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New Perspectives on Genomic Imprinting, an Essential and Multifaceted Mode of Epigenetic Control in the Developing and Adult Brain

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Abstract

Mammalian evolution entailed multiple innovations in gene regulation, including the emergence of genomic imprinting, an epigenetic regulation leading to the preferential expression of a gene from its maternal or paternal allele. Genomic imprinting is highly prevalent in the brain, yet, until recently, its central roles in neural processes have not been fully appreciated. Here, we provide a comprehensive survey of adult and developmental brain functions influenced by imprinted genes, from neural development and wiring to synaptic function and plasticity, energy balance, social behaviors, emotions, and cognition. We further review the widespread identification of parental biases alongside monoallelic expression in brain tissues, discuss their potential roles in dosage regulation of key neural pathways, and suggest possible mechanisms underlying the dynamic regulation of imprinting in the brain. This review should help provide a better understanding of the significance of genomic imprinting in the normal and pathological brain of mammals including humans.

Keywords

genomic imprinting; parental bias; gene dosage; neural development; energy balance; behavior

INTRODUCTION

Genomic imprinting, a unique form of epigenetic regulation found in mammals and flowering plants, leads to the preferential expression of the maternal or the paternal allele of certain genes, with widespread implications for the development and function of the brain. The surprising concept that the two parentally inherited genomes of mammalian cells are functionally distinct originates from pronuclear transplantations in which embryos with uniparental (solely maternally or paternally derived) diploid genomes failed to develop normally (McGrath & Solter 1984, Surani et al. 1984), thus uncovering the requirement for distinct epigenetic imprints acquired in parental gametes. Following the discovery of the first

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imprinted genes (Barlow et al. 1991, Bartolomei et al. 1991, DeChiara et al. 1991), the search for the identity and functions of imprinted genes has thrived (Morison et al. 2005). Early studies implicated many imprinted genes with the control of developmental processes, with maternally and paternally imprinted genes often seen to promote and oppose growth, respectively, providing support for interesting evolutionary theories (see the sidebar, Evolutionary Theories of Genomic Imprinting).

EVOLUTIONARY THEORIES OF GENOMIC IMPRINTING

Genomic imprinting waives the diploid advantage of buffering recessive mutations accumulating throughout the development of multicellular organisms (Otto & Gerstein 2008). Several theories have attempted to formalize the fitness advantages associated with the evolution of genomic imprinting in mammals and flowering plants. These have been thoroughly discussed elsewhere (Haig 2014, Patten et al. 2014, Spencer & Clark 2014), and we provide here a short summary of evolutionary ideas particularly relevant to genomic imprinting in the brain.

In mammals, mothers are the main nurturers of offspring, and progeny likely originates from multiple fathers owing to promiscuous mating systems. Based on these observations, the kinship theory proposes that a conflict between the parental genomes arises in offspring over the distribution of maternal resources (Wilkins & Haig 2003), such that maternally and paternally expressed genes tend to reduce and increase demand of maternal resources, respectively. Indeed, genes involved in acquiring resources (such as the *Igf2* growth factor) are paternally expressed, whereas genes involved in conserving resources (such as the *Igf2r* growth repressor) are maternally expressed. The kinship theory also predicts that genes will be imprinted in organs that are engaged in social interactions, both during pregnancy (e.g., in the placenta) and postnatally (e.g., in the brain). However, the biological functions of many imprinted genes in the developing and adult brain are difficult to explain based solely on these predictions.

In a different theory, Keverne (2013) addressed more specifically the role of genomic imprinting in the brain, suggesting that this phenomenon helps coordinate the functions of the placenta, maternal hypothalamus, and developing fetal hypothalamus to ensure optimal embryonic and postnatal nurturing. This idea is based primarily on the observations that deletion of the paternally expressed *Peg3* leads to impaired hypothalamic function in pups (e.g., poor suckling ability) and poor maternal care in rearing mothers (e.g., impaired milk letdown) (Curley et al. 2004). Furthermore, programs of gene expression appear to be synchronized in the placenta and developing hypothalamus at E12.5, which is controlled partially by the transcription factor PEG3 (Broad & Keverne 2011).

Wolf & Hager (2006) introduced a model suggesting that genomic imprinting evolved to optimize mother:offspring coadaptation. Matching (or mismatching) the offspring's expressed allele with its mother's allele in pleiotropic loci affecting both maternal and offspring traits benefits their interaction. This view is supported by maternal *Grb10* expression, which in pups reduces nutrient demand and in mammary glands of lactating mothers enhances milk supply, thereby achieving an optimal effect on pup growth

(Cowley et al. 2014). This theory, however, rationalizes the function of a limited set of imprinted genes, some of which are also explained by the kinship theory (Úbeda & Gardner 2015).

Additional hypotheses about the evolution of imprinting have been suggested (Patten et al. 2014, Spencer & Clark 2014). However, their explanatory power of the actual function of imprinted genes is often vague and fails to interpret key aspects of imprinting, such as parent-of-origin-specific expression, uniqueness to mammals, and postnatal and brain-specific functions.

The relevance of genomic imprinting to the brain emerged when two disorders with significant developmental and neurological deficits, Prader–Willi syndrome (PWS) and Angelman syndrome (AS), were linked to paternally and maternally transmitted mutations, respectively, on human 15q11–13 (Nicholls et al. 1989). This notion was reinforced by the discovery that chimeric embryos containing gynogenetic (two maternal genomes) cells develop abnormally large brains in contrast to chimeric embryos containing androgenetic (two paternal genomes) cells, which develop abnormally small brains (Keverne et al. 1996), pointing to an essential role for parent-of-origin information in brain development. Moreover, gynogenetic cells were observed exclusively in the cortex, striatum, and hippocampus, whereas androgenetic cells occupied hypothalamic regions, indicating distinct roles for maternally and paternally inherited information in various brain regions. The central role of genomic imprinting in brain function has been supported further by the extensive neural and behavioral phenotypes of mutants of imprinted genes and by the widespread expression of imprinted genes throughout the brain (Gregg et al. 2010, Wilkinson et al. 2007). Thus, the brain has emerged as a main target of genomic imprinting, generating great interest on how this epigenetic regulation provides stable transcriptional control of neural development and behavior.

We summarize here the vast literature on the role of genomic imprinting in the developing and mature brain, where imprinted genes often serve as control hubs in regulatory networks of brain functions. Although many of these findings came from studies in the mouse, strong correlates exist in humans as inferred from disorders associated with abnormal imprinting (see the sidebar, Human Brain Disorders Associated with Imprinting Dysregulation). Traits encoded by imprinted genes follow non-Mendelian inheritance, such that heterozygous mutants are often indistinguishable from controls if mutations are carried by the silenced parental allele but are similar to homozygotes when mutations are carried by the expressed parental allele. In addition, imprinted genes are commonly dosage sensitive, such that phenotypes are observed following alteration of the expressed allele as well as in loss of imprinting seen in derepression of the normally silenced allele.

HUMAN BRAIN DISORDERS ASSOCIATED WITH IMPRINTING DYSREGULATION

In humans, dysregulation of imprinted gene expression resulting from null mutations, deletions, duplications, uniparental disomies, or alterations in epigenetic marks often affects brain function and behavior. Other imprinting dysregulations leading to disorders

without strong neurological or behavioral components are not detailed here, even though some of the involved genes are expressed in the brain (Eggermann et al. 2015).

The 15q11–13 interval includes several paternally expressed noncoding RNAs and protein coding genes, as well as *UBE3A*, which exhibits brain-specific maternally biased expression (Angulo et al. 2015). Prader-Willi syndrome (PWS) results from loss of the 15q11–13 paternally expressed genes, which most frequently includes the *SNORD116* small nucleolar RNAs (snoRNAs) cluster that is hence regarded as the critical contributor to the PWS phenotype (Sahoo et al. 2008). PWS runs a biphasic clinical course, starting with reduced fetal activity followed by postnatal poor muscle tone and diminished swallowing and suckling. By age two, these features are replaced with hyperphagia, food foraging behavior, and lack of satiety leading to obesity. Intellectual disability and behavioral patterns such as temper tantrums, stubbornness, skin picking, and obsessive compulsions are later observed. PWS also features sleeping abnormalities, hypogonadism due to impaired puberty, and short stature due to hypothalamic growth hormone deficiency. Angelman syndrome (AS), which results from null mutations or loss of expression of *UBE3A*, has a strikingly different clinical manifestation, characterized by an abnormally happy demeanor with inappropriate laughter and excitability, severe motor and intellectual disability, autism spectrum disorder–like speech impairment, epilepsy, sleep disorders, and seizures (Bird 2014).

The *GNAS* locus produces several isoforms with different parent-of-origin expression biases in which null mutations lead to pseudohypoparathyroidism type 1a (PHP1a) when maternally transmitted and pseudopseudohypoparathyroidism (PHPP) when paternally transmitted (Turan & Bastepe 2013). PHP1a features resistance to various hormones, skeletal abnormalities, obesity, and cognitive impairments (Mouallem et al. 2008), likely due to the tissue specificity of maternal *GNAS* isoform expression. PHPP is characterized mainly by neonatal metabolic and growth defects.

The 7q21–31 interval harbors several imprinted genes and is linked with autism susceptibility (Schanen 2006). Paternally transmitted mutations in the sarcoglycan- ϵ (*SGCE*) gene cause myoclonus-dystonia syndrome (Zimprich et al. 2001), characterized by early adolescence onset of myoclonic jerks (Asmus et al. 2002) and psychiatric symptoms such as obsessive-compulsive disorder, panic attacks, anxiety, depression, agoraphobia, and alcohol dependence (Peall et al. 2013).

The 8q24 interval includes the maternally expressed potassium channel *KCNK9*, which is expressed primarily in the brain and for which maternally transmitted null mutations lead to Birk-Barel syndrome, characterized by moderate to severe intellectual disability, hyperactivity, low muscle tone and feeding difficulties in infancy, and unique facial dysmorphism (Barel et al. 2008). 8q24 also includes *TRAPPC9* for which recessive mutations cause intellectual disability (Mochida et al. 2009). *Trappc9* isoform-specific imprinting has been demonstrated in mouse (Gregg et al. 2010), and it was recently reported to be imprinted in humans (Babak et al. 2015).

Genomic imprinting has classically been defined as the full silencing of one of the two parental alleles (Bartolomei & Ferguson-Smith 2011). We discuss new evidence from mice

and humans showing that genomic imprinting encompasses a wide range of parental expression biases with important functional significance, supporting a conceptual expansion of genomic imprinting to the parent-of-origin regulation of gene dosage.

IMPRINTED GENES AND EPIGENETIC CONTROL OF NEURAL DEVELOPMENT

Studies of mouse chimeras containing either gynogenetic or androgenetic cells provided initial evidence for the differential contributions of the maternal and paternal genomes in the developing brain (Keverne et al. 1996). Since then, extensive evidence has implicated genomic imprinting in key neurodevelopmental processes including neural progenitor expansion, migration and differentiation, and cell polarization. We describe here how imprinted genes regulate these essential neurodevelopmental processes (Figure 1).

Neurogenesis

Neural stem cells (NSCs) of the ventricular zone proliferate asymmetrically to produce differentiated neurons or glia or to generate intermediate progenitor cells (IPCs), which further divide symmetrically to produce either IPCs or neurons (Kriegstein & Alvarez-Buylla 2009). NSC fate decisions are highly regulated by imprinted genes through intricate control pathways. Cortical NSCs are maintained through N-cadherin-mediated adhesion. N-cadherin expression is repressed by the maternally expressed miRNAs—miR369-3p, miR496, and miR543 of the *Mir379-410* cluster—thereby promoting the shift from NSC proliferation to cell differentiation and migration (Rago et al. 2014). NSCs strongly express *PLAGL1* (Valente et al. 2005), a paternally expressed zinc finger protein, which induces expression of the maternally expressed cyclin-dependent kinase inhibitor *Cdkn1c*. In turn, *Cdkn1c* promotes NSC cell cycle arrest and subsequent differentiation by inhibiting cyclin-dependent kinases (Cdk) (Schmidt-Edelkraut et al. 2014); later, *Cdkn1c* promotes a shift from proneural to proglial NSC differentiation (Joseph et al. 2009). The self-renewal of neuroepithelial progenitors and NSCs is promoted by *Igf2*, which is biallelically expressed in the choroid plexus and vascular compartments (yet preferentially maternally expressed in other regions of the brain and paternally expressed outside the brain), and is secreted into the cerebrospinal fluid (DeChiara et al. 1991, Lehtinen et al. 2011). Finally, the proliferative capacity of IPCs is repressed by the paternally expressed *NDN*, which inhibits *Cdk1* expression (Minamide et al. 2014). In the adult brain, NSCs persist in unique niches of the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus. In the SVZ, a soluble *DLK1* isoform is secreted by niche astrocytes and signals through a membrane-tethered alternative isoform of *DLK1* expressed by NSCs to maintain NSC self-renewal (Ferrón et al. 2012). Interestingly, this paracrine mode of *DLK1* signaling requires derepression of its maternal allele to achieve biallelic expression in both astrocytes and NSCs. Similarly, derepression of the *Igf2* maternal allele to achieve biallelic expression in the SVZ is also required for NSC self-renewal postnatally, suggesting a remarkable mechanism of transcriptional dosage control in adult neurogenesis through imprinting regulation (Ferrón et al. 2015). In the SGZ, the maternally expressed *CDKN1C* facilitates the maintenance of NSC quiescence (Furutachi et al. 2013), and in contrast to the SVZ,

IGF2 is paternally expressed and operates in an autocrine manner to regulate NSC survival (Bracko et al. 2012, Ferrón et al. 2015).

Neuronal differentiation requires the induction of multiple transcription factors to activate neuron-specific transcriptional programs. The roles of imprinted genes during this process are widespread. In the developing cerebellum, transcription of the paternally expressed *Plagl1* is restricted to the ventricular zone and external granule layer of specific lobules, where it promotes differentiation of GABAergic interneurons and Golgi cells (Chung et al. 2011). Paternally expressed DIO3 protects the developing cerebellum from premature stimulation by thyroid hormone, which controls granule-cell formation in the external germinal layer, their migration to the internal layer, cerebellar foliation, and dendritic arborization of Purkinje cells (Peeters et al. 2013). Accordingly, *Dio3* deletions show accelerated external layer disappearance, premature expanded molecular layer, and locomotor defects.

The midbrain dopaminergic (mdDA) system plays a critical role in the control and modulation of emotional, motivational, and cognitive behaviors as well as voluntary movements. The development of this system is targeted particularly by imprinted genes. The transcription factors LMX1A and NURR1 are essential for early and terminal differentiation of mdDA neurons, respectively (Hoekstra et al. 2013, Jacobs et al. 2009), by inducing transcription of the paternally expressed *Grb10* and of *Dkl1*, and of the maternally expressed *Cdkn1c*. Interestingly, enhanced maternal care during early life increases *Cdkn1c* expression in the maturing ventral tegmental area accompanied by enhanced survival of mdDA neurons (Peña et al. 2014). Survival of mdDA neurons also requires expression of the paternally biased *Bcl-x*, which protects from developmental and Parkinson's disease-related apoptosis (Savitt et al. 2005). Finally, loss of the maternally expressed *UBE3A* in AS patients results in fewer substantia nigra mdDA neurons and Parkinson's-like motor impairments (Mulherkar & Jana 2010) but increased nucleus accumbens (NAc) dopamine transmission (Riday et al. 2012).

Neuronal Migration

In the developing brain, neuronal migration to appropriate sites is essential for the establishment of proper identity and functional connectivity. As discussed below, it is mediated by cellular processes that are influenced highly by genomic imprinting. Actin polymerization, which is critical for cell motility within the cortical plate, is promoted by CDKN1C and the maternally biased PPP1R9A (Causeret et al. 2007, Tury et al. 2012). Additionally, silencing of DCX by the maternally expressed miR134 inhibits cortical neuron migration (Gaughwin et al. 2011). Tangential migration of differentiating GABAergic interneurons from the basal forebrain to the cortex requires enhanced transcriptional activity of the DLX2-NDN complex (Kuwajima et al. 2006). Accordingly, the cortical GABAergic system is impaired in *Ndn* paternal deletions (Kuwajima et al. 2010). Migration of gonadotropin-releasing hormone (GnRH) neurons from the olfactory placode to the medial preoptic area (mPOA) also depends on DLX proteins and is reduced in *Ndn* paternal deletions (Miller et al. 2009). The majority of PWS patients lack NDN and exhibit hypogonadism and impaired puberty (Cassidy et al. 2012), a phenotype consistent with

defects in GnRH neurons. Neuronal activity is also critical for neuronal migration. In particular, the maternally expressed KCNK9 controls resting potentials and neuronal excitability, and maternally transmitted mutations that cause Birk-Barel syndrome in humans (see the sidebar, Human Brain Disorders Associated with Imprinting Dysregulation) impair neuronal migration and delay dendritic maturation (Bando et al. 2014).

Axonal and Dendritic Outgrowth

High motility of the axonal growth cone allows navigation in extracellular environments and identification of synaptic targets. PPP1R9A-mediated actin polymerization regulates growth-cone motility and directionality (Nakanishi et al. 1997). Furthermore, centrosome-based cytoskeletal rearrangements that promote axonal outgrowth are regulated by FEZ1 and BBS4, the proteasomal degradation of which is prevented by the paternally expressed NDN and MAGEL2 (Lee et al. 2005). In addition, both axonal extension and growth-cone motility rely on active transport across microtubules, mediated by motor proteins including the paternally biased dynein subunit DYNC1H1 (Ori-McKenney & Vallee 2011). Growing axons require signaling cues for proper guidance. In sympathetic neurons, axonal pathfinding and tissue innervation is regulated by the maternally biased endothelin-3, which is secreted by the carotid vasculature (Makita et al. 2008).

The signals received by a neuron are determined by the growth of its dendrites, as well as by the density, shape, and synaptic targets of its dendritic spines. Imprinted genes both promote and oppose these processes. Downregulation of the maternally biased *Ago2* in the absence of the transcription cofactor NCOA3 results in abnormally high dendritogenesis (Störchel et al. 2015). miR134 regulates the abundance of the pumilio2 RNA-binding protein, and its over- or underexpression reduces dendritogenesis (Fiore et al. 2009). Dendrite arborization is promoted by both maternally biased PPP1R9A and COBL through their regulation of actin filaments (Ahuja et al. 2007, Zito et al. 2004). Spine growth is negatively regulated by the X-linked chromatin remodeling maternally expressed genes *Xlr3b* and *Xlr4b*, which are repressed by the CUX1 and CUX2 transcription factors (Cubelos et al. 2010). Finally, alternative splicing and allele-specific expression of protocadherins provide single-neuron diversity that is essential for dendritic self-avoidance and neuronal wiring (Chen & Maniatis 2013). Interestingly, three beta-protocadherins, *Pcdhβ20*, *Pcdhβ12*, and *Pcdhβ10*, were discovered to be imprinted (the former paternally and the latter two maternally biased) in the developing cerebellum (Perez et al. 2015).

Apoptosis

In the developing nervous system, apoptosis serves to control the overall neuronal pool and matching of pre- and postsynaptic neurons. Internal and external stimuli regulate apoptosis by shifting the balance between proapoptotic and antiapoptotic proteins. In a proapoptotic state, mitochondrial-membrane permeability is increased, and the release of cytochrome c leads to caspase activation and subsequent cell death. Generally, paternally expressed genes are mostly antiapoptotic, whereas maternally expressed genes are more pleiotropic (Perez et al. 2015). The paternally biased *Bcl-x_L* is a major antiapoptotic *Bcl-2* family member in the brain, as its deletion results in massive death of postmitotic immature neurons (Motoyama et al. 1995). Remarkably, deletion of the paternal but not maternal *Bcl-x* allele reduces brain

size significantly, suggesting increased apoptosis (Perez et al. 2015). Absence of paternally expressed *Peg3* results in increased P53-dependent apoptosis in forebrain, striatal, amygdalar, and hypothalamic regions (Broad et al. 2009). Interestingly, these abnormalities vary between males and females, suggesting that *Peg3* function regulates the establishment of sexual dimorphisms. Absence of *Peg3* or *Mage12* also reduces hypothalamic oxytocin neurons (Li et al. 1999, Schaller et al. 2010). NDN prevents apoptosis in cerebellar granule cells by blocking E2F transactivation of proapoptotic targets (Kurita et al. 2006). During ischemia and hypoxia, however, PEG3 and BCL-X_L induce apoptosis (Ofengeim et al. 2012, Yamaguchi et al. 2002), whereas NDN prevents apoptosis (Hasegawa & Yoshikawa 2008). On the maternal side, granule cell death, which contributes to numerically matching with their postsynaptic Purkinje cell targets, is mediated by KCNK9-dependent apoptosis (Patel & Lazdunski 2004). The maternally expressed MEG3 may also play a proapoptotic role in the brain based on its pituitary tumor suppression activity, transcriptional upregulation of *p53*, and downregulation of P53-degrading genes (Zhou et al. 2012). Brain-specific deletions of *Cdkn1c* show massive P53-dependent apoptosis in the developing brain, thought to result from hyperactivation of E2F1 (Matsumoto et al. 2011), whereas in nonbrain tissues it promotes apoptosis (Yan et al. 1997). UBE3A may also play an antiapoptotic role by ubiquitinating P53 (Mishra & Jana 2008), as its maternal deletions reduce brain weight (Jiang et al. 1998).

FUNCTIONS OF IMPRINTED GENES IN THE POSTNATAL BRAIN

Phenotypic studies of mouse mutants and human disorders have uncovered the vast significance of genomic imprinting in the postnatal brain, encompassing all essential adult neural functions from key elements of synaptic transmission and plasticity (Figure 2) to the control of energy balance and metabolism, as well as emotional, social, and cognitive behaviors (Figure 3).

Synaptic Transmission

Synaptic transmission underlies the propagation of information throughout the brain and directs proper wiring of neuronal circuits. Multiple imprinted genes participate in baseline transmission and activity dependent modifications of neuronal excitability.

Action potentials—Voltage-insensitive K⁺ leak channels set resting potentials and thus influence the likelihood of action potentials and neuronal firing patterns. The maternally expressed KCNK9 potassium channel hyperpolarizes neurons according to extracellular pH, bivalent cation concentration, and phospholipase C signaling (Bista et al. 2015). Interestingly, KCNK9 deletion reduces the membrane resting potential and changes firing patterns from burst to tonic firing (Brickley et al. 2007, Musset et al. 2006). Initiation of action potentials occurs in the axon initial segment where densely clustered voltage-gated Na⁺ channels power depolarization. In *Ube3a* maternal deletions, hippocampal action potentials exhibit increased amplitudes associated with increased α 1-NaKA channel levels (Kaphzan et al. 2011). Crossing *Ube3a* maternal deletions with α 1-NaKA null heterozygotes restores normal action potentials and synaptic plasticity (Kaphzan et al. 2013).

Presynaptic regulation—The number of available presynaptic vesicles determines in part the strength of postsynaptic stimulation. Ca^{2+} import induces BCL- X_L translocation into clathrin-coated vesicles, enhancing formation and replenishment of the vesicle pool (Li et al. 2013). Importantly, the endocytic rate is increased and decreased by BCL- X_L overexpression and knockdown, respectively. *Ube3a* maternal deletions exhibit reduced capacity to replenish the presynaptic vesicle pool in L4 inhibitory interneurons after repeated stimulation, resulting in weaker inhibitory postsynaptic currents (Wallace et al. 2012). Presynaptic deficits are also observed when *Ube3a* is overexpressed (Smith et al. 2011).

Postsynaptic regulation—Mechanisms of excitatory synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) are dependent on *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors (NMDARs and AMPARs, respectively), which initiate signaling cascades of immediate as well as long-term adaptations. Most imprinted genes known to regulate synaptic plasticity are maternally expressed and for the most part promote synaptic potentiation (Figure 2). Several imprinted genes mediate immediate synaptic responses. UBE3A promotes LTP by preventing inhibition of NMDARs (Sun et al. 2015) and of the Ca^{2+} -regulated kinase CaMKII (Weeber et al. 2003) and also by preventing activity-regulated cytoskeletal-associated protein mediated internalization of membrane AMPARs (Greer et al. 2010). Furthermore, PPP1R9A prevents inhibitory dephosphorylation of the AMPAR GLUR1 subunit (Wu et al. 2008). In the postsynapse, Ca^{2+} is the main second messenger regulating both LTP and LTD. The paternally biased ACTN1 binds to L-type Ca^{2+} channels to prevent their endocytic internalization. This interaction is relieved by activity-dependent Ca^{2+} influx and thus represents a negative-feedback response to Ca^{2+} levels (Hall et al. 2013). Recently, an essential and sufficient role of apoptotic genes in LTD induction was identified (Jiao & Li 2011, Z. Li et al. 2010), such that proapoptotic genes induce modest levels of active caspases in the postsynapse, which in turn induce AMPAR internalization. BCL- X_L inhibits caspases activation and thus AMPAR internalization and LTD.

Local protein synthesis (LPS) operates at intermediate timescales in synaptic plasticity and provides neurons with effective dosage control of proteins, such as channels, receptors, and scaffolds, in spatially and temporally restricted domains. The maternally biased AGO2 regulates mRNA-miRNA interactions that prevent LPS in an activity-dependent manner. For instance, prior to membrane depolarization, LPS of the scaffold-encoding *Psd95* is prevented by interactions between AGO2, miR125a, and FMRP (Muddashetty et al. 2011). Additionally, AGO2 is part of dendrite-specific, P-body-like structures potentially involved in mRNA transport toward active synapses (Cougot et al. 2008). Recently, profiles of ribosome-linked dendritic RNAs have suggested activity-dependent translation of >1,000 genes, including several imprinted genes such as *Ago2* and *Ube3a* and paternally expressed *Bcl-x* and *Rasgrf1* (Ainsley et al. 2014). Additionally, pharmacological inhibition of NMDAR leads to LPS of the paternally expressed *Nnat* (Oyang et al. 2011).

Long-lasting synaptic potentiation relies on activity-induced transcription by cAMP response element-binding protein (CREB) and other transcription factors. Paternally expressed *Rasgrf1* encodes a Ca^{2+} -dependent GTP exchange factor that activates small G

proteins RAS and RAC, which in turn activate transcription through MAP kinases (Ye & Carew 2010). RASGRF1 induces RAS-dependent LTP and RAC-dependent LTD in the amygdala and hippocampus, respectively (Brambilla et al. 1997, Li et al. 2006). Overexpression of the maternally expressed *MiR134* prevents CREB synthesis, thereby reducing hippocampal LTP (Gao et al. 2010). Lasting potentiation often induces modifications in dendritic spine size and number (Bailey et al. 2015). Loss of *MiR134*, which normally silences the spine growth-inducing kinase LIMK1A, results in spine overgrowth (Schratt et al. 2006). Spine density is reduced in *Ube3a* maternal deletions (Dindot et al. 2008) but augmented when UBE3A ligase activity is increased (Yi et al. 2015).

Homeostatic plasticity—Intrinsic mechanisms to maintain excitatory-inhibitory balance within a circuit require widespread adaptations of the underlying synapses. Increasing the ratio of excitation over inhibition in cultured neurons induces synaptic changes in protein levels and structural plasticity, which are impaired in the absence of either the maternally expressed *MiR134* or *MiR485* (Cohen et al. 2011, Fiore et al. 2014).

Critical periods—Critical periods are temporal windows of increased plasticity when sensory experiences shape cortical circuits. Monocular deprivation during the critical period of the visual cortex fails to induce ocular dominance plasticity in *Ube3a* maternal deletions, indicating a role in experience-dependent plasticity (Sato & Stryker 2010, Yashiro et al. 2009).

Learning and Memory

The role of imprinted genes in synaptic function and plasticity suggests a more general role in learning and memory. Manipulations of multiple imprinted genes lead to deficits in hippocampus-based spatial and contextual memories. For instance, *Ube3a* maternal deletions perform poorly in paradigms of contextual memory (Jiang et al. 1998, Sun et al. 2015), but they can be rescued by constitutively dephosphorylated CaMKII (van Woerden et al. 2007), α 1-NaKA reductions (Kaphzan et al. 2013), and SK2 channel inhibition (Sun et al. 2015). Deficiencies in contextual memory are also observed when *Ago2*, *Ppp1r9a*, or *Rasgrf1* are absent (Batassa et al. 2010, d'Isa et al. 2011, Giese et al. 2001, Wu et al. 2008).

After a memory is acquired, it remains labile for several hours during its consolidation. In the rat hippocampus, IGF2 is increased hours after training, which is necessary for memory consolidation (Chen et al. 2011). Moreover, administration of IGF2 after training enhances memory consolidation. Memory retrieval within a few days of learning returns it to a labile state, allowing its modification (reconsolidation), which is also enhanced by IGF2 administration. Mechanisms by which IGF2 affects memory require protein synthesis and are accompanied by increments in synaptic AMPARs, suggesting a synaptic effect. IGF2 action is dependent on IGF2R, which, in the brain, can signal through the protein kinase C pathway (Hawkes et al. 2006). This is in remarkable contrast to the IGF2R-mediated lysosomal degradation of IGF2, observed in other tissues where *Igf2* and *Igf2r* are exclusively expressed from the paternal and maternal alleles, respectively. In the brain, however, *Igf2* is maternally biased, whereas *Igf2r* fluctuates between maternally biased and

biallelic expression (Perez et al. 2015, Yamasaki et al. 2005). Accordingly, upregulation of IGF2 during the process of memory reconsolidation is contributed mainly by the maternal allele (Ye et al. 2015). Finally, enhanced contextual memory is also observed when *Ndn* is paternally deleted (Muscatelli et al. 2000).

Sleep—Sleep serves multiple homeostatic functions including enhancement of memory consolidation. *Ube3a* maternal deletions show reduced sleep induction after extended wakefulness and overall reductions in rapid eye movement (REM) sleep (Colas et al. 2005), recapitulating AS hallmarks (Bird 2014). Fragmented sleep is also observed in *Kcnk9* deletions, accompanied by reduced REM and increased non-REM sleep (Gotter et al. 2011, Pang et al. 2009). In contrast, overexpression of maternally biased *Gnas* decreases REM and increases non-REM sleep (Lassi et al. 2012). Consistent with the role of sleep in memory, both *Kcnk9* deletion and *Gnas* overexpression are accompanied with impaired contextual memory (Lassi et al. 2012, Linden et al. 2007).

Working memory—Working memory represents an interface between incoming and previously stored information, which mediates activity and behavior. This cortex-regulated process is impaired in *Kcnk9* deletions specifically during phases of general inactivity (Gotter et al. 2011, Linden et al. 2007). Strikingly, theta II oscillations, characteristic of immobile animals processing sensory stimuli relevant to motor responses, are completely absent in *Kcnk9* mutants (Pang et al. 2009). The neuronal mechanisms underlying this effect are unknown.

Neural Regulation of Energy Balance

Genomic imprinting plays a key role in the regulation of growth and energy balance during embryonic and placental development, as well as in nonneuronal tissues (Charalambous et al. 2007, Tunster et al. 2013). Ultimately, the brain controls energy balance and metabolism of the entire organism, and this homeostatic function is performed primarily by the hypothalamus, which senses internal energy states and orchestrates visceral responses. Here we describe key roles played by imprinted genes in this process in neonates and adults.

Energy balance in early life—The brain regulates nutrient acquisition by neonates through milk suckling, a behavior targeted by multiple paternally expressed genes. For instance, mice carrying paternal deletions of *Mage12* fail to suckle and thus die, a phenotype associated with reduced oxytocin levels that can be rescued by a single oxytocin injection (Schaller et al. 2010). Paternal *Peg3* deletion also reduces suckling, resulting in perinatal death (Curley et al. 2004). The developing brain controls neonatal metabolism and growth through thyroid-hormone regulation. DIO3, which inactivates the thyroid hormone T3, is paternally biased in a brain-region specific manner (Martinez et al. 2014). Interestingly, hypothalamic paternal biases of DIO3 decrease with age (Martinez et al. 2014), correlated with its reduced activity (Hernandez et al. 2006). Pups carrying *Dio3* deletions exhibit growth retardation, associated with abnormally fluctuating T3 levels due to hypothalamic, pituitary, and thyroid impairments (Hernandez et al. 2007). Additionally, the paternally expressed NDN participates in hypothalamic negative feedback responses to increased T3 (Hasegawa et al. 2012).

Synchronization of growth by the neonatal brain relies on hypothalamic secretion of growth hormone (GH)-releasing hormone (GHRH) and somatostatin, which stimulate and inhibit GH and thus IGF1 secretion, respectively. Expression of *Rasgrfl* is detected mainly in the brain and changes from exclusively paternal before weaning to preferentially paternal afterward (Drake et al. 2009). Mice with *Rasgrfl* paternal deletions are normal at birth but growth retarded by weaning (Itier et al. 1998), and loss of *Rasgrfl* imprinting increases growth and weight after birth (Drake et al. 2009). Importantly, levels of both GH and IGF1 decrease or increase when *Rasgrfl* is missing or overexpressed, respectively. Because *Rasgrfl* is expressed in the hypothalamus but not in the pituitary, these effects are likely due to hypothalamic impairments. Indeed, hypothalamic expression of GHRH and somatostatin is increased with *Rasgrfl* loss of imprinting (biallelic expression). Similarly, pups lacking the paternal *Snord116* exhibit drastically reduced IGF1 levels and are smaller with reduced organ sizes.

Thermoregulation is another key aspect of energy expenditure essential to early-life survival. Pups perform nonshivering thermogenesis through sympathetic control of energy breakdown in brown adipose tissue. Pups with paternal deletions of *Peg3* have a lower temperature that decreases further after maternal separation (Curley et al. 2004), whereas *Dlk1* and *Dio3* overexpression results in abnormal thermoregulation, failure to adapt to postweaning life, and eventually death (Charalambous et al. 2012). Although expression of these genes is enriched in the hypothalamus (Meister et al. 2013), a brain origin of this phenotype has not been demonstrated.

The *Gnas* locus is a complex transcriptional unit responsible for remarkably distinct defects in neonate physiology according to the affected parental allele. *Gnas* encodes the ubiquitously expressed G-protein α -subunit $G_s\alpha$, which is maternally biased in a tissue-specific manner, as well as *GnasXL*, which is translated into a distinct G-protein α -subunit called *XL α s* and exhibits a brain region-specific paternal expression pattern (Krechowec et al. 2012, Peters & Williamson 2007). Maternal deletions affecting $G_s\alpha$ result in pup overgrowth, hyperactivity, and early death (Yu et al. 1998). In contrast, paternal deletions affecting *GnasXL* result in impaired suckling, growth retardation, inactivity, and early death (Plagge et al. 2004). Remarkably, overexpression of *Gnas* recapitulates some phenotypes observed in the absence of *GnasXL*, whereas overexpression of *GnasXL* recapitulates some phenotypes observed in the absence of *Gnas* (Ball et al. 2013). However, matched dosages of *Gnas* and *GnasXL*, even if both are overexpressed, results in normal development indicating that balanced expression of both proteins is essential. Interestingly, mutations specific to *GnasXL*'s first exon, which encodes ALEX, alter suckling, suggesting a role of ALEX in this process (Eaton et al. 2012, Kelly et al. 2009). In humans, children with maternally transmitted *GNAS* mutations are obese, whereas paternally transmitted *GNAS* mutations exhibit perinatal growth retardation, severe feeding difficulties, and reduced adiposity (Bastepe 2012).

Circuits regulating energy balance are still developing around weaning, and imprinted genes of the PWS cluster are thought to play a role in the transition to adult metabolic programs. A hallmark of PWS, associated primarily with paternal deletions of the *SNORD116* locus, is the early transition from weak and hypophagic neonates to hyperphagic and obese infants

(Sahoo et al. 2008). Similarly, newborn mice carrying *Snord116* paternal deletions fail to gain weight and are substantially leaner than wild types by weaning (Ding et al. 2008). As adults, these mice develop hyperphagia but, contrary to humans, their increased metabolism maintains a leaner phenotype. In mouse neonates carrying mutations equivalent to human PWS, pro-opiomelanocortin (*Pomc*) mRNA levels are elevated tenfold compared to wild types (Bittel et al. 2007). As discussed below, the effects of multiple imprinted genes converge in the function of adult POMC-expressing neurons.

Energy balance in the adult brain—Regulation of adult weight by imprinted genes generally involves maternally expressed genes contributing to reduced weight as a function of metabolic rate and food intake, whereas paternally expressed genes contribute to increased weight. Paradoxically, imprinted genes that decrease metabolism also decrease food intake, but those that increase metabolism also increase food intake. The actions of multiple imprinted genes in adult metabolism appear to converge into the regulation of POMC-expressing neurons of the arcuate nucleus. POMC neurons are stimulated by leptin to induce satiety and energy expenditure through regulation of melanocortin 4 receptor (MC4R)-expressing neurons in the paraventricular nucleus (PVN) (Gao & Horvath 2007). In POMC neurons, expression of maternally biased *Asb4* decreases during fasting, whereas localized leptin administration increases *Asb4* expression (J.Y. Li et al. 2005, 2010). Conditional overexpression of *Asb4* in these neurons increases ambulatory activity and energy expenditure as well as food intake, resulting in leaner animals resistant to high-fat diet-induced obesity. These animals also exhibit increased levels of *Pomc* mRNA (J.Y. Li et al. 2010). Together, these results indicate that ASB4 action on POMC neurons accelerates metabolic rate. By contrast, paternal deletions of *Mage12* exhibit reduced food intake and increased weight, indicative of hypometabolism (Bischof et al. 2007). *Mage12* knockout mice display elevated leptin and develop leptin resistance, which is associated with fewer adult POMC neurons (Mercer et al. 2013). Moreover, leptin stimulation of remaining POMC neurons is absent, whereas normal inhibition by leptin is observed in AGRP neurons (Pravdiviyi et al. 2015). Similarly, *Peg3* paternal deletions exhibit reduced food intake but slower metabolism and increased adiposity (Curley et al. 2005) in addition to elevated leptin and leptin resistance.

MC4R neurons in the PVN are essential for the neuroendocrine control of visceral responses, including the metabolic regulation by sympathetic nervous system (SNS) activity (Gao & Horvath 2007). As in neonates, the opposed effects of the maternally and paternally expressed *Gnas* and *GnasXL*, respectively, are maintained in adulthood with far-reaching metabolic consequences. Maternal deletions of *Gnas* slow metabolism and increase weight (Chen et al. 2005), whereas its overexpression reduces weight and increases ambulatory activity (Xie et al. 2008). Circulating levels of norepinephrine are positively correlated with *Gnas* expression, suggesting alterations in SNS activity. Accordingly, brain-specific *Gnas* deletions exhibit increased weight, hypometabolism, and impaired thermoregulation due to lagging SNS activity (Chen et al. 2009). Furthermore, PVN-specific deletions recapitulate some but not all the effects observed in whole-brain deletions, indicating that *Gnas* imprinting regulates metabolism across multiple areas (Chen et al. 2012). Consistently, adult obesity is common in human maternally transmitted *GNAS* mutations (Turan & Bastepe

2013). Similarly, paternal deletions of *GnasXL* result in adult hyperphagia, hypermetabolism, and increased body temperature (Plagge et al. 2004, Xie et al. 2006), a phenotype caused by increased SNS activity (Nunn et al. 2013). Remarkably, the increased metabolic rate observed after *Gnas* overexpression is rescued by *GnasXL* complementary overexpression (Ball et al. 2013). Together, these results indicate a delicate balance between *Gnas* and *GnasXL* activities in central metabolic control.

Finally, a homozygous deletion of a brain-specific enhancer reduces *Igf2* expression drastically in the brain and results in increased weight and decreased food intake, indicating reduced metabolic rate (Jones et al. 2001). Thus, contrary to its growth-promoting role during gestation, *Igf2*, which switches from paternally expressed in most tissues to maternally biased in the adult brain (Gregg et al. 2010, Perez et al. 2015), appears to decrease adipose storage.

Circadian rhythms—Animals synchronize their general activity and behaviors to the circadian light/dark cycle. In mammals, the suprachiasmatic nucleus (SCN) is the master pacemaker that coordinates circadian oscillations in the activity of the brain and peripheral tissues. Rhythmicity of individual SCN neurons is established by a delayed negative feedback loop in the activity of the transcription factors CLOCK and BMAL1, which orchestrates periodic changes in gene transcription, among which are the imprinted paternally expressed *Magel2* and *Peg3* and the maternally expressed *Bicap* and *Calcr* (Panda et al. 2002). *Magel2* expression is restricted to arginine-vasopressin positive cells of the SCN and is highest during the day yet absent at night. When placed in constant darkness, mice with *Magel2* paternal deletions exhibit abnormal general activity amplitudes across the 24-h period (Kozlov et al. 2007). Abnormal periodicity and accelerated adjustment to light/dark changes was documented in *Ube3a* maternal deletions and is associated with lack of UBE3A-mediated degradation of BMAL1 (Shi et al. 2015). Deletions of *Peg3* or *Kcnk9* cause increased nocturnal activity (Curley et al. 2005, Linden et al. 2007).

Although synchronized by the SCN, functionally significant circadian oscillations in transcription are autonomous properties of individual cells across the body (Mohawk et al. 2012). These cell-autonomous oscillations alter the expression of genes to enable different tissues to coordinate their unique functions according to the circadian cycle. In neurons, splicing of a long noncoding RNA (lncRNA) at the paternally expressed *Snord116* locus produces intronic 116 small nucleolar RNAs (snoRNAs) and the spliced 116 host gene (116HG). 116HG RNA accumulates in its transcription site, creating a cloud-like structure that condenses and expands during the light and dark phase, respectively (Powell et al. 2013). Deletion of the *Snord116* locus causes phase-specific differential expression of thousands of genes, including core components of the cell autonomous clock such as cryptochrome and period genes. Interestingly, *Snord116* deletions have increased fat metabolism during the light period, but it is currently unclear whether the 116 snoRNAs or 116HG is responsible for this phenotype. Cloud-like structures are also observed for maternally expressed host genes of snoRNA in the *Dlk1-Dio3* cluster (Vitali et al. 2010), where expression of multiple transcripts undergoes circadian regulation (Labielle et al. 2008).

Imprinted Genes in the Social Brain

Increments in social interactions were likely a key driving force in the evolution of the size and processing capacity of mammalian brains (Dunbar & Shultz 2007). By virtue of their parent-of-origin regulation, parents influence their progeny through imprinted genes in parallel to the social relation that is parenting. Thus, genomic imprinting may have either contributed to, or been shaped by, the evolution of social behaviors.

Mother-pup interactions—Parenting in mammals is essential for infant survival. Mutations affecting the paternally expressed *Mest* and *Peg3* result in a striking lack of maternal care (Curley et al. 2004, Lefebvre et al. 1998, Li et al. 1999), which supports the notion that genomic imprinting is associated with the evolution of social behaviors. In turn, pup behavior influences maternal responses strongly. Maternally inherited deletions encompassing *Ube3a* and the neighboring *Atp10a* and *Gabrb3* increase ultrasonic vocalizations (USVs), specifically in the presence of maternal but not stranger's bedding (Jiang et al. 2010). This behavior has been interpreted as increased demand for maternal attention, which may be analogous to the happy disposition of AS patients (Isles 2011).

Reproductive behavior and puberty—The control of reproductive behavior and its development is an important target of genomic imprinting. Inbreeding is believed to be selected against to avoid harmful costs of homozygosity. Male and female hybrids of inbred as well as wild-derived mice avoid urine of their maternal strains and prefer to mate with their paternal strains (Isles et al. 2002, Montero et al. 2013), indicating a parental effect of unknown origin. Indeed, mate recognition is under the control of several imprinted genes. Males with *Peg3* paternal deletions have impaired odor preferences for estrous females (Swaney et al. 2008), reduced sexual behavior, and hypothalamic responses to female cues (Swaney et al. 2007). Similarly, males with *Mage12* paternal deletions show impaired preference for female odors (Mercer & Wevrick 2009).

Several aspects of sexual development are influenced strongly by imprinted genes. In humans, a genome-wide association study found significant parent-of-origin effects on late-onset menarche in polymorphic sites near the paternally expressed *NDN*, *MAGEL2*, and *MKRN3* (supporting abnormal PWS puberty and hypogonadism) and within the maternally expressed *KCNK9* and paternally expressed *DLK1* (Perry et al. 2014). Male hypogonadism and reduced testosterone levels are observed in human paternally transmitted *MAGEL2* null mutations and in mouse paternal *Mage12* deletions, respectively (Schaaf et al. 2013). In female mice, *Mage12* deletions also delay sexual maturation (Mercer & Wevrick 2009). Interestingly, *Peg3* deletions in female mice also delay sexual maturation (Curley et al. 2004). Both *MKRN3* null mutations (Abreu et al. 2013) and chromosome 14 maternal uniparental disomies exhibiting abnormal expression of *DLK1*, among other genes, cause human precocious puberty (Kotzot 2004). *MKRN3* likely represses the onset of puberty, as its mouse hypothalamic expression declines at this time point (Abreu et al. 2013). In contrast, *Dlk1* mouse hypothalamic expression rises at this time point, similar to the major activator of GnRH secretion: Kisspeptin (Villanueva et al. 2012). Finally, GnRH neuron migration to the mPOA is facilitated both by *NDN* (Miller et al. 2009) and by

glycoconjugates synthesized by the maternally biased *B3gnt2*-encoded enzyme (Bless et al. 2006).

Social interactions and autism—Imprinted genes are involved in the regulation of social behavior between adult conspecifics. Mice with *Grb10* paternal deletions are less likely to back down to opponents in tube tests and to remove the facial hair of their cage mates, which has been interpreted as increased social dominance (Curley 2011, Garfield et al. 2011).

Impaired reciprocal social interactions and other autistic traits are typically observed in mutations affecting the PWS and AS 15q11–13 interval. For instance, compulsive skin scraping is a common repetitive behavior in PWS individuals (Dykens et al. 2011) and is recapitulated in mice lacking *Ndn* (Muscatelli et al. 2000). Similarly, truncating mutations of human *MAGEL2* result in autistic features (Schaaf et al. 2013), and male mice carrying paternal deletions of *Mage12* show reduced social interactions and novel object exploration (Meziane et al. 2015). These mice exhibit multiple defects including reduced oxytocin and oxytocin receptor binding sites in the lateral septum. Remarkably, injecting oxytocin during the first postnatal week or 24 h before testing restores normal social behavior.

In humans, both paternal and maternal duplications or triplications of 15q11–13 result in neurodevelopmental deficits and, frequently, autism (Hogart et al. 2010). In mice, paternal duplications of the homologous region result in reduced social interactions, failure to adjust to novel conditions in multiple memory tests, and abnormal pup USVs (Nakatani et al. 2009). In addition, triplications of *Ube3a* normal expression in mice causes autism-like phenotypes, including reduced social recognition and interactions and abnormal USVs during social interactions, whereas doubling *Ube3a*'s dosage impairs these behaviors mildly (Smith et al. 2011). This is consistent with more pronounced autistic features observed in humans with 15q11–13 maternal triplications than duplications, suggesting that the brain is highly sensitive to *UBE3A* dosage (Hogart et al. 2010, Noor et al. 2015). Recently, a mutation enhancing *UBE3A* ubiquitin ligase activity has been implicated in autism (Yi et al. 2015). Because *UBE3A* self-ubiquitinates, its protein levels were actually reduced in individuals and mice carrying this mutation, suggesting that besides dosage, spatiotemporal control of *UBE3A* activity is critical. In support of potentially different etiologies between *Ube3a* overexpression and ligase hyperactivity, mice with *Ube3a* triplication had impaired pre- and postsynaptic transmission but normal spine density (Smith et al. 2011), whereas the missense mutation substantially increased spine density (Yi et al. 2015).

Emotional and Cognitive Behaviors

A growing body of evidence implicates imprinted genes in the regulation of complex brain functions, including emotions and cognition, relevant to human neuropsychiatric disorders. Studies in rodents may recapitulate specific neurobiological and behavioral components of these complex disorders (Donaldson & Hen 2015).

Anxiety and depression—In humans, anxiety disorders are highly comorbid with major depression, and the two are thought to affect common neural substrates (Ressler & Mayberg 2007). Increased hypothalamic-pituitary-adrenal axis activity under chronic stress

diminishes glucocorticoid receptor (GR) action in the hippocampus and is associated with anxiety and depression (Arnett et al. 2015). UBE3A interacts with GR to induce its transcriptional activity while also inducing GR proteasomal degradation (Godavarthi et al. 2012). Importantly, *Ube3a* maternal deletions exhibit downregulation of GR and GR-targeted genes in the hippocampus, which is associated with increased corticosterone and anxiety-like behavior. Neuronal circuits of monoamine neurotransmitters are associated strongly with human anxiety and depression. Mutations in the human paternally expressed sarcoglycan-*e* (*SGCE*) cause myoclonus dystonia (see the sidebar, Human Brain Disorders Associated with Imprinting Dysregulation) and are accompanied by high incidence of anxiety (Peall et al. 2013). Both motor deficits and anxiety- and depression-like behaviors are observed in mice with paternal *Sgce* deletions (Yokoi et al. 2006). Importantly, dopamine levels are increased in these animals, likely due to reductions in the dopamine autoreceptor D2R (Zhang et al. 2012). Paternal duplication of the PWS genes increases depression- and anxiety-like behaviors, which is associated with reductions in serotonin levels (Nakatani et al. 2009, Tamada et al. 2010). Maternally expressed KCNK9 regulates resting potentials of serotonergic neurons (Washburn et al. 2002) and some of their downstream neurons responsible for the mammalian startle reflex (Weber et al. 2008). Importantly, *Kcnk9* deletions also show decreased depression-like behavior (Gotter et al. 2011).

Adult hippocampal neurogenesis is reduced by chronic stress, impaired in rodent models of depression, and increased by antidepressant treatment (Miller & Hen 2015). IGF2, which promotes adult neurogenesis (Bracko et al. 2012, Ferrón et al. 2015), is downregulated in animals exhibiting depression-like behavior after chronic stress (Luo et al. 2014). Remarkably, overexpression of *Igf2* in the dentate gyrus reverses these behaviors, but whether this effect is dependent on adult neurogenesis remains to be tested.

Addiction—Drug addiction involves neuronal plasticity in the mesolimbic reward pathway, which is influenced by several imprinted genes. The paternally expressed SNORD115 is thought to prevent editing of the serotonin receptor *Htr2c* mRNA (Kishore & Stamm 2006). Repeated cocaine administration in mice reduces *Snord115* expression in the NAc, whereas NAc overexpression of either *Snord115* or *Htr2c* attenuates cocaine addiction significantly (Chen et al. 2014). Conditional knockouts of the maternally biased *Ago2* in dopamine receptor D2-expressing neurons fail to develop addiction in a cocaine self-administration paradigm (Schaefer et al. 2010). The knockout additionally revealed downregulation of many miRNAs, the majority of which are maternally expressed. Administration of cocaine leads to upregulation of the maternally expressed miR369, which targets key addiction-implicated genes, including *FosB*.

Cognition and associated disorders—Executive functions rely on the neuronal underpinnings of attention, which are frequently impaired in neuropsychiatric disorders. PWS patients manifest deficits in attentional switching, working memory, and organization and planning skills (Jauregi et al. 2007, Woodcock et al. 2009). Furthermore, patients with PWS specifically due to maternal uniparental disomy, who lose paternal expression of PWS genes and have doubled *Ube3a* expression, develop psychosis and schizophrenia (Boer et al. 2002). A mouse model of the maternal uniparental disomy shows reduced performance in

attentional tasks and reduced prepulse inhibition, endophenotypes commonly observed in schizophrenics (Relkovic et al. 2010). Finally, a mouse model of DiGeorge syndrome (DS), a disorder with increased risk for schizophrenia, shows reduced adult hippocampal neurogenesis accompanied by lower *Igf2* expression (Ouchi et al. 2013). Strikingly, IGF2 injections in the dentate gyrus restore neurogenesis and behavioral defects of DS mice, supporting IGF2 as a promising treatment for multiple neuropsychiatric disorders.

FROM MONOALLELIC EXPRESSION TO PARENTAL BIAS

Initial studies of genomic imprinting identified this phenomenon as the silencing of one of the parental alleles and the monoallelic expression of the other. However, imprinted genes such as *Ube3a*, *Phlda2*, and *Gnas* were shown to display parental allelic bias rather than strict monoallelic expression (Albrecht et al. 1997, Qian et al. 1997, Yu et al. 1998). Furthermore, the number of reported imprinted genes displaying parental biases has increased dramatically (Figure 4a), and specific genes display monoallelic or parentally biased expression, depending on the tissue or developmental stage (Martinez et al. 2014). Thus, genomic imprinting clearly manifests itself as a continuum from monoallelic to weakly biased parental expression, and we review here the functional and mechanistic implications of these findings.

Studies Across Organs and Organisms

Species exhibiting genomic imprinting show evidence of both parentally biased and monoallelically expressed genes and many parentally biased genes are shared across species. For instance, *Dio3* and *Igf2* are parentally biased in mouse and rat brains (Gregg et al. 2010, Martinez et al. 2014, Sittig & Redei 2014, Ye et al. 2015), *IGF2R* is parentally biased in humans and macaques (Babak et al. 2015, Cheong et al. 2015), and *GNAS* and *BLCAP* are parentally biased in human and mouse (Babak et al. 2015). Genes may also exhibit various degrees of parental biases in different species. For instance, *L3mbtl* exhibits a paternal bias in the mouse hypothalamus (Bonthuis et al. 2015), whereas its human ortholog is paternally expressed in most tissues (Babak et al. 2015). Finally, in flowering plants, the only other organisms outside mammals exhibiting parent-of-origin imprinting, most imprinted genes display parental biases rather than monoallelic expression (Gehring 2013). Because flowering plants and mammals are thought to share similar imprinting epigenetic machinery, a continuum from parental bias to monoallelic expression may reflect general properties of this epigenetic regulation and indicate selective advantages or constraints of partial, rather than complete, silencing of certain genes.

Highly sensitive expression measurements, such as RNA sequencing (RNA-seq), applied over many biological samples, analyzed with robust statistical methods, and independently validated, have led to accurate detection of a large spectrum of parental allelic biases (Bonthuis et al. 2015, Crowley et al. 2015, Perez et al. 2015) (Figure 4a). In whole brain, specific adult and developing brain regions, and muscle (Bonthuis et al. 2015, Crowley et al. 2015, Perez et al. 2015), the distribution of parental allelic expression ratios displays a clear bimodal shape, with one mode showing strong bias to monoallelic expression, whereas the other mode exhibits a weak bias (Figure 4b). This pattern was observed neither in the liver,

which expresses very few imprinted genes (Bonthuis et al. 2015), nor in the placenta, where the latter is likely due to contamination from the maternal decidua (Finn et al. 2014, Okae et al. 2012).

Recent studies show that parental biases, in contrast to monoallelic expression, tend to be regulated dynamically according to tissue and developmental stage, particularly in the brain (Figure 5a) (Perez et al. 2015). The majority of biased genes either shift between parentally biased and biallelic expression in different tissues, brain regions, or developmental stages, or they display changes in the strength of parental bias in various tissues or brain regions. For some genes, the preferentially expressed parental allele even switches according to tissue. Fluctuations in parental biases can be shared among genes both within and among different clusters, suggesting coregulation of parental biases. These widespread tissue-specific and developmental changes in parental biases highlight the existence of intricate programs of imprinting regulation in the brain and raise the following important questions: (a) Are they a property of individual cells, or do they result from mixes of cells exhibiting monoallelic and biallelic expression? (b) Are their underlying epigenetic mechanisms common with those of monoallelic expression? And ultimately, (c) Is parental bias functionally relevant to the fitness of the organism, as is assumed for monoallelic expression?

Cellular Basis of Parental Biases

Although researchers have investigated and validated parental biases thoroughly in dissected tissues, their manifestation at the cellular level is still largely unknown (Gregg 2014). One model postulates that parental biases are present in each individual cell (Figure 5b), such that a chromatin state is able to partially repress expression. This model is consistent with the phenotype of heterozygous mutants for the maternally biased *Gnas*, which, in maternal versus paternal deletion, shows reduced but still detectable expression in cells of renal proximal tubules (Yu et al. 1998) and PVN (Chen et al. 2009). Similarly, a paternal *Commd1* duplication due to chromosome 11 uniparental disomy exhibits fainter, yet similarly patterned, expression as wild types, suggesting its preferential-maternal rather than exclusive-maternal expression in all cells (Wang et al. 2004).

In a second model, parental biases result from coexisting cells exhibiting either monoallelic or biallelic expression (Figure 5b). Maternal transmission of a *Ube3a-Yfp* reporter shows strong labeling in both glia and neurons, whereas paternal transmission shows strong glial labeling yet faint neuronal signaling (Dindot et al. 2008), suggesting biallelic and nearly exclusive maternal expression in glia and neurons, respectively. Consistently, *Ube3a* is maternally expressed in neuronal cultures but biallelic in glial cultures (Yamasaki et al. 2003). Similarly, *Snx14* appears biallelically expressed in cortex homogenates but is paternally expressed in sorted neurons (Huang et al. 2014).

A third model postulates that parental biases result from a mixture of cells with monoallelic expression, with the parental identity of the expressed allele different from cell to cell (Figure 5b). The parental identity of the expressed allele may be cell-type-specific, such as with *Grb10*, which, through alternative promoter usage, is paternally expressed in neurons but maternally expressed in glia (Yamasaki-Ishizaki et al. 2007). In another scenario, a cell selects only one allele for expression but with a probability that is higher for one parent of

origin than the other (a biased coin flip). Parental biases of the beta-protocadherin genes in the brain support this model. Similar to other clustered protocadherins, the promoter of one beta-protocadherin is believed to be selected at each allele by an enhancer, resulting in monoallelic expression of 2 of the 22 *Pcdh*βs (one from each allele) in most neurons (Hirano et al. 2012). In homogenized cerebella, *Pcdh*β12 and *Pcdh*β10 show maternal biases, whereas *Pcdh*β20 is paternally biased (Perez et al. 2015), suggesting that the probability of promoter selection, with respect to each, is higher for the preferentially expressed allele.

High-resolution in situ hybridization (ISH) studies appear well suited to interrogate parental biases at the single-cell level. Attempts in culture so far have highlighted significant variation in the allele-specific expression among single cells, making the results difficult to interpret (Herzing et al. 2002, Jouvenot et al. 1999). In mouse brain sections, Bonthuis et al. (2015) reported monoallelic ISH nascent mRNA signals in a large fraction of cells for several parentally biased genes. However, because parental identity of the alleles was unavailable, monoallelic signals due to transcriptional bursts unsynchronized between the alleles cannot be ruled out. Thus, the nature of imprinting in single cells remains largely unresolved and will benefit from future progress in quantitative allele-specific expression analyses at the single-cell level.

Functional Significance of Parental Biases

Perhaps the most important question raised by the existence of widespread parental biases is that of their functional relevance to the organism. Genetic analyses of behavioral and neurological defects highlight that normal brain development and function require a fine regulation of gene dosages, such that even small deviations may disturb the balance of the biological pathways they control, leading to striking neural dysfunctions. This has been observed for nonimprinted genes such as *MECP2* in Rett syndrome and *MECP2* duplication disorder (Chao & Zoghbi 2012), as well as variation in posttranscriptional regulation of *MECP2* levels (Gennarino et al. 2015). In fragile X intellectual disability (FXS), *FMRP* mutations lead to increased metabotropic glutamate receptor (mGLUR) signaling, and reductions in *mGluR* dosage in an FXS mouse model was shown to rescue cognitive phenotypes (Dölen et al. 2007). In an intervention that may be analogous to dosage regulation, chronic treatment of FXS mice with an mGLUR inhibitor also rescued the cognitive defects (Michalon et al. 2012).

Similarly, are changes in the parental biases of certain imprinted genes regulating the overall dosage of a gene? Remarkably, developmental variations in the parental biases of many imprinted genes in the mouse cerebellum were shown to be associated with overall expression changes (Perez et al. 2015) (Figure 5c). For most genes, both the parental bias and overall expression are higher during development, and a downregulation of the preferentially expressed allele is observed from development to adulthood, suggesting a tight control of imprinted gene dosages during critical developmental points, similar to what is seen with *Mecp2* and *mGluRs*. These transcriptional changes may occur within individual cells or may reflect changes in cell types populating the cerebellum at different developmental stages.

Pathways regulating apoptosis and monoamine neurotransmission appear preferentially enriched among parentally biased and monoallelically imprinted genes (Figure 6). Recent genetic analyses of these pathways suggest that even moderate parental biases exert key roles in assuring normal brain development and function.

The paternally biased *Bcl-x_L* produces an essential antiapoptotic signal during brain development (Motoyama et al. 1995). Paternal but not maternal deletion of *Bcl-x* was shown to reduce brain size and, in the cortex, led to specific loss of excitatory neurons, thus demonstrating the functional significance of this gene's parental biases during brain development (Perez et al. 2015). The antiapoptotic *Bag3* shows stronger maternal biases in brain regions where *Bcl-x_L* shows weaker paternal biases and vice versa, suggesting that parental biases of these two genes may influence apoptosis in distinct brain regions. The proapoptotic *Bmf* and *Blcap* also exhibit spatially regulated maternal biases in the brain (Perez et al. 2015). These observations support the notion that the life-death balance of brain cells is regulated partly by parental biases in pro- and antiapoptotic imprinted genes (Figure 6a).

In the brain monoaminergic system (Figure 6b), maternally biased genes generally increase monoamine levels, whereas paternally biased genes may selectively reduce their postsynaptic effects (Bonthuis et al. 2015). Most notably, tyrosine hydroxylase (TH), which limits the rate of dopamine and norepinephrine synthesis, shows a weak maternal bias in monoaminergic nuclei. Maternal deletion of *Th* was shown to exhibit lower anxiety- and anhedonia-like behavior than paternal deletions, thus supporting the functional significance of this gene's maternal bias (Bonthuis et al. 2015). Interestingly, DOPA decarboxylase, an enzyme necessary for the synthesis of all monoamines, is maternally biased in monoaminergic nuclei. *Tgfb11*, which encodes a dopamine transporter inhibitor (Carneiro et al. 2002), is also maternally biased in all monoaminergic nuclei (Bonthuis et al. 2015). Finally, *Ahi1*, whose encoded protein increases feeding by downregulating 5-HT_{2C}R in the arcuate nucleus (ARN) (Wang et al. 2012), shows paternal biases in the ARN and monoaminergic nuclei. Considering the extensive effects of brain monoamines, these results suggest widespread influences of parental biases on brain function.

The Regulation of Parentally Biased Expression

Differential DNA methylation of regulatory regions in one parental gamete but not the other instructs the chromatin machinery to silence alleles in *cis*, leading to parent-of-origin expression in imprinted genes (Bartolomei & Ferguson-Smith 2011). Most known monoallelically expressed genes are clustered around at least one germ-line differentially methylated region (gDMR), whereas approximately 70% of parentally biased genes localize to the periphery of these clusters. The remaining 30% of parentally biased genes are isolated, among which four genes appear near a gDMR (Perez et al. 2015). The location of parentally biased genes at the periphery of imprinted clusters suggests that they may experience *cis* acting signals differently than monoallelic genes. Consistently, and although the three-dimensional effects in the nucleus are not accounted for, the strength of parental bias decays as a function of the genomic distance from the gDMR (Figure 7a) (Perez et al.

2015). Moreover, the synteny of weakly biased genes in imprinted clusters is strongly conserved in mammals, suggesting selective constraints on this genomic organization.

Mechanistically, the function of the maternal gDMR within the *Kcnq1* cluster suggests a model underlying the spread of imprinting regulation initiated at gDMRs and the generation of parental biases (Figure 7b). The gDMR of this cluster restricts expression of *Kcnq1ot1*, an lncRNA, to the paternal allele. KCNQ1OT1 spreads peripherally and recruits repressive chromatin machinery, including polycomb repressive complexes (PRCs), to promoters of nearby genes (Mancini-Dinardo et al. 2006, Terranova et al. 2008). The diffusion rate and/or half-life of the KCNQ1OT1 lncRNA (Figure 7b), the silencing capacity of the recruited repressive chromatin, and the resulting three-dimensional position in the nucleus may thus affect the degree of repression. Mechanisms reminiscent of position effect variegation, which in flies consists of the stochastic spread of heterochromatin to adjacent genes (Elgin & Reuter 2013), may represent alternative models.

However, the fact that most parentally biased isolated genes are not associated with gDMRs, suggests mechanisms independent of DNA-methylation. PRC2 represents an attractive candidate because its genomic position can be conserved after cell division (Steffen & Ringrose 2014). Indeed, PRC2-associated histone modifications are present in *Smbft2* and *Gab1* maternal alleles, two isolated paternally expressed genes in the placenta which lack DMRs (Okoe et al. 2012, Wang et al. 2011).

Finally, genome-wide methylation profiles of mouse and human cortical neurons have revealed that non-CG DNA cytosines accumulate methylation during postnatal development (He & Ecker 2015, Lister et al. 2013). It was additionally found that intragenic and near-transcription start site non-CG as well as CG methylation levels are higher in cells in which the corresponding genes are not expressed (Mo et al. 2015). This pattern is paralleled by accumulation of hydroxymethyl CGs (hmCs), the oxidized form of methylated CGs catalyzed by TET hydroxylase proteins, thought to represent an intermediate between methylated and nonmethylated cytosines (He & Ecker 2015, Lister et al. 2013). Although Xie et al. (2012) observed higher levels of non-CG methylation in the silenced allele at a few imprinted loci in the mouse brain, the relationships between this type of methylation as well as that of hmC with imprinting and parental bias are not yet known, and they represent an interesting avenue for future research.

CONCLUDING REMARKS

Although early studies of genomic imprinting highlighted its roles during embryonic and placental growth, its pleiotropic influences on brain development and function have emerged more recently. These include positive and negative controls by both maternally and paternally preferentially expressed genes of the generation, wiring, and survival of cells in the developing and adult brain. Consistent with the kinship theory of genomic imprinting (see the sidebar, Evolutionary Theories of Genomic Imprinting), paternally expressed genes promote suckling and growth in newborns, and to a lesser extent, maternally expressed genes reduce growth and increase metabolic rate in both newborns and adults. These results are also consistent with the roles of imprinted genes in embryonic development (Tunster et

al. 2013). Paternally expressed genes also appear to contribute to the regulation of puberty as well as to reproductive and maternal behaviors. Interestingly, maternally expressed genes appear to be the main contributors of positive and negative regulation of emotional and cognitive behaviors.

The importance of imprinted genes in brain function is evidenced by the devastating neurological and behavioral conditions resulting from mutations in these loci in humans and mice. Strikingly, recent advances suggest that imprinting disorders may be amenable for therapeutic intervention and that their pathological manifestations could be, at least partially, rescued by reactivating the usually unaffected repressed allele. Indeed, reactivation in a mouse model of AS of the repressed *Ube3a* paternal allele rescued cognitive features, even in adults (Huang et al. 2012, Meng et al. 2014). However, the rescue of other AS phenotypes may require embryonic intervention (Silva-Santos et al. 2015).

An emerging theme is that many imprinted genes exhibit various degrees of parental expression biases. Many of these biases were evidenced recently thanks to the increased resolution afforded by RNA-seq, suggesting that additional imprinted genes may still be discovered, particularly within tissues of high cellular and functional diversity such as the brain. Consequently, single cell-resolution studies will be necessary for a better mechanistic and biological understanding of parental biases in the brain and other complex tissues. Finally, researchers have proposed that imprinted genes form a regulatory network influencing common biological functions (Al Adhami et al. 2015, Varrault et al. 2006), possibly impinging on nonimprinted genes (Mott et al. 2014). Such a network may be impaired by dosage alterations in specific genes and compensated by titration in other genes, therefore representing a unique opportunity to study brain function at a polygenic level.

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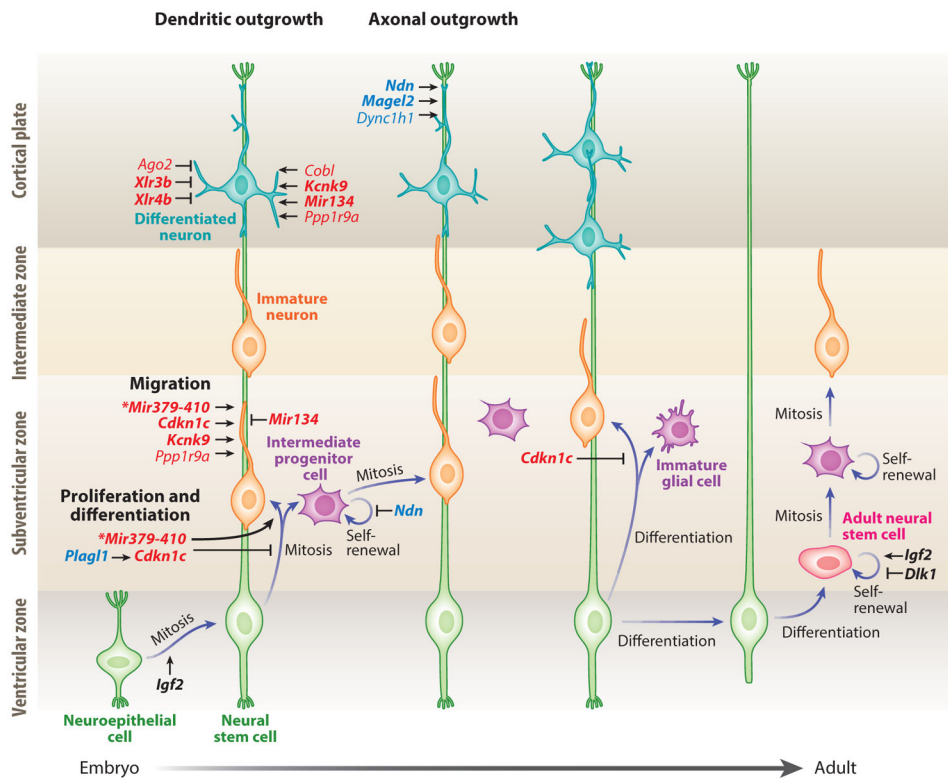


Figure 1. Roles of imprinted genes during cortical neurogenesis. Genes preferentially expressed from the maternal and paternal allele appear in red and blue, respectively. In black are imprinted genes that are biallelically expressed in this context. Strongly biased and monoallelically expressed imprinted genes are in bold. Lines with arrowheads indicate enhancement, and lines with notched ends indicate reduction of the biological function. The asterisks by *Mir379–410* indicate that the corresponding biological functions are regulated by three miRNAs of this cluster: *Mir369-3p*, *Mir496*, and *Mir543*.

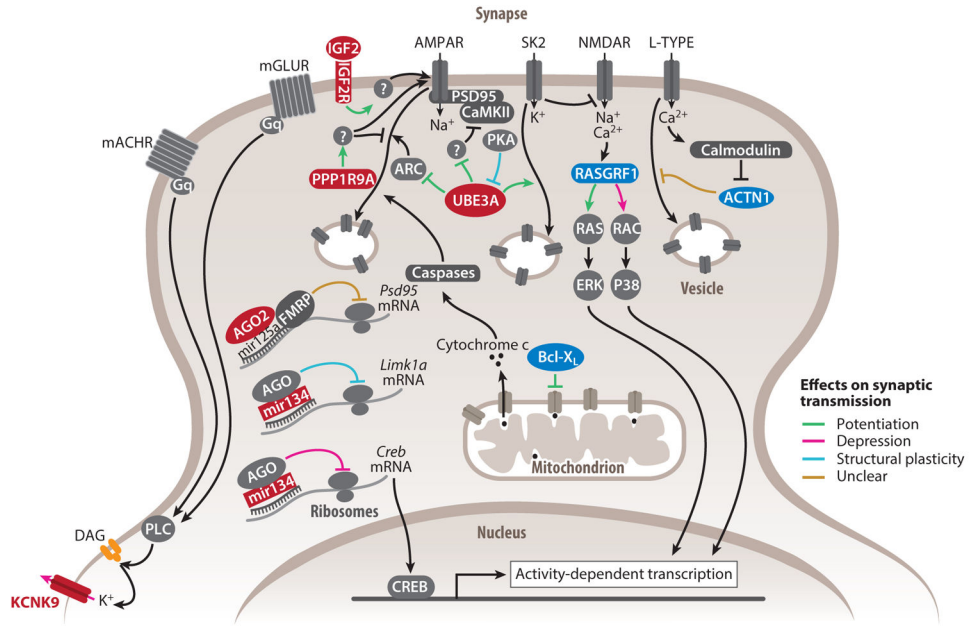


Figure 2. Functions of imprinted genes in synaptic transmission and plasticity. Products of genes preferentially expressed from the maternal and paternal allele appear in red and blue, respectively. Products of biallelically expressed genes appear in dark gray. Products of strongly biased and monoallelically expressed imprinted genes are in bold. Lines with arrowheads represent stimulatory molecular interactions, whereas lines with notched ends represent inhibitory molecular interactions. The overall role of imprinted genes in synaptic plasticity is shown in green to indicate synaptic potentiation or activation, in pink to indicate synaptic depression or inhibition, in blue to indicate the induction of structural changes, and in brown when the contribution to synaptic transmission or plasticity remains unclear. White-filled circles with beige borders represent vesicles containing membrane receptors or channels.

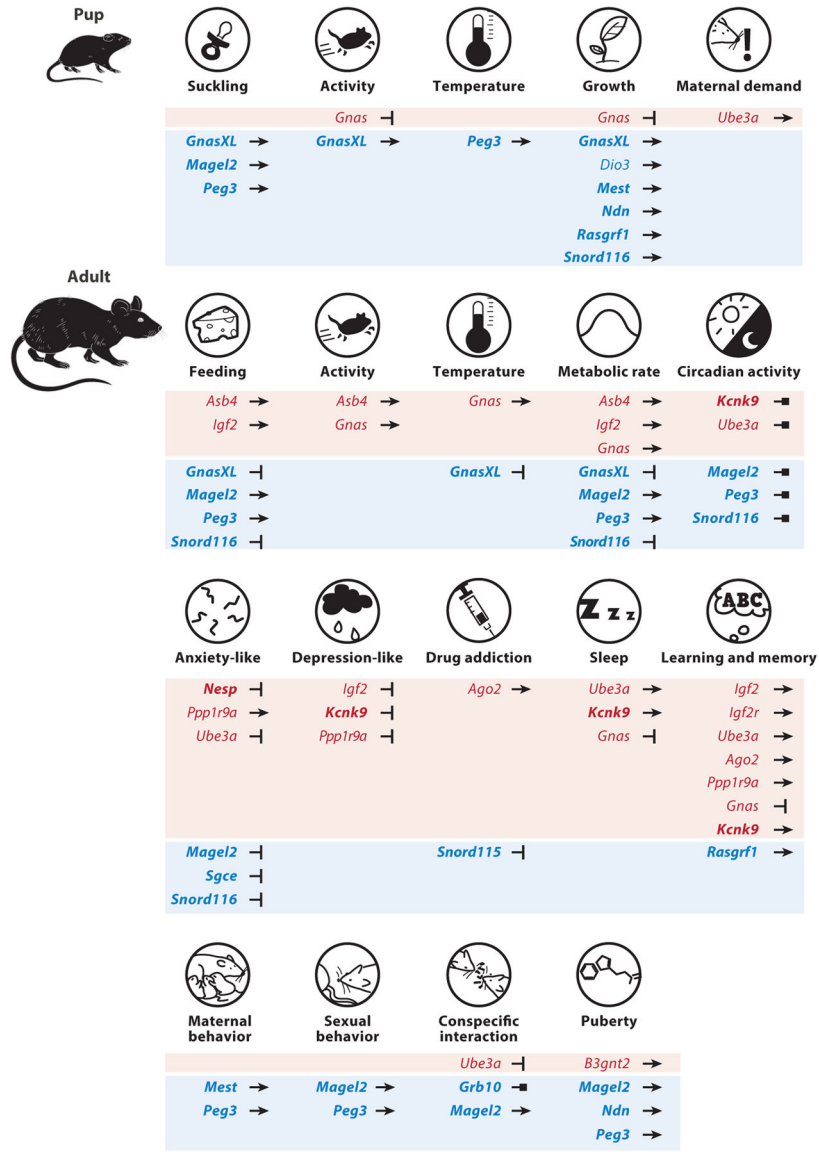


Figure 3. Mouse phenotypes influenced by imprinted genes. Genes associated with specific metabolic, social, emotional, and cognitive phenotypes are listed. Genes preferentially expressed from the maternal and paternal allele appear in red and blue, respectively. Strongly biased and monoallelically expressed imprinted genes are in bold. Lines with arrowheads and notched ends indicate stimulation and inhibition, respectively, of the given phenotype, whereas lines with square ends indicate functions that cannot be defined as enhancement or reduction.

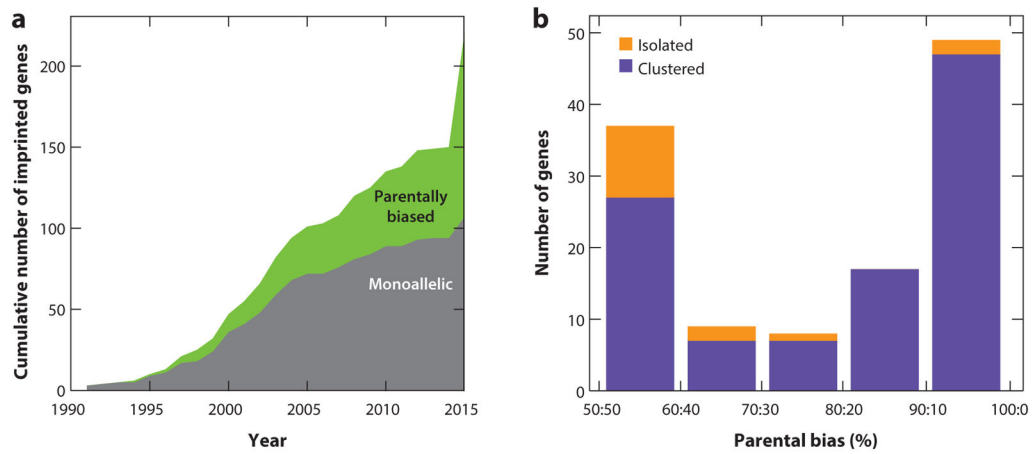


Figure 4. Monoallelic and parentally biased genes in mouse. (a) Cumulative increase in the number of imprinted genes reported in the literature. (b) The distribution of parental allelic expression ratios of clustered and isolated imprinted genes in the developing and adult cerebellum. Figure adapted from Perez et al. (2015).

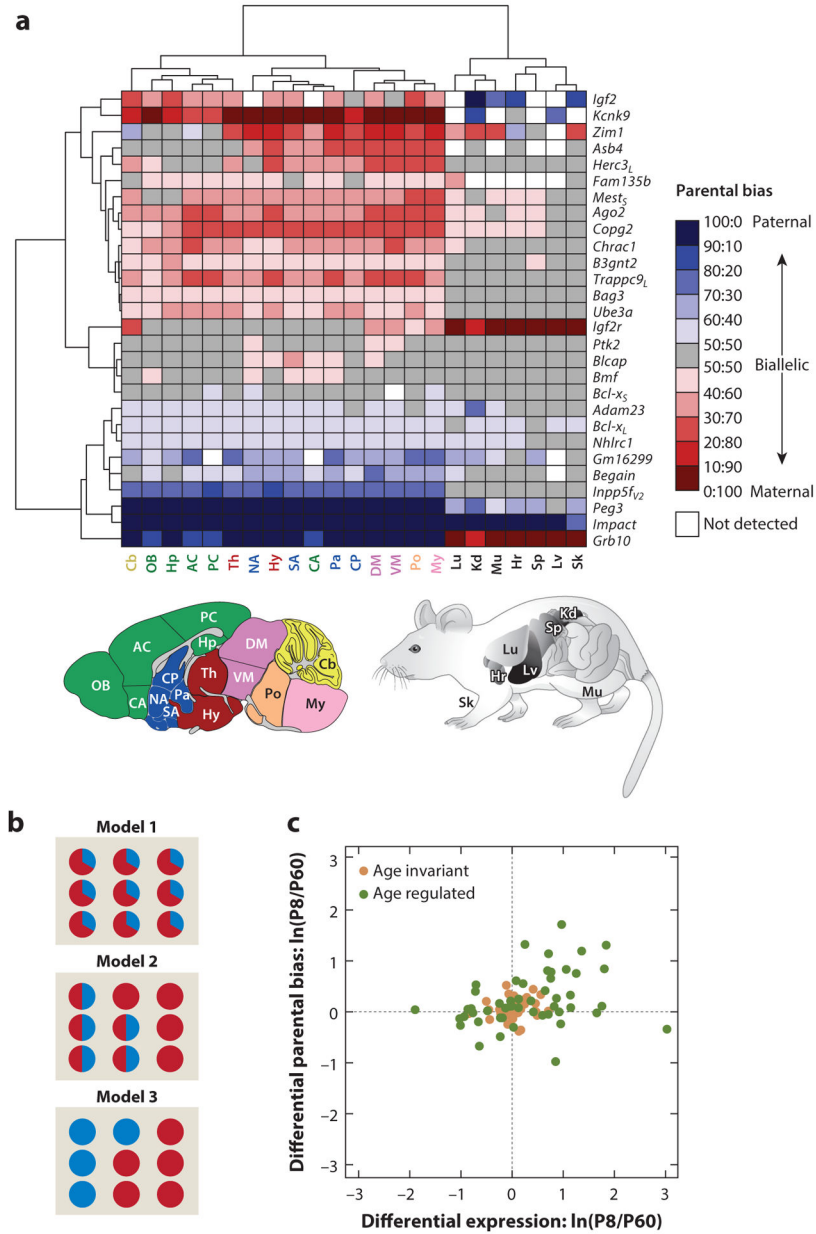


Figure 5. Regulation of parentally biased imprinted genes in mouse. (a) Spatial regulation of imprinting represented by a hierarchically clustered heat map of the deviation from biallelic gene expression. Panel adapted from Perez et al. (2015). L and S subscripts in the gene names indicate long and short isoforms, respectively, and V2 indicates variant 2 splice form. Acronyms of brain regions (color coded according to their broad developmental relatedness): AC, anterior cortex; CA, cortical amygdala; Cb, cerebellum; CP, caudate putamen; DM, dorsal midbrain; Hp, hippocampus; Hy, hypothalamus; My, medulla; NA, nucleus accumbens; OB, olfactory bulb; Pa, pallidum; PC, posterior cortex; Po, pons; SA, striatum-like amygdala; Th, thalamus; VM, ventral midbrain. Acronyms of nonbrain tissues: Hr, heart; Kd, kidney; Lu, lung; Lv, liver; Mu, muscle; Sk, skin; Sp, spleen. (b) Models

providing the single cell–level bases for the parental biases observed in tissue homogenates. Each circle represents a single cell within the homogenized tissue. Red represents maternal expression, and blue represents paternal expression. In model 1, parental biases are identically present in each individual cell. In model 2, parental biases result from a mixture of cells exhibiting monoallelic expression with cells exhibiting biallelic expression. In model 3, parental biases result from a mixture of cells that monoallelically express either the maternal or paternal allele. (c) Age fold change {developing (P8) and adult (P60) cerebella [$\ln(P8/P60)$]} in the magnitude of parental biases versus their age fold change in overall expression level. Panel adapted from Perez et al. (2015). Most genes exhibiting significant age-dependent changes in parental biases also show significant changes in overall expression, with the largest effects for both categories observed during development (Pearson correlation coefficient = 0.33; $P = 4 \times 10^{-4}$). Age-regulated imprinted genes are represented by green circles (those located near the origin show weak yet statistically significant age effects), and age-invariant imprinted genes are represented by brown circles.

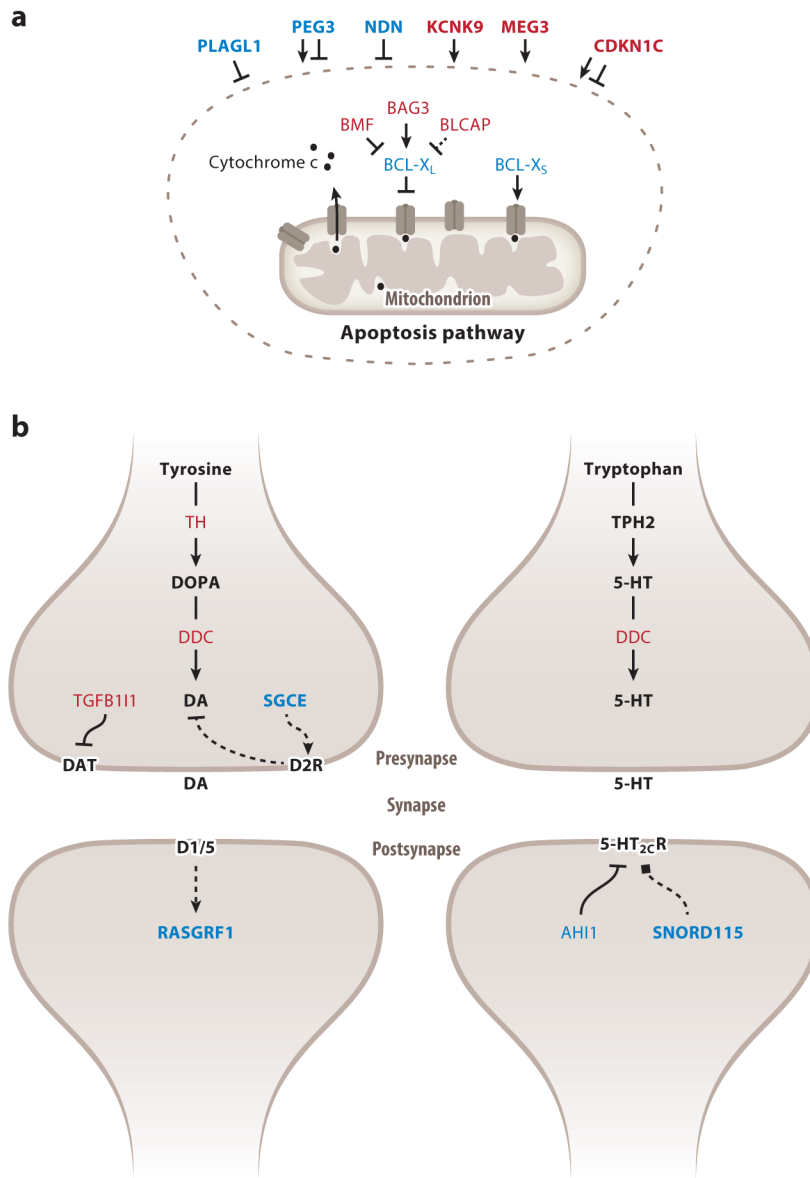


Figure 6. Parentally biased and strongly imprinted genes are enriched in two biological pathways in the brain. (a) Regulation of apoptosis. Within the circle are products of imprinted genes that interact directly with the apoptosis machinery, and outside the circle are products of imprinted genes that influence pro- or antiapoptosis. L and S subscripts in the gene names indicate long and short isoforms, respectively. (b) Brain monoaminergic pathway. Genes preferentially or exclusively expressed from the maternal and paternal allele appear in red and blue, respectively. Products of strongly biased or monoallelically expressed genes are in bold. Lines with arrowheads and lines with notched ends indicate stimulation and inhibition, respectively, of the given phenotype, whereas lines with square ends indicate functions that cannot be defined as enhancement or reduction. Full lines indicate direct interactions, whereas dashed lines indicate indirect effect. Abbreviations: 5-HT, serotonin; 5-HT_{2C}R, 5-

HT_{2C} receptor; D1/5, dopamine receptor 1 or 5; D2R, dopamine receptor 2; DA, dopamine; DAT, dopamine transporter; DDC, DOPA decarboxylase; TH, tyrosine hydroxylase.

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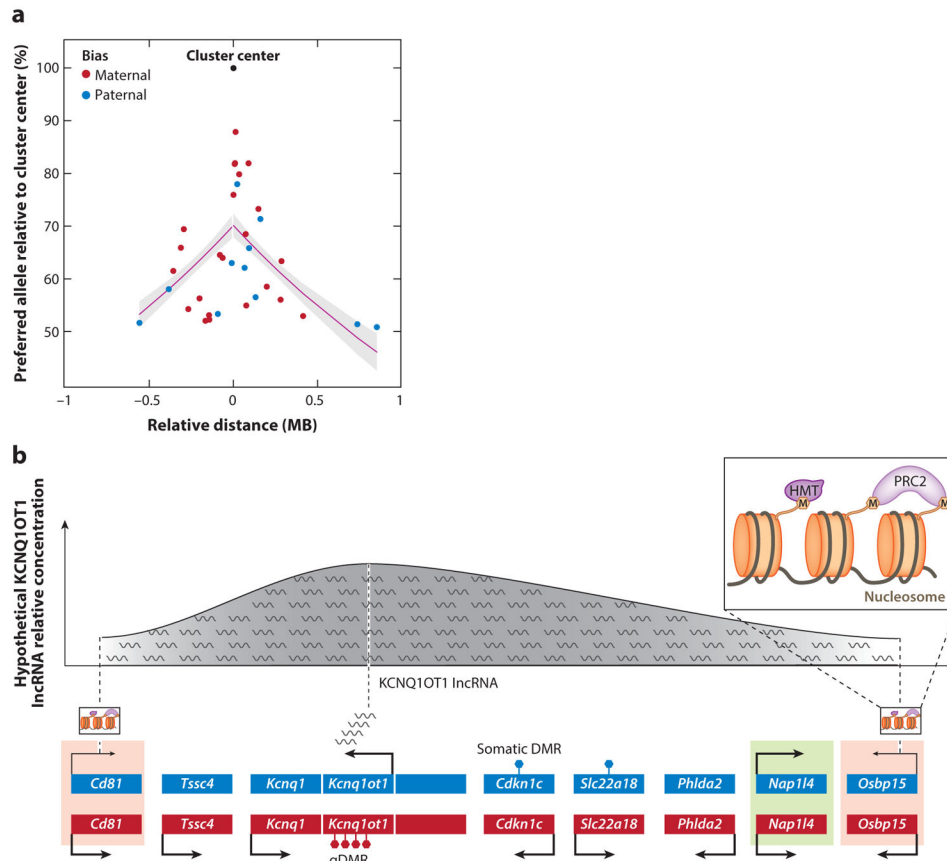


Figure 7. Mechanistic models of parentally biased expression. (a) The decay of parental bias of imprinted genes as a function of their relative linear genomic distance from an imprinted cluster center (which is defined as the location of the monoallelically expressed imprinted genes in the cluster) in the cerebellum. The regression line is shown in magenta, and the gray shading indicates corresponding standard errors (Perez et al. 2015). (b) Known mechanisms of genomic imprinting in the mouse *Kcnq1* imprinted cluster and their potential extrapolation to mechanisms of parental biases. The *Kcnq1* intergenic, maternally methylated gDMR induces paternal-specific expression of *Kcnq1ot1*, an lncRNA that orchestrates imprinting of multiple genes at both ends of this cluster (Mancini-Dinardo et al. 2006, Terranova et al. 2008). In the placenta, genes closer to the gDMR, such as *Cdkn1c*, are monoallelically expressed in a DNA methylation–dependent manner (indicated by filled hexagons on top of gene bodies), whereas genes at the cluster periphery, such as *Cd81* and *Osbp15*, exhibit DNA methylation–independent maternal biases (*red shading*) (Lewis et al. 2004, Umlauf et al. 2004). Another peripheral gene, *Nap114*, is biallelically expressed (*green shading*). Imprinting in these maternally biased genes is dependent on interactions between their respective promoters and *Kcnq1ot1* transcripts, which recruit HMTs and PRC2, forming a contracted nuclear domain (Pandey et al. 2008, Terranova et al. 2008). Importantly, KCNQ1OT1 lncRNA does not interact with the *Nap114* promoter. We suggest a potential model explaining parentally biased expression in this cluster (depicted on *top*) where the effective concentration or activity of the KCNQ1OT1 lncRNA across the length of

the cluster may exhibit a normal distribution centered in its transcriptional site that decreases gradually toward the ends. In this model, the differences in KCNQ1OT1 lncRNA concentration or activity may explain its different actions in central and peripheral genes. Abbreviations: gDMR, germ-line differentially methylated region; HMT, histone methyltransferase; lncRNA, long noncoding RNA; PRC2, polycomb repressive complex 2.