromosomes.

Ube3a, *Phlda2, Dio3*), and furthermore, different biases are found at different developmental stages and in different tissues (Perez et al., 2015, 2016). But what do parent-specific allelic biases actually mean? These effects may be caused by all cells in a sample exhibiting a bias in expression from one parental chromosome compared to another, or may represent pure mono-allelic expression in a subset of cells within the population, with others expressing equivalently from both parental chromosomes. Some are found at the edges of existing imprinted gene domains and their 'weak' imprinting may reflect incomplete influence of the ICR (Perez et al., 2016).

Currently, a number of novel imprinted genes, including those with isoform-specific parental biases, parental biases of various strengths, and temporally and spatially restricted biases, have been described (Andergassen et al., 2017; Perez et al., 2015), with some yet to be validated by independent methods. Figure 2 (and Table S1) reports the latest list (December 2018) of such imprinted genes in humans and mice. Interestingly, many genes appear imprinted in multiple brain areas, but not in other somatic tissues, and display striking variation across functionally distinct brain regions. The functional significance of this phenomenon has just begun to be genetically assessed. For instance, the neural-specific deletion of the paternal, but not maternal, allele of the paternally biased Bcl2l1 results in loss of specific neuron types (Perez et al., 2015). We have now begun to genetically assess the functional significance of this phenomenon. The genetic analysis of paternally biased genes in neurons supports the idea that the parental regulation of gene dosage may be required for normal brain development and function (Perez et al., 2016).

Genomic Imprinting and Developmental Physiology

From the initial embryological investigations of Surani and Solter it has become clear that a major function for imprinted genes is in the placenta. Multiple studies have subsequently found that imprinted genes regulate resources to the growing fetus via their contributions to placental development and morphological organization as well as via signaling pathways that directly regulate nutrient transport. Since the classical studies of the *Igf2* gene (Constância et al., 2002; DeChiara et al., 1990), numerous imprinted genes have been shown to directly or indirectly modulate fetal growth and these have been extensively reviewed elsewhere (Cleaton et al., 2014; Peters, 2014).

More recently however, imprinted genes expressed in the placenta have been shown to have effects other than just nutrient transport and fetal growth. The maternal *Phlda2* is strongly expressed in the endocrine lineages of the placenta that signal, via hormones such as placental lactogens, to the mother (Tunster et al., 2016). Fascinatingly, altering the level of expression

of *Phlda2* in the fetal placenta, either by loss (maternal knockout) or modeling loss-of-imprinting (two-fold overexpression), leads to changes in gene expression in the brain of the mother and influences the quality of maternal care provided to the pups postnatally (Creeth et al., 2018).

Postnatal Effects: The Dlk1 *Gene*

An excellent example of an imprinted gene with dynamic temporal regulation that modulates postnatal physiology is the *Dlk1* gene, a paternally expressed imprinted gene on mouse chromosome 12 (da Rocha et al., 2008; Takada et al., 2000). DLK1 expression during development acts at multiple levels to modulate metabolic axes, having consequences on lifelong energy homeostasis. The region of syntenic homology on human chromosome 14 is the critical region for the Temple and Kagami-Ogata syndromes (Howard and Charalambous, 2015), characterized by intrauterine growth restriction, failure to thrive, and early-onset obesity. Loss of *Dlk1* expression is thought to cause the phenotypes associated with Temple Syndrome (Briggs et al., 2016). *Dlk1* encodes a single-pass transmembrane protein, which can also be cleaved to produce a soluble endocrine form (da Rocha et al., 2008).

Deletion of *Dlk1* in mice causes growth retardation with postnatal catch-up and early-life adiposity (Cleaton et al., 2016). Conversely, overexpression of *Dlk1* is associated with altered metabolic fuel usage in the fasted state; animals with increased DLK1 levels use lipids as fuel during fasting conditions more readily and consequently have reduced adipose tissue stores (Charalambous et al., 2014). These phenotypes are at least partially due to alterations of the growth hormone axis mediated by DLK1 actions in the developing pituitary gland (Charalambous et al., 2014; Cheung et al., 2013).

Like most imprinted genes, *Dlk1* functions after gastrulation in tissue and organ growth and development. Studies have shown that DLK1 can act in an autocrine, paracrine, or endocrine manner, with prenatal functions being shown in the development of multiple organ systems, especially those of mesodermal origin. DLK1 notably functions as a preadipocyte factor in the development of adipose tissue and in postnatal adaptations, including regulating non-shivering thermogenesis via brown fat development, adult neurogenesis, and maternal metabolic partitioning during pregnancy (Cleaton et al., 2016).

The analysis of *Dlk1* in postnatal neurogenesis has provided further useful insights into its function. In both neurogenic and hippocampal neurogenic niches, reductions in *Dlk1* levels result in age-dependent compromised neurogenesis. Importantly, this effect is initiated during the early postnatal period when *Dlk1* mutant neural stem cells inappropriately exit quiescence, thus depleting the stem cell pool. Interestingly, membrane-bound DLK1 is specific to neural stem cells, while secreted DLK1 is generated by the niche astrocytes, and both are required for postnatal neurogenesis (Ferrón et al., 2011).

One key aspect of *Dlk1* function in the postnatal neurogenic niche is that *Dlk1* shows a selective absence of imprinting. Both maternal and paternally inherited alleles of *Dlk1* are expressed, and this switch from an imprinted to a non-imprinted state provides a dosage that appears to be important since both maternal and paternal heterozygotes have phenotypes that are intermediate to the homozygous mutant.

Genomic Imprinting in Adult Behavior and Disease

Although mainly studied in the context of early embryonic development, imprinted genes are also highly expressed in both adult and developing brains and have been implicated in multiple aspects of brain function, including behavior (Davies et al., 2015; Wilkinson et al., 2007). Some early works include the discoveries of the roles of *Peg1/Mest* and *Peg3* in maternal behavior (Lefebvre et al., 1998; Li et al., 1999). Recent RNA-seq efforts focused on allelic bias in the adult brain (Perez et al., 2016; Perez et al., 2015) and suggest a plethora of new roles for imprinting in adult functions, most of which are currently unexplored. A role for imprinted genes in behavior after weaning, and therefore distinct from an intrinsic role in influencing growth and body composition, has been shown in several studies (Box 2).

More generally, the extent to which imprinted genes influence adult neurobiology and behavior remains unanswered. The occurrences of specific and reciprocal neurological defects in Prader-Willi Syndrome (PWS) and Angelman Syndrome (AS), two neurodevelopmental disorders with opposite imprinting profiles, called attention to the role of genomic imprinting in the brain. However, it is too soon to know whether there is a functional pattern to the outcomes mediated by paternally expressed imprinted genes and another (perhaps reciprocal) one conferred by maternally expressed imprinted genes that might provide further insights into the evolution of imprinting.

AS and PWS are caused by reciprocal deletion of the human chromosome interval 15q11-q13 (Figure 3). AS, caused by the lack of maternal *UBE3A* gene expression, and PWS, caused by loss of the paternal expression of several contiguous genes, are both neurodevelopmental disorders, but they are characterized by very distinct phenotypes. PWS can arise via the deletion of the paternal copy of 15q11-q13, chromosomal maternal uniparental disomy (mUPD15), or ICR deletion. All of these genotypes lead to the loss of gene expression normally from the paternally inherited chromosome, but both mUPD15 and ICR deletion are expected to effectively double the expression of the maternally expressed gene *UBE3A*. These two genotypes are also far more associated with psychotic illnesses in individuals with PWS than individual gene deletion genotypes (~68% incidence versus ~8% incidence) (McNamara and Isles, 2013). A mouse model of PWS ICR deletion was used to show that the lack of PWS gene expression and doubled *Ube3a* expression are associated with behavioral and cognitive changes, including abnormal sensory-motor gating and impaired attentional function, that are often associated with psychotic illnesses (Relkovic et al., 2010). AS is mainly due to paternal uniparental disomy (pUPD15) or point mutations in UBE3A.

Recently, the imprinted gene cluster on 15q11-q13 (Prader-Willi Angelman Critical Region, PWACR) has attracted more general interest, as copy number variation (CNV) mutations that include this interval give rise to a number of neurodevelopmental disorders independently of AS/PWS; indeed, maternal duplications at 15q11-q13 (dup15q) resulting in at least one extra maternal copy of the PWACR remain the strongest known genetic contributors to autism. Maternal CNV duplication at 15q11-q13 can also lead to psychotic illness (Ingason et al., 2011). More recently, rare paternal duplications were shown to be associated with more variable and sometimes different

Box 2. Imprinted Genes Modulate Reward-Based and Social Phenotypes

Experimental evidence is lending increasing weight to the theory that genomic imprinting exerts a role in high cognitive processes in adulthood (McNamara and Isles, 2014). Genetic models combined with behavioral tasks implemented in mice offer a valid experimental platform to investigate the roles of imprinted genes in behavioral traits. The maternally expressed *Nesp55* transcript was first demonstrated to regulate reactivity to novelty (Plagge et al., 2005), the response of a mouse to a novel stimulus or environmental condition. This phenomenon has recently been expanded to impulsivity, as loss of maternal *Nesp55* results in a decreased willingness to wait for a larger reward and preference for an immediate, smaller reward in a delayed reinforcement task (Dent et al., 2016), whereas loss of paternal *Grb10* results in an *increased* willingness to wait for a larger reward and reduced preference for an immediate, smaller reward in a delayed reinforcement task (Dent et al., 2018). These reciprocal findings have led to speculation that risk-taking and impulsive behavior may be a substrate for the evolution of imprinting (Wilkinson et al., 2019). A change in reward processing because of altered imprinted gene dosage has also been reported for the *Cdkn1c* gene, expressed from the maternally inherited chromosome (McNamara et al., 2016). In a loss-of-imprinting (LOI) model, increased *Cdkn1c* expression induced an altered hedonic and motivational state, which was associated with changes in hypothalamic neuron numbers (McNamara et al., 2018; McNamara et al., 2016).

Another example of imprinted genes modulating primitive behavioral aspects comes from studies in which the loss of *Gnas* imprinting affected behavioral timing and response to fear in mice (Lassi et al., 2012). The capability to time short intervals (e.g., seconds to minutes) is a primitive function that is pivotal to expressing high-level cognitive processes, such as attention, learning, and decision making. Specifically, a certain degree of uncertainty in timing is necessary in some behavioral contexts, such as threatening situations. Mouse mutants with biallelic *Gnas* expression due to LOI showed sharper timed responses but failed to respond in a fear-conditioned setting. Therefore, in behavioral ecology terms, the imprinted *Gnas* gene leads to a more advantageous set of behaviors in mice. An impact of imprinting on short-time perception has also been observed in mice that carry a deletion of the imprinted *Snord116* gene within the PWS genomic region (Lassi et al., 2016a). However, how these effects of imprinted genes on specific behavioral functions relate to specific brain circuitries remains to be understood.

Separate from reward-based processing, social behavior in adult animals has also been suggested to be influenced by genomic imprinting (McNamara and Isles, 2014). Indeed, loss of paternal *Grb10* expression in the brain resulted in altered social behavior, with *Grb10*-KO animals being more likely to win an encounter in a tube test task of social dominance (Garfield et al., 2011). The same behavioral phenotype was also observed in the *Cdkn1c* LOI model with increased expression (McNamara et al., 2018), which suggests the possibility of functional convergence. However, further studies on social behavior, particularly within a group setting, are likely to provide intriguing insights into the functions of this class of genes. A recent investigation of attachment behaviors in mice revealed important genetic parent-of-origin effects in the type of attachment a mouse develops in different developmental conditions and showed that a secure or insecure attachment style will impact the social adult behaviors of the mouse (Lassi and Tucci, 2017). The latter study advocates for a role of imprinted genes in attachment behaviors, although non-imprinted parental effects may also play a role. Whether this concept can be generalized to other imprinted genes remains to be seen.

neurodevelopmental phenotypes. However, unlike maternal duplications, paternal duplications do not increase psychotic illness risks (Isles et al., 2016). This study refines the distinct roles of maternal and paternal duplications at 15q11-q13, underlining the critical importance of maternally active imprinted genes to psychotic illness incidences. Moreover, it will have tangible benefits for patients with 15q11-q13 duplications by aiding genetic counseling.

An Emerging Role of Genomic Imprinting in Sleep and the Circadian Clock

The earth's rotation around its axis, a nearly 24-h cycle, brings two main environmental changes that influence almost all physiological processes: illumination and temperature. Both stimuli serve as signals to entrain our biology to daily cycles and guide metabolic and behavioral changes throughout the day. Different organisms have developed different strategies to adapt to these environmental stimuli. However, the two most important biological processes, shared across all species, are sleep-wake cycles, a phenomenon that is homeostatically regulated, and the circadian clock, which is self-sustained and mainly cell-autonomous (Jagannath et al., 2017). Recently, imprinted genes have begun to emerge as important players in the regulation of both the circadian clock and sleep homeostasis (Tucci, 2016). Although many imprinted genes show circadian oscillations (see Figure 4 and Table S1), the interplay between circadian clock machinery and imprinting remains still largely unexplored. We know the core molecular mechanisms that cell-autonomously dictate the circadian clock (Takahashi, 2017); however, new cell non-autonomous processes may indicate DNA methylation as a novel epigenetic process providing phenotypic plasticity to circadian physiology. Indeed, DNA methylation has been shown as a dynamically regulated process throughout the 24 h circadian period (Coulson and LaSalle, 2018; Powell and LaSalle, 2015).

Gene expression in the dorsolateral prefrontal cortex has been associated with a 24 h rhythmic DNA methylation profile, especially at the promoter level of active genes (Lim et al., 2014). Furthermore, DNA methylation and hydroxymethylation profiles can be reshaped by alterations of circadian-influencing phenomena, such as sleep deprivation, with over 4,000 genomic large effects being reported, which involve pathways that control neuritogenesis and synaptic plasticity (Massart et al., 2014). In addition, a light schedule shifting from 22 h to 24 h has been shown to induce circadian behavioral changes in mice that are associated with changes in DNA methylation (Azzi et al., 2014). Very recently, it was reported the methylome circadian rhythmicity within the mouse cortex and its control by the imprinted sleep and circadian modulator *Snord116* (Coulson et al., 2018).

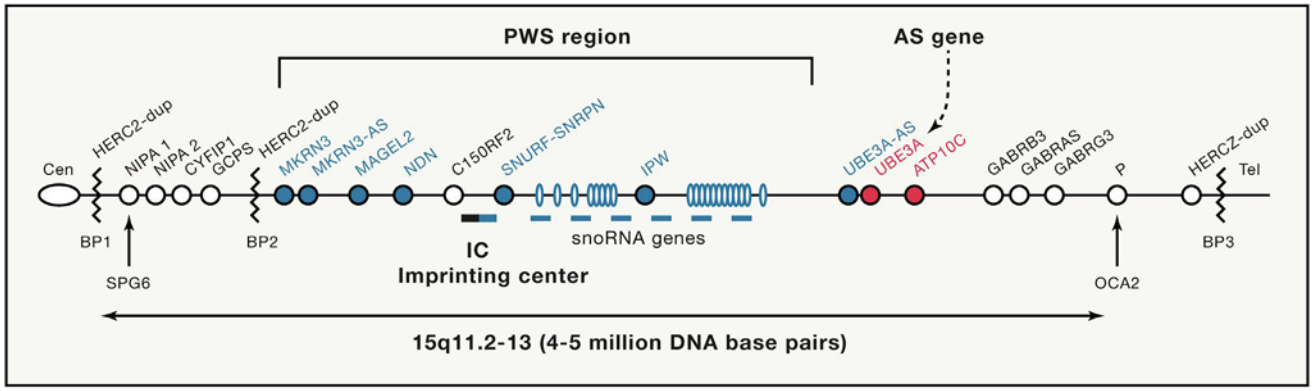

Figure 3. PWS-AS Region
Schematic representation of the Prader-Willi syndrome and Angelman syndrome region.

Gnas, an important imprinted gene, plays an important role in REM (rapid eye movement) sleep in mice, specifically due to thermoregulatory instability (Lassi et al., 2012). Moreover, a recent GWAS study exploring genetic associations with insomnia complaints in 113,000 individuals collected within the UK Biobank highlighted *GNAS* as the strongest candidate gene within the female subnetwork (Hammerschlag et al., 2017), confirming the previous report in mice (Lassi et al., 2012). In addition, both *Snord116* (Lassi et al., 2016b) and *Ube3a* (Ehlen et al., 2015), within the PWS-AS region, were associated with REM sleep abnormalities, which recapitulate the typical sleep abnormalities reported in both PWS and AS. Both genes are highly expressed in the SCN and in the lateral hypothalamus, which represent the main pacemaker of circadian rhythms and the switch mechanism between sleep and wake, respectively.

Other imprinted genes associated with circadian machinery include *Magel2* and *Peg3*, although these genes influence the amplitude of the activity rather than a clock-like regulatory process. Deletion of *Magel2*, which is paternally expressed in SCN, alters the activity of mice when their internal clock is not entrained to light-dark schedules (Kozlov et al., 2007). Furthermore, PEG3 is also an imprinted modulator which in this context affects the temperature and behavioral activity of mice throughout the 24 h cycle (Curley et al., 2005).

Sleep is the longest state in development, and genomic imprinting is crucial in developmental growth and neurogenesis. The monoallelic expression of certain genes is a fine-regulatory mechanism during the perinatal period of an organism, a time frame that is crucial for brain plasticity in developmental biology (Wiesel, 1999). REM sleep is abundant during development and is characterized by intense metabolic and neuronal activity (Siegel, 2011). REM sleep reportedly plays a role in brain plasticity, and this hypothesis has been tested by studying the plasticity of the visual system. Interestingly, REMs appears to provide an endogenous source of activity that has been shown to prevent the pruning of neuronal connections due to a lack of stimulation in addition to other effects (Tucci, 2016). Moreover, REM alterations throughout the brain are accompanied by significantly impaired olfactory discriminative functions in awake animals (Rodrigues et al., 2014), and imprinted genes are fundamental in olfactory system development.

Sleep homeostasis depends on the genetic background and parent-of-origin effects are important in this regulatory process. Some strains (e.g., AKR/J mice) are known to show high rebound after 6 h of sleep deprivation, while other strains (e.g., DBA/2J mice) show only a mild response. By studying reciprocal crosses of the AKR/J and DBA/2J lines, differences in gene expression rebounds were reported (Tinarelli et al., 2014), proving parent-of-origin effects in the homeostatic response to sleep loss. Currently, 9 genes differentially regulated in AKR/JxDBA/2J sleep-deprived F1 mice, and 7 genes differentially regulated in DBA/2JxAKR/J sleep-deprived F1r mice have been annotated (Tinarelli et al., 2014). Bioinformatic prediction analyses of specific upstream mechanisms of regulation indicated signaling pathways, growth factors, and transcriptional regulators that were modulated by parental effects and need further investigation.

An Evolutionary Perspective of Genomic Imprinting

The evolutionary explanation that has been most successful in accounting for the phylogenetic and functional distributions of imprinted genes is the kinship theory, which extends inclusive fitness or kin selection thinking to account for an allele's parental origin (Wilkins and Haig, 2003). Inclusive fitness accounts for the fact that an allele may not only affect the fitness of the individual carrying that allele but may also affect that of other individuals who may have inherited an identical copy of the allele depending on the relatedness between the two individuals. The fundamental insight of the kinship theory is that maternally and paternally inherited alleles are, in general, related to different sets of other individuals. Therefore, the expression pattern that maximizes the inclusive fitness of an allele when it is maternally inherited may be different from the expression pattern that maximizes the inclusive fitness of the same allele when it is paternally inherited.

We often discuss this concept as an intragenomic evolutionary conflict between maternally and paternally inherited alleles, although it is more accurate to describe it as a form of phenotypic plasticity. When the inclusive fitness calculations for an

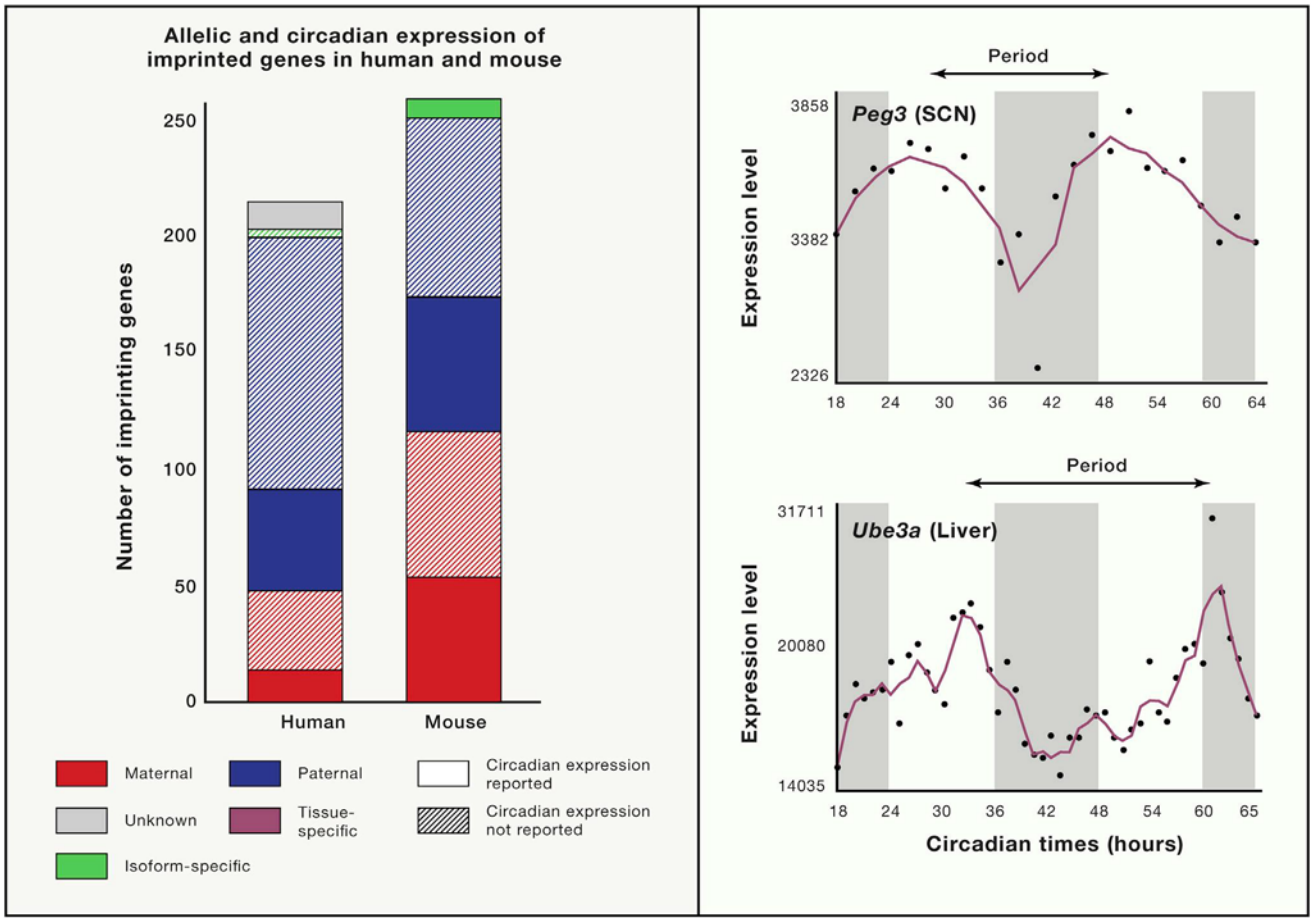

Figure 4. Circadian Oscillations and Imprinted Genes

The histogram (left panel) show the number of imprinted genes that were reported to have circadian expression profile by CircaDB (http://circadb.hogeneschlab.org) (maternally expressed in red; paternally expressed in blue; isoform-specific in green; unknown in gray) and those that have not been reported (white). The right panels show the circadian oscillation (in mice) of two representative imprinted genes in which the background shaded and white areas represent the cycle of dark and light, respectively. See also supplementary Excel File for further information.

allele differ sufficiently between its "maternally inherited" and "paternally inherited" environments, natural selection may favor the evolution of two different conditional expression strategies, resulting in genomic imprinting. For a single locus considered in isolation, the evolutionarily stable outcome of this process is monoallelic expression, with transcription occurring from only the allele for which higher overall expression is favored, termed the "loudest voice prevails" principle (Haig, 1996).

When two or more loci with different imprinting statuses affect the same phenotype, the evolutionarily stable outcome is not necessarily obvious. Alleles at a maternally expressed locus will be selected to maximize the matrilineal inclusive fitness, while alleles at a paternally expressed locus will be selected to maximize the patrilineal inclusive fitness. If no single organismal phenotype maximizes both, an arms race among loci will continue until some countervailing factor arises to oppose the selective advantage of further escalation (Wilkins and Haig, 2001). This countervailing factor could come in different forms, including the accumulation of deleterious pleiotropic effects. This suggests that, in very general terms, one consequence of intragenomic conflicts among imprinted loci may be to drive the evolution of suboptimal or maladaptive phenotypes. Several different possibilities exist for the specific types of deleterious effects that might accumulate depending on the molecular and cellular mechanisms involved.

One class of deleterious effects is decanalization, an increase in phenotypic variance due to processes that counter or undermine developmental or genetic robustness mechanisms. This effect is clearly observed in loss-of-function mutations to the expressed allele at an imprinted locus as well as in "LOI" mutations or epimutations that inappropriately reactivate the silenced allele. The fact that evolutionary arms races drive increased gene expression and activity indicates that these perturbations will have a greater phenotypic impact than they would at an otherwise analogous biallelic, conflict-free locus. Evolutionary arms races can also drive increases in phenotypic variance, leading to the increased frequencies of extreme, maladaptive phenotypes (Wilkins, 2011). Another class of deleterious effects is a more generalized pleiotropy. Whereas decanalization may lead to the increased frequencies of deleterious phenotypes

within a population, deleterious pleiotropy can actually drive the fixation of deleterious phenotypes, resulting in universally shared suboptimality (Wilkins, 2010).

Conclusions and Perspectives

In addition to canonical processes that control imprinted gene expression, recent discoveries have enlarged the epigenetic repertoire of allelic expression especially through the identification of genes which have parent-of-origin biases in their expression specifically in the brain. These new potential imprinted genes remain to be validated. However, this significantly enhances the range of potential functions regulated by imprinting. Moreover, the epigenetic control of imprinting mechanisms appears to be richer and more dynamic than initially believed, with the identification of H3K27me3-dependent imprinting control in very early development and transient imprinting. How such transiently imprinted regions influence later physiology requires further investigation. Among the hundreds of candidates, expectations suggest a full range of possibilities. Some may have no biological relevance, being silent byproducts of substantial DNA methylation differences inherited from the parental gametes perhaps acting on adjacent genes, some may exert an immediate effect on embryogenesis, and some will trigger an indelible cascade with long-term phenotypic consequences.

Genomic imprinting is pivotal in a range of processes during the life course. Such functions are controlled by their complement of genes, which are expressed in specific tissues or cell types and present dose-dependent expression modalities that confer various degrees of control to developmental and physiological systems. To understand how epigenetic regulatory processes, such as genomic imprinting, control developmental, and physiological pathways is a future challenge for emerging technology development (e.g., single-cell epigenetic analysis combined with single-cell RNA sequencing)

There is a growing interest in genomic imprinting, particularly in the investigation of brain physiology, as this promises to reveal novel insights into the organization and integration of neuronal functions. The brain has extraordinary compartmental organization (e.g., areas, nuclei, and cell types), which undergo intense information processing (e.g., connectome) across many states (e.g., wake and sleep) and timed regulatory processes (e.g., synaptogenesis during development, circadian rhythms, short-interval neuronal and behavioral processes). With its rich cell-specific architecture and generally post-mitotic state, the brain offers a unique model system to investigate imprinted transcriptional regulatory mechanisms including at the single-cell level.

The role of imprinted genes in developmental processes remains the largest area of investigation. In the long term, understanding how lifelong health is programmed during early life has potential to elucidate new interventions during pregnancy or lactation to combat human obesity and related metabolic health disorders. Furthermore, it will aid our fundamental understanding of epigenetics and how nature and nurture synergistically result in phenotype.

Finally, genomic imprinting provides an important avenue for investigating our daily rhythms and their impact on phenotype. The gene-centric approach toward understanding sleep and the circadian clock, has elucidated core mechanisms at the cellular level (i.e., core interlocking transcriptional and translational feedback loops (Takahashi, 2017)). However, this approach remains insufficient to explain the full complexity of phenotypic variations, such as in disease and phenotypic plasticity mechanisms. Such interplay between environmental, genetic, and epigenetic factors not only determines the pathomechanisms of many diseases but also the natural physiological variations that allow entrainment with daily and seasonal environmental changes. Using imprinting as a model process to explore these events will not only influence our understanding of rhythm biology, but also has the potential to uncover novel concepts associated with genome-epigenome-environment interactions.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one table and can be found with this article online at https://doi.org/10.1016/j.cell.2019.01.043.

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AUTHOR CONTRIBUTIONS

Conceptualization, V.T., A.R.I., G.K., and A.F.S.; Writing – Original Draft, V.T. and all authors; Writing – Review & Editing, All authors.

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