# Chapter 12
# Genomic Imprinting in the Mammalian Brain

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**Abstract** Genomic imprinting has been primarily studied in the context of embryonic growth and development. However, over the past several years new insights into the roles of imprinted genes in the brain have emerged. Using a novel approach based on next-generation sequencing we recently uncovered hundreds of genes exhibiting complex imprinting effects in the brain, including imprinting effects that are brain region specific, developmental stage specific, and sex specific. Here, we provide a historical perspective on genomic imprinting to introduce this exciting area to the neuroscience field. Further, we comment on emerging concepts related to imprinting in the brain revealed by next-generation sequencing. This work suggests a major frontier exists to understand the functional roles of imprinted genes in the regulation of brain development, function, and behavior.

## 12.1 Discovery of Imprinting and Roles for Imprinted Genes in Brain Function and Behavior

In a classical Mendelian genetic view, genetic inheritance involves equal contributions from the mother and the father to diploid offspring. This general model is applicable to many conditions, but many complex traits remain unexplained (Fradin et al. 2006). Advances in the field of molecular genetics have revealed many factors that contribute to complex non-Mendelian patterns, including epigenetic effects (Mohtat and Susztak 2010), genetic-environment interactions (Dempfle et al. 2008), and parent-of-origin effects (Wolf et al. 2008). Parent-of-origin effects have been recognized to influence the phenotype and behavior of offspring for centuries (Thomas et al. 1970).

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Parent-of-origin effects may arise from a number of mechanisms that include maternally inherited mitochondrial DNA (mtDNA) (Giles et al. 1980), small ncRNAs differentially transmitted by sperm versus egg (Bourc'his and Voinnet 2010), uterine environment during development (Wolff et al. 1998), and genomic imprinting (Guilmatre and Sharp 2012; Abramowitz and Bartolomei 2012). Genomic imprinting is a process that causes genes to be asymmetrically expressed in offspring depending on their parental origin. The phenomenon has been observed at both the chromosomal level and at the level of individual genes. The first use of "imprinting" to describe epigenetic parent-of-origin effects was in the context of the elimination of paternal chromosomes during spermatogenesis in sciarid flies (Crouse 1960). *Sciara* male and female embryos selectively eliminate a paternally inherited X chromosome, and Crouse proposed that chromosomal imprints are established through the germline in order to functionally distinguish maternal and paternal X chromosomes in the embryo.

The first example of imprinting at the level of a single gene was described in plants 40 years ago (Kermicle 1970). Through experiments focused on the inheritance of maize kernel coloration, Kermicle recognized parent-of-origin effects influencing alleles affecting the red color (anthocyanin pigmentation) of the endosperm's outer layer, the aleurone. Strains were uncovered with red color (*R*) alleles that gave full pigmentation when maternally inherited in a cross with a colorless strain (*r/r*) but mottled pigmentation when paternally inherited. In vertebrates, genomic imprinting was initially uncovered at the chromosomal level for the X chromosome. Imprinting of the X chromosome occurs in female marsupials, such that the paternally inherited X chromosome (Xp) is preferentially silenced in both embryonic and extraembryonic tissues (Cooper et al. 1971). In mice, the Xp is silenced specifically in extraembryonic tissues, but in the embryo proper, both the maternally inherited X (Xm) and the Xp undergo random inactivation (Takagi and Sasaki 1975; West et al. 1977). The first individual imprinted autosomal genes in mammals would not be discovered until 1991 in mice. *Igf2r* (insulin-like growth factor type 2) was mapped to mouse chromosome 17 and identified as a maternally expressed gene (Barlow et al. 1991). The Igf2 gene (insulin-like growth factor type 2) was revealed as a paternally expressed imprinted gene (DeChiara et al. 1991). Finally, the H19 gene (fetal hepatic cDNA clone 19), which is a long noncoding RNA, was demonstrated as a maternal expressed imprinted gene closely located to the Igf2 locus (Bartolomei et al. 1991).

Nuclear transplantation experiments in mice first revealed that maternal and paternal genomic complements are not equivalent in mammals and that both maternally and paternally inherited chromosomes are essential for development. It was discovered by Barton et al. and McGrath and Solter (Surani and Barton 1983, 1984; McGrath and Solter 1984; Barton et al. 1984) that parthenogenetic (PG) and androgenetic (AG) (with a diploid maternally or paternally derived genome, respectively) embryos exhibit early embryonic lethality. The early experimental work also revealed major differences between AG and PG embryos. AG embryos showed reduced fetal growth and excessive extraembryonic growth, whereas PG embryos showed more advanced fetal development with relatively poor extraembryonic growth. The discrepancy in the phenotype between PG and AG embryos implied that paternally expressed genes

(PEGs) have functionally distinct roles compared to maternally expressed genes (MEGs) in offspring and that these effects are tissue specific.

Studies of imprinting in the brain using PG and AG chimeric mice suggested distinct roles for PEGs and MEGs in the regulation of cortical versus hypothalamic brain regions. To overcome the developmental lethality of AG and PG embryos, chimeric mice were generated with wild-type cells that could survive to adulthood (Allen et al. 1995). With regard to brain development, PG chimeras have small bodies with relatively enlarged brains compared to controls, whilst AG chimeras have large bodies, but relatively small brains (Allen et al. 1995). To determine where the PG/AG cells were located in the brain, a lacZ reporter was utilized to label PG and AG cells. Cells with a maternal genome (PG) preferentially contributed to cortical and limbic regions, but were selectively eliminated from hypothalamic regions. In contrast, AG cells contributed preferentially to the hypothalamus, septum, and the preoptic area of the stria terminalis (Keverne et al. 1996). These pioneering studies suggested that alleles that come from mothers and fathers have potentially distinct roles in the development and functions of cortical versus hypothalamic brain regions, respectively (Keverne 1997).

Subsequently, mice with altered dosage of individual or multiple imprinted genes have provided insights into the functional roles of imprinted genes. Many studies have indicated that imprinted genes are involved in fetal growth, postnatal energy homeostasis, organ development, and in several behaviors (Charalambous et al. 2007). Insights into the roles of imprinted genes in humans have largely come from congenital disorders, such as Prader–Willi syndrome (PWS), Angelman syndrome (AS) (Buiting 2010), Beckwith–Wiedemann syndrome (Choufani et al. 2010), and Silver–Russell syndrome (Abu-Amero et al. 2008). Further, recent studies have revealed roles for imprinted genes in complex diseases. A study assessed the relationship between parental origin and disease risk in Iceland and found that a number of alleles within known imprinted loci significantly influenced the risk of breast cancer, basal-cell carcinoma, and type II diabetes (Kong et al. 2009). Major neuropsychiatric disorders have also been associated with imprinted loci, including autism (Arking et al. 2008; Lamb et al. 2005), schizophrenia (DeLisi et al. 2002; Francks et al. 2003), alcoholism (Liu et al. 2005; Wyszynski and Panhuysen 1999), and bipolar affective disorder (Pinto et al. 2011). In addition to clinical studies, bioinformatic approaches suggest that imprinted genes are associated with psychosis, obesity/diabetes, and autism (Sandhu 2010).

Maternal and paternal imprinting effects on human behavior and neurodevelopment have been most extensively explored in PWS and AS. PWS is characterized by mental handicap, severe hypotonia, hypogonadism, poor temperature regulation, and obesity (Cassidy and Driscoll 2009). Infants with PWS show poor suckling reflexes following birth and often show failure to thrive in early infancy, followed by the emergence of hyperphagia and obesity in early childhood. A distinctive behavioral character with temper tantrums, obsessive-compulsive characteristics, and psychiatric disturbance are common findings. The clinical features of AS include mental retardation, microcephaly, gait ataxia, seizures, and repetitive, uncoordinated, but symmetrical movements. Affected individuals with AS usually

exhibit inappropriate laughter and excitability (Williams et al. 2006). These two disorders were the first examples of a human imprinting disease (Buiting 2010). Previous studies reported that the prevalence rate of these two disorders is 1 per 15,000–25,000 live births (Burd et al. 1990; Butler 1996). A deletion in the same chromosome region, 15q11–q13, was identified in patients with PWS and AS (Knoll et al. 1989; Ledbetter et al. 1981; Nicholls et al. 1989). It was initially unclear how two phenotypically distinct syndromes arose from the same genetic mutation.

The chromosomal region 15q11–q13 is the location of a cluster of imprinted genes, expressed from either the paternally or maternally inherited allele in the brain. Paternally expressed transcripts from the relatively centromeric part of this locus, including *NDN* (Jay et al. 1997), *SNRPN* (Leff et al. 1992), and its associated noncoding small nucleolar RNAs (snoRNA) gene *SNORD* (Sahoo et al. 2008), are not expressed in PWS and are implicated in this syndrome. In contrast, AS is caused by loss of the UBE3A transcript, which is maternally expressed (Matsuura et al. 1997). How loss or aberrant dosage of these genes affects neuronal function and causes the phenotype of these disorders is a major area of research and has been recently reviewed (Cassidy et al. 2012; Mabb et al. 2011). Several studies have provided enticing mechanistic insights. For example, *Ndn* knockout mice show hypothalamic deficits, including a reduction in oxytocin-producing and luteinizing hormone-releasing hormone-producing neurons, which are similar with the general phenotype of hypothalamic deficit in PWS (Muscatelli et al. 2000). Further, a role for snoRNAs encoded in the PWS locus and pre-mRNA splicing that is essential for neurodevelopmental processes and serotonin signaling has been suggested (Yin et al. 2012; Kishore and Stamm 2006). In terms of etiology of AS, transgenic ablation of maternal Ube3A leads to behavioral deficits that are associated with abnormal dopamine signaling (Riday et al. 2012).

## 12.2 Regulation of Imprinting

Like the PWS/AS locus mentioned above, greater than 80 % of known imprinted genes are clustered into 16 genomic regions that contain two or more imprinted genes (Edwards and Ferguson-Smith 2007). The fact that imprinting often occurs in clusters implies that the imprinting mechanism is often not exerted in a gene-specific manner. Indeed, for several known imprinted loci, a long-range cis-acting control element called an imprint control element (ICE) or imprint control region (ICR) has been identified (Barlow 2011). Although not all imprinted gene clusters follow the same rules of regulation, in general imprinting involves a differentially methylated ICE region and the expression of a long noncoding RNA with a regulatory role in the maintenance of allele-specific expression.

A well-studied imprinted gene locus regulated by a paternally methylated ICR is the *H19/Igf2* imprinting locus. *H19* and *Igf2* compete for two enhancers located downstream of *H19* (Webber et al. 1998; Bartolomei et al. 1991, 1993; DeChiara et al. 1991). The ICR has 4 binding sites for the insulator protein, CTCF, which binds to the unmethylated maternal allele (Bell and Felsenfeld 2000; Hark et al. 2000).

CTCF binding blocks the enhancer region from interacting with the *Igf2* promoter, leading to exclusive expression of *H19* from the maternal allele. Methylation at the ICR on the paternal allele prevents CTCF from binding and allows the *Igf2* promoter to interact with the enhancers, resulting in paternal Igf2 expression. Maternal *H19* expression is directly involved in regulating the paternal expression of *Igf2,* such that loss of *H19* results in activation of the maternal *Igf2* allele (Leighton et al. 1995). In the developing brain, some differences exist in the regulation of imprinting at this locus that are poorly understood, *H19* is maternally expressed (Hemberger et al. 1998), but *Igf2* expression has been reported to be biallelic (Leighton et al. 1995; Hemberger et al. 1998).

A well-studied example of imprinting involving a maternally methylated ICR is the *Igf2r/Airn* locus. The *Igf2r* gene is maternally expressed (Barlow et al. 1991), and *Airn* gene, which is a long noncoding RNA, is expressed from the paternal allele (Wutz et al. 1997). In this case, the ICR lies within an intron of *Igf2r* (Stoger et al. 1993) and involves a differentially methylated promoter site, for which the maternal allele is methylated. *Airn* is transcribed from the unmethylated paternal allele in an antisense direction to *Igf2r* and represses the expression of cis-linked genes from the paternal allele (Lyle et al. 2000; Wutz et al. 1997), including *Igf2r*, *Slc22a2,* and *Slc22a3* (Sleutels et al. 2002). Conversely, *Airn* expression is repressed on the maternal allele due to methylation at the ICR, allowing expression of cis-linked genes. It is suggested that lncRNAs regulated by differentially methylated ICRs represent a general mechanism that controls gene expression at several imprinted gene clusters. For example, this mechanism also occurs at the *Kcnq1* cluster (Fitzpatrick et al. 2002), *Snrpn* cluster (Horsthemke and Wagstaff 2008), and *Gnas* cluster (Williamson et al. 2011).

Imprinting can occur in a cell-type-specific or developmental-stage-specific manner for many genes. A recent study of the *Dlk1* locus provides some important mechanistic insights into cell-type-specific imprinting in the brain. *Dlk1* is exclusively expressed from the paternal allele during embryogenesis. However, Ferron et al. have demonstrated in the neurogenic niche of the developing and adult brain that *Dlk1* selectively loses imprinting in both NSCs and niche astrocytes resulting in expression of both alleles (Ferron et al. 2011). The underlying mechanism is associated with postnatally acquired hypermethylation at the intergenic DMR that regulates *Dlk1* imprinting. This study reveals that epigenetic mechanisms can dynamically control imprinted gene expression in specific cell types of the brain.

## 12.3 Next-Generation Sequencing and the Analysis of Imprinting in the Brain

Microarray technology revolutionized our ability to profile and compare levels of gene expression in specific tissues or under different treatment conditions. However, a genome-wide approach to study expression from maternally versus paternally inherited chromosomes has been lacking. To address this problem, Gregg and colleagues developed an approach to compare imprinting in different brain regions

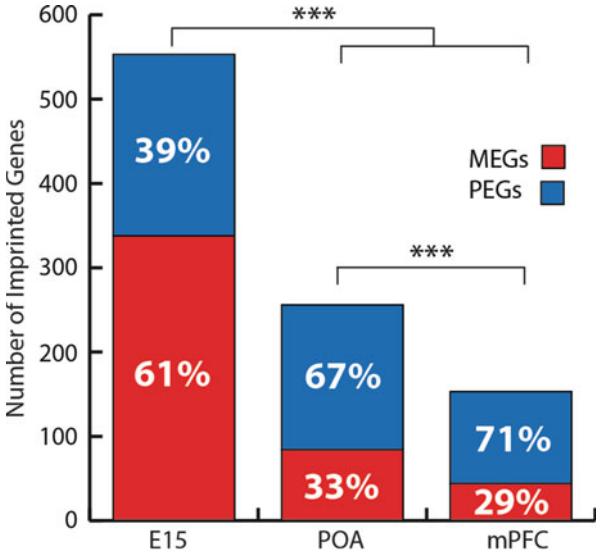


**Fig. 12.1** Numbers of maternally and paternally expressed imprinted genes discovered by next-generation sequencing in the embryonic day 15 (E15) brain and preoptic area (POA) and medial prefrontal cortex (mPFC) of the adult brain. The data reveals that the largest numbers of imprinted genes were uncovered in the developing brain and, in the adult brain, the POA had significantly more imprinted genes that the mPFC. In addition, the majority of imprinted genes in the adult brain exhibited a paternal expression bias, while the majority of genes in the developing brain exhibited a maternal bias

and tissues using high-throughput sequencing (Gregg et al. 2010a, b). In this approach, RNA is harvested from microdissected brain regions of F1 hybrid mice generated from reciprocal crosses of the distantly related C57BL/6J (C57)×CAST/EiJ (Cast) mouse strains. Single-nucleotide polymorphisms (SNPs) in the RNA-Seq data are used to distinguish expression from maternally versus paternally inherited alleles. The authors used this high-resolution approach to ask many questions for the very first time. Imprinting was analyzed in the cortex versus the hypothalamus to test the idea that biased maternal control exists in cortical regions and biased paternal control in hypothalamic regions, as discussed above. The authors further tested whether imprinting differs in the adult brain compared to the developing brain and whether sex-based differences in imprinting effects might exist.

The study revealed 256 imprinted genes expressed in the adult preoptic area of the hypothalamus, compared to 153 in the medial prefrontal cortex and 553 in the embryonic brain. Only 47 of the ~100 previously known murine imprinted genes were found to be expressed and imprinted in the brain. Thus, the findings suggested profound differences in imprinting developmentally and between brain regions. Additionally, differences were uncovered between males and females. Remarkably, these results further revealed that a substantial *paternal bias* exists among autosomal imprinted genes expressed in the adult brain, but a maternal bias exists in the developing brain (Fig. 12.1). In both cortical and hypothalamic regions of the brain,

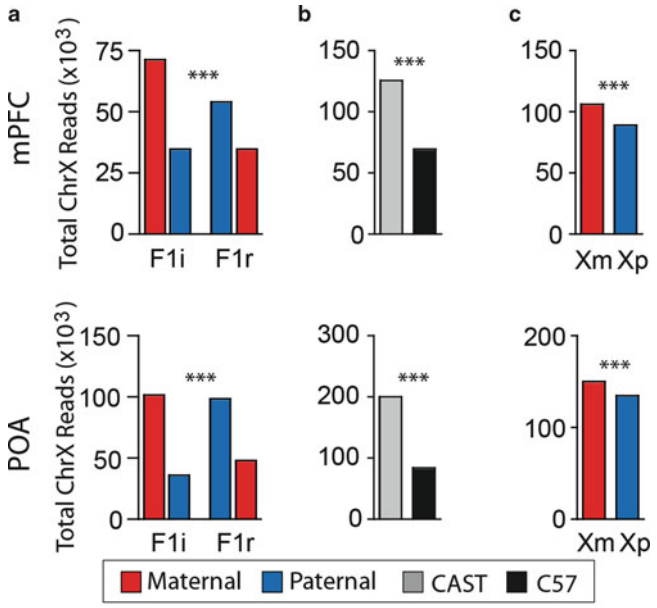


**Fig. 12.2** A significant bias to express the maternally inherited X chromosome was uncovered in the mPFC and POA of the adult female brain by next-generation sequencing as revealed using a fisher's exact test (**a**) or a chi-square test on all Xm versus all Xp reads (**c**). Preferential expression of the CAST/EiJ (Cast) X chromosome was also uncovered (**b**, chi-square test)

~70 % of the imprinted genes identified exhibited a paternal expression bias. Thus, the study did not find evidence for maternally biased control over cortical regions and paternally biased control over hypothalamic regions in terms of total numbers of MEGs or PEGs.

These studies also revealed the surprising insight that the maternal X chromosome (Xm) is preferentially expressed in the adult female brain (Fig. 12.2). This observation opposes the long-held assumption that X-inactivation leads to a random mosaic of Xm- and Xp-expressing cells in females. Interestingly, the authors propose that the X chromosome may represent a nexus of maternal influence over gene expression in the adult brain. This proposal is partly inspired by the fact that the X chromosome is enriched for genes that regulate brain function (Nguyen and Disteche 2006; Zechner et al. 2001), that males only inherit a maternal X chromosome, and that the X is postulated to be preferentially influenced by selection effects that act in maternal interests (Haig 2006).

Sexually dimorphic imprinting effects were also uncovered on the autosomes and involved an estimated 347 candidate genes imprinted specifically in males or females. The majority of sex-specific imprinting effects were observed in the preoptic area of the female brain. *Mrpl48* and *Il18* are examples of genes that exhibit sex-specific imprinting in the brain (Fig. 12.3). Interestingly, *Il18* is linked to inflammation and autoimmune diseases, such as multiple sclerosis, which are highly

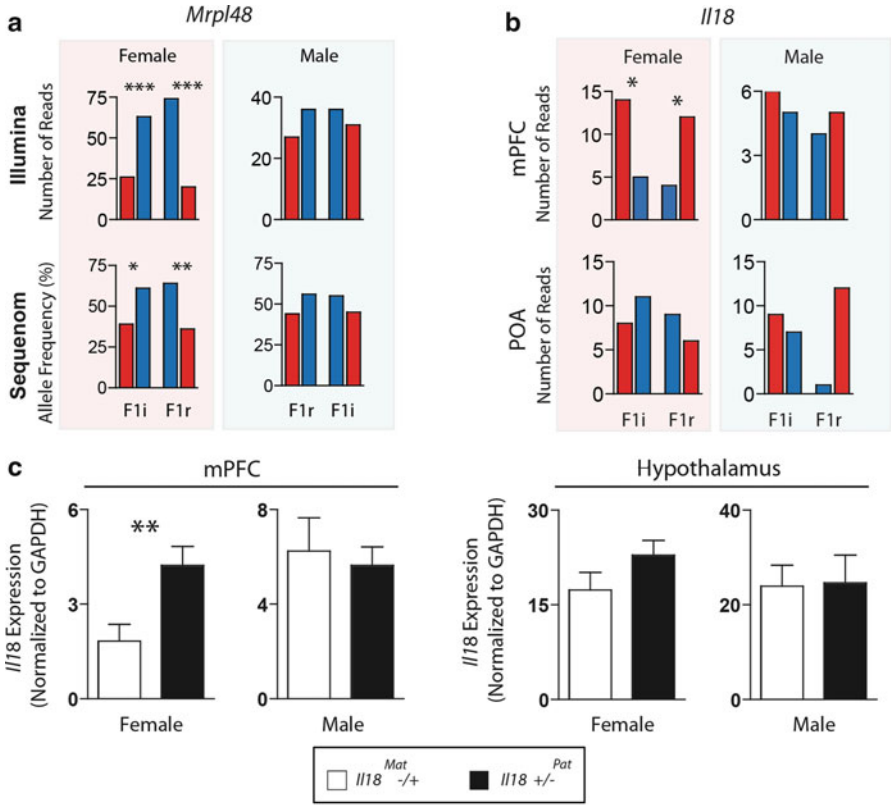


**Fig. 12.3** Sex-specific imprinting effects were uncovered for *Mrpl48* and *Il18*. (**a**) The paternal allele is preferentially expressed for the gene *Mrpl48* in the female POA and the effect was independently validated by sequenom. (**b**) *Il18* is maternally expressed in the mPFC of the female brain. The maternal effects were confirmed using *Il18* mutant mice and qPCR. (**c**) *Il18* expression was higher in the mPFC of *Il18* −/+ females compared to *Il18* +/− females, consistent with a maternal expression bias. This effect was not observed in males *Sources*: All figures were previously published in Science by the authors. These can be reproduced in book contributions by the original authors without permission

sexually dimorphic diseases. These new insights into sex-specific imprinting effects may help understand the underlying genetic and epigenetic architecture of these diseases.

Interestingly, none of the new imprinted genes uncovered in these studies exhibited the complete allele-specific silencing that is often associated with canonical imprinting. It was found that the vast majority of novel imprinting effects involve biases in allele-specific gene expression, and future studies are needed to understand the functional significance of these allele-specific biases. One untested explanation is that the biases emerge due to cell-type-specific imprinting effects. Finally, the studies by Gregg et al. offer additional insights and directions for future studies of imprinting in different regions of the brain. The authors mapped the expression pattern of 45 known imprinted genes in 118 different adult mice brain regions to determine whether particular brain regions are relatively enriched for imprinted gene expression

(Gregg et al. 2010b). They found 26 brain regions that exhibited enrichments for the expression of known imprinted genes, and most of these were monoaminergic and hypothalamic nuclei in the brain, such as the dorsal raphe nucleus, the arcuate nucleus, and the preoptic area (Gregg et al. 2010a). Future studies of imprinting in the brain might initially focus on these neural systems.

## 12.4 Future Directions

Next-generation sequencing allows us to observe genetic imprinting effects from a new prospective. In the same way that microarray technology contributed to the emergence of system-level analyses of gene expression, we anticipate that next-generation sequencing studies of allele-specific gene expression will similarly contribute to allele-specific gene network-level analyses that elucidate maternal versus paternal influences over gene expression in specific regions of the developing and adult brain. Currently, these studies of imprinting are limited to mice and new approaches will need to be devised to uncover imprinting effects in the primate brain. Further, improved RNA-Seq technologies will permit the study of imprinting in specific cell populations of the brain to elucidate maternal versus paternal influences over the function of molecularly defined circuits in the brain. A major question that is largely unaddressed with the exception of a few pioneering studies is whether imprinting can change in response to environmental factors or physiological states. The use of next-generation sequencing to profile imprinting will be fundamental to address these different issues. Importantly, extensive genetic and behavioral studies are required to reveal the function(s) of these complex imprinting effects and how they may contribute to disease susceptibility. We anticipate that insights into the roles of imprinted genes in the brain will provide insights into the evolutionary pressures that shaped the development and function of the brain and of the behavior of different species. Further, given the complex, polygenic nature of neuropsychiatric diseases and disorders, uncovering maternal and paternal epigenetic influences over gene expression in the brain may provide new insights into the biological basis of some of these disorders. Roles for imprinted genes in autism and schizophrenia have already been clearly established through studies of PWS and AS (Wilkinson et al. 2007). In summary, the application of next-generation sequencing to the study of genomic imprinting in the brain has opened an exciting new frontier with many avenues for study.

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