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Review

Role of genomic imprinting in mammalian development

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Non-mendelian inheritance refers to the group of phenomena and observations related to the inheritance of genetic information that cannot be merely explained by Mendel's laws of inheritance. Phenomenon including Genomic imprinting, X-chromosome Inactivation, Paramutations are some of the best studied examples of non-mendelian inheritance. Genomic imprinting is a process that reversibly marks one of the two homologous loci, chromosome or chromosomal sets during development, resulting in functional non-equivalence of gene expression. Genomic imprinting is known to occur in a few insect species, plants, and placental mammals. Over the years, studies on imprinted genes have contributed immensely to highlighting the role of epigenetic modifications and the epigenetic circuitry during gene expression and development. In this review, we discuss the phenomenon of genomic imprinting in mammals and the role it plays especially during fetoplacental growth and early development.

Keywords. Genomic imprinting; imprinted genes; epigenetic modifications; DNA methylation; histone modifications; placenta

Abbreviations: SNP, single nucleotide polymorphism; ncRNA, non-coding RNA; ICR, imprint control region; DMR, differentially methylated region; gDMR, germline DMR; dpc, days post coitum; lncRNA, long non-coding RNA; eRNA, enhancer RNA; sDMR, somatic DMR; IG-DMR, intergenic DMR; ART, assisted reproductive techniques; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; IGN, imprinted gene network; PGC, primordial germ cells; TGC, trophoblast giant cells; BPA, bisphenol A

Genomic imprinting is a process that reversibly marks one of the two homologous loci, chromosome or chromosomal sets during development, resulting in functional non-equivalence of gene expression. The monoallelic expression of an imprinted gene is parent-of-origin dependent. The phenomenon was recognized in mammals due the pioneering work in 1980s on mouse embryonic development and human genetic disorders. Over the years, studies on imprinted genes have contributed immensely to highlighting the role of epigenetic modifications and the epigenetic circuitry during gene expression and development.

1. Discovery of imprinted genes

Both parents, male and female contribute equal genetic material to an offspring in a diploid organism. But it was soon observed that parthenogenesis, the ability to produce offspring from unfertilized eggs, wide-spread in invertebrates was not observed in vertebrates especially mammals. In 1970s several attempts were made to generate mammalian parthenotes. Most of the activated mouse eggs could not develop beyond 25-cell somite stage and died shortly post-implantation (Surani *et al.* 1984; Barton *et al.* 1984). These observations triggered many questions in the field of embryo development such as the role of sperm genome and egg cytoplasm in development of embryos and differentiation of tissues and role of haploid and diploid gene expression in

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embryo development. Several hypotheses such as nuclear or cytoplasmic deficiencies which include non-equivalence of male and female nucleus, homozygosity of lethal genes, lack of extra-genetic contribution by fertilizing sperm, lack of proper environment within the egg cytoplasm that could mimic natural fertilization by sperm were proposed to explain the death of parthenogenetic embryos (Mcgrath and Solter 1984). Reconstitution of zygotes with either two maternal or two paternal pronuclei by McGrath and Solter and independently by Surani *et al.* in 1984 established non-equivalence of the male and female nucleus as a major cause of the non-viability of androgenetic and parthenogenetic embryos (Mcgrath and Solter 1984; Barton *et al.* 1984). The lethality of biparental androgenetic and parthenogenetic embryos dismissed the notion of homozygosity of lethal genes as a major cause of death of gynogenic embryos (Barton *et al.* 1984). The differential functioning of the maternal and paternal chromosome had already been observed in the process of sex determination in two insect species, Sciara and the Mealybugs, as well as for X-chromosome inactivation in extra-embryonic tissues of mice (Crouse 1960; Brown and Nur 1964; Khosla *et al.* 2006). Another well-studied case of differential chromosomal functioning was T^{hp} mice mutant (Leighton *et al.* 1995). T^{hp} mice mutant with a large deletion on chromosome 17 exhibited opposing phenotype depending on the parent from which the mutation is acquired. Inheritance of T^{hp} allele from male parents produced viable embryos whereas T^{hp} allele, when inherited from a female, died *in utero*. Reciprocal nuclear transplantations between the single cell embryo from $T^{hp}/+$ and +/+ females, confirmed the necessity of a functional maternal chromosome 17 (not paternal) for normal embryo development (Leighton *et al.* 1995). Similar to the opposing phenotype of heterozygous T^{hp} mice, defects in the development of androgenetic and gynogenetic embryos were strikingly different. Androgenetic embryos were highly underdeveloped even when trophoblastic tissues were well developed. Gynogenetic embryos developed to 25-cell somite stage and had underdeveloped trophoblastic tissues (Surani *et al.* 1984; Mcgrath and Solter 1984; Barton *et al.* 1984). Similar observations were made in abnormal human pregnancies such as Hydatidiform mole and triploid human embryos. Hydatidiform moles, abnormal human pregnancies which were karyotypically normal and diploid, were found to be of paternal origin and followed developmental abnormality of androgenetic embryos (Jacobs *et al.* 1980). The phenotype of the triploid human embryos depended from which parent the embryo acquired an extra set of the chromosome. Diandric triploids exhibited trophoblastic hyperplasia and malformed fetus. The fetal development of digynic triploid embryos was severely retarded with sparse extra-embryonic tissues (McFadden *et al.* 1993; Tycko 1994). Further studies on disomic mice and pedigree analysis of several human genetic disorders indicated differential functioning of genes or parts of chromosome when inherited through the male and female germline (Cattanach and Kirk 1985; Spence *et al.* 1988; Knoll *et al.* 1989; Voss *et al.* 1989; Tycko 1994). *Igf2*, *Igf2r,* and *H19* were the earliest genes discovered to be imprinted in mice (Dechiara *et al.* 1991; Barlow *et al.* 1991; Bartolomei *et al.* 1991). Targeted deletion of genes, positional cloning, nuclease protection assay and *in situ* hybridization experiments on RNA isolated from wild-type and mutant mice, differential display and differential cDNA screen of androgenetic and parthenogenetic embryos, restriction landmark genome scanning, microarray based on SNP etc were used to uncover imprinted genes. As more and more imprinted genes and their functions were discovered, genomic imprinting was recognized as one of the major cause of lethality of uniparental embryos. Currently, 149 mouse and 256 human genes have been discovered to be imprinted.

2. Imprinted gene expression

Imprinted genes are genes that are expressed only from one allele in a parent-of-origin-specific manner (Surani *et al.* 1984). Most of the imprinted genes are found in clusters (Barlow 2011). An imprinted cluster may consist of more than three or four genes and span 1MB and code at least one ncRNA. Most of the genes within the imprinted cluster show monoallelic expression but a few genes might escape the imprinting and are expressed from both the alleles. Sixteen such genomic regions with a cluster of imprinted genes have been identified in the mouse genome (Barlow 2011). A few imprinted genes are not located within these clusters. These are referred to as micro-imprinted loci. Some of these micro-imprinted loci consist of two genes – with one gene located within the intron of the other and are known as intronic-host imprinted loci (Mccole and Oakey 2008). The intronic gene in most cases is imprinted whereas the host gene codes for various transcripts and displays transcript-specific imprinted expression (Mccole and Oakey 2008; Thamban *et al.* 2019).

The functionality of the allele that is expressed depends on whether the allele is recognized by the

transcriptional machinery. The regulation of gene transcription within a locus is dependent on various epigenetic marks present on the chromatin. Hence the imprinting requires that the two alleles be marked differentially to regulate the transcription process. The regulatory elements or regions within an imprinted locus that regulate the monoallelic expression of the loci through its differential DNA methylation, histone modifications, and chromatin organizations is known as Imprint Control Regions (ICRs) (Bartolomei and Tilghman 1999; Ideraabdullah *et al.* 2008; Barlow 2011). The differential epigenetic modifications present on the two alleles of an imprinted act in *cis* and renders one of the allele transcriptionally active and the other silent (Bartolomei and Tilghman 1999; Ideraabdullah *et al.* 2008; Barlow 2011).

2.1 *Epigenetic modifications within imprinted genes: the allele-specific imprints*

Other than its ability to regulate transcription, the imprint that distinguishes the two alleles of an imprinted gene should be faithfully replicated as the cells undergo division. Another characteristic of imprint mark is that the mark should be established on the maternal and paternal allele when the paternal and maternal genomes are separate from each. These marks must be erased and new marks put on in the developing gametes depending on the gender of the organism (figure 1).

2.1.1 *DNA methylation:* DNA methylation was the first epigenetic modification to be correlated with parent-of-origin expression of imprinted gene (Reik *et al.* 1987; Sapienza *et al.* 1987). DNA methylation at various *cis*-elements such as promoters, silencers, enhancers, and insulators has a profound effect on transcription. One of the well-studied imprinted loci *H19/Igf2* locus consists of a lncRNA that is transcribed from the maternal allele and the *Igf2* protein-coding gene, which is transcribed from the paternal allele (Ideraabdullah *et al.* 2008). The ICR of the locus is present 2 kb upstream of the start of *H19* transcription and 80 kb downstream of *Igf2* (Thorvaldsen *et al.* 1998). The ICR was found to be an insulator and on the unmethylated maternal allele it bound to CTCF protein blocking the interaction of downstream enhancers with *Igf2* promoters (Kaffer *et al.* 2000; Szabo *et al.* 2004). The downstream enhancer interacts with the H19 promoter and results in transcription of *H19* lncRNA from the maternal allele (Kaffer *et al.* 2000; Szabo *et al.* 2004). CTCF is unable to bind to the ICR on the paternal allele when it is methylated and downstream enhancers then are able to interact with the *Igf2* promoter and activate its transcription whereas *H19* transcription is repressed (Kaffer *et al.* 2000; Szabo *et al.* 2004).

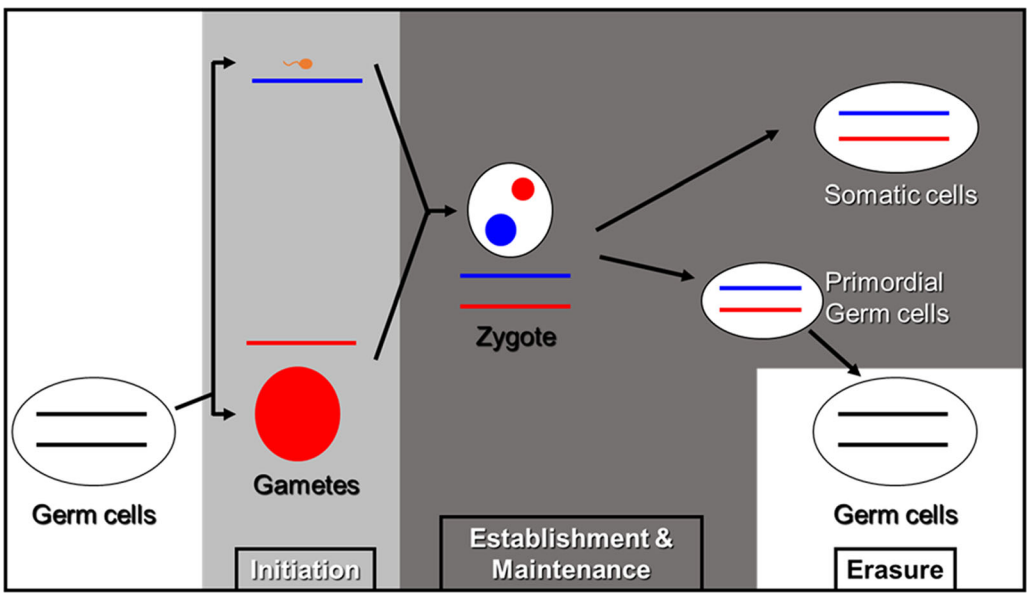

Figure 1. During development, paternal imprints (blue chromosome) and maternal imprints (red chromosome) are established in a sex-specific mode in the mature germ line cells. Once founded, these imprints are maintained in the course of post fertilization global DNA methylation changes triggered by demethylation of the paternal and maternal genomes. These imprints are retained throughout in the somatic cells. However, in primordial germ cells (PGCs), the imprints undergo erasure and are reset for the next generation.

DNA methylation has the ability to regulate transcription and can be faithfully replicated as the cells undergo division. DNA methylation dynamics during germ cell development ensures the erasure and re-establishment of DNA methylation in paternal and maternal genome separately. Thus DNA methylation fulfills all criteria to be the "imprint mark" (Barlow 2011).

Role of DNA methylation as imprint marks was established through transgene studies. Further studies in mutant mice confirmed this notion. *Dnmt1* knockout mice exhibited impaired imprinting of *Igf2r*, *Igf2* and *H19* expression (Li *et al.* 1993). Homozygous mutant *Dnmt3l* females gave birth to heterozygous progeny that were devoid of maternal imprints and thus resulted in biallelic expression of imprinted genes (Bourc'his *et al.* 2001). Studies in mutant mice showed *Dnmt3l* and *Dnmt3a* cooperatively establish methylation marks (Hata *et al.* 2002). The differential DNA methylation established at the time of gametogenesis on the parental alleles is termed as gDMR (germline-DMR) or primary DMRs (Barlow 2011; Kelsey *et al.* 2013). When these gDMRs withstand the demethylation wave at the early embryonic stage and are faithfully replicated in the somatic cells, it can act as imprint control mark (Kelsey *et al.* 2013). Targeted deletions of several gDMRs resulted in the loss of imprinting (Thorvaldsen *et al.* 1998; Wutz and Barlow 1998; Fitzpatrick *et al.* 2002; Lin *et al.* 2003; Williamson *et al.* 2006; Kim *et al.* 2012). Most of these gDMRs were found to act as ICR. 23 ICRs are methylated on the maternal allele (apart from 11 putative maternal ICR) and 4 on the paternal allele (Wang *et al.* 2014; Stewart *et al.* 2016). Sometimes imprinted loci can contain two gDMRs as in the case of *Gnas* and *Pws*.

The timeline and acquisition of DNA methylation at male and female differ considerably. In line with the above observation, imprints are established prenatally in prospermatogonia whereas, in female gametes, imprint establishment occurs after birth in the growing oocyte as in *de novo* methylation of other regions (Stewart *et al.* 2016).Before imprint acquisition, the previous imprint marks have to be deleted and new imprint marks established according to the gender of the embryo. The imprint erasure takes place at the second wave of PGC demethylation and involves TET1 and TET2. The time of imprint erasure differs from ICR to ICR and occurs within the window of E10.5 –E12.5 dpc. Paternal gDMRs are completely established by E17.5 dpc and is a pre-meiotic event that has to be faithfully replicated as male gametes undergo mitotic and meiotic divisions. All of the maternal gDMRs identified are CpG rich promoters and found in intragenic regions. The maternal gDMRs are established post-meiosis and methylation proceeds with the growth of the oocyte with no further cell divisions. All gDMRs are not established simultaneously but over a period of time as *de novo* methylation begins and proceeds in the germlines. Dnmt3a along with Dnmt3l is required for imprint establishment at both the paternal and maternal allele. Only ICR to be methylated by Dnmt3b is the *Rasgrf1* DMR.

It has now been concluded that there is no specific imprinting machinery involved in establishing gDMRs but rather gDMRs are established as part of universal DNA methylation system. After fertilization, both paternal and maternal genome undergoes active and passive DNA demethylation. Most of the DNA methylation acquired by the gametes is erased at this stage except for those on imprinted loci. Thus imprinting seems to be a consequence of protection from DNA demethylation wave at the early embryonic stage (Seisenberger *et al.* 2013).

2.1.2 *Histone modifications:* Around 147bp of DNA is wrapped twice around the nucleosome octamer composed of H2A, H2B, H3, and H4. Various post-translational modifications of these histone proteins affect the interaction of DNA and nucleosome and can regulate transcription.

Histone modifications play an important role in regulating the transcription of imprinted genes. Rather than imprint establishment, histone modifications are probably involved in the somatic maintenance of imprints (Weaver and Bartolomei 2014). Several imprinted domains consist of allele-specific deposition of histone modifications at the imprint control region as well as at the promoters of the imprinted genes. H3 acetylation, H4 acetylation, H3K4me2, and H3K4me3 are associated with normally active unmethylated allele whereas H3K27me3, H3K9me2 and H3K9me3 are found on inactive methylated allele (Mcewen and Ferguson-Smith 2010). It was found that all the ICR except one, had tri-histone mark consisting of H3K4me3, H3K9me3, and H4K20me3 (Mcewen and Ferguson-Smith 2010).Though H3K27me3 was present on ICRs, but not on all (Mcewen and Ferguson-Smith 2010). H3K27me3 marks were mostly found to be involved with the developmental regulation of imprinted gene expression (Mcewen and Ferguson-Smith 2010).

The imprinting of the *Dlk1–Gtl2* locus is regulated by interactions between DNA methylation and histone modification. *Dlk1–Gtl2* consists of two DMRs- IG-DMR

that controls the imprinted expression on the maternal allele and Gtl2 DMR that regulates imprinting of both parental alleles (Carr *et al.* 2007). Allele-specific histone acetylation was found only on the *Gtl2* DMR on the maternal allele. Insertion /deletion of sequences upstream of *Gtl2* promoter disrupted the imprinted expression concomitant with loss of DNA methylation and gain of paternal histone acetylation at the *Gtl2* DMR (Carr *et al.* 2007). The ICRs of maternally imprinted regions such as *Snrnpn*, *Igf2r*, *U2af1-rs1* genes exhibit allele-specific histone modifications with H3 acetylation and methylation of H3K4 on the unmethylated paternal allele and H3K9me3 enrichment on the methylated maternal allele. Furthermore, MBD proteins such as MeCP2, MBD1 are found to be enriched on the maternal allele of the *U2af1-rs1* gene. These proteins can interact with histone deacetylase complexes (such as NuRD, Sin3A, and Sin3B) and might recruit them to the maternal allele whereas on the paternal allele H3K4methylation prevents such recruitment. G9a histone methyltransferase that methylates H3 at lysine 9 has been implicated in genomic imprinting in placenta and embryonic stem cells (Wagschal *et al.* 2008; Zhang *et al.* 2016). Knockout of G9a in mouse led to impairment of placenta-specific imprinting with a concomitant loss in H3K9me3 and H3k9me2 (Wagschal *et al.* 2008). Knockdown or knockout of G9a in ESCs led to widespread loss of DNA methylation at ICR along with the loss of H3K9me2 marks (Zhang *et al.* 2016). Allele – specific DNA methylation loss in G9a-deficit cells is dependent on TET1/TET2 that also mediates DNA demethylation in PGCs (Zhang *et al.* 2016). More importantly, H3K9me2 marks are protected from TET3 mediated DNA demethylation by its binding to PGC7/Stella. Another protein ZFP57 that binds to methylated DNA recruits SETDB1 and HP1α that ultimately increases H3K9me3 deposition and compaction of chromatin. Methylated ICRs are marked by H3K9me3 as well as H4K20me3 (Pannetier *et al.* 2008). Knockdown of SUV4-20H that methylates H4K20me1 in MEFs led to decrease in H4K20me3 as well as H3K9me3 on the methylated ICRs without affecting its DNA methylation (Pannetier *et al.* 2008). Thus histone modifications can interact with one another to reinforce the silencing of the methylated allele. Methylated ICRs are marked by H3K9me3 as well as H4K20me3 (Pannetier *et al.* 2008). Though H3K9me2/3 are implicated in the maintenance of gDMRs, H3K4me2/3 marks are associated with maternal imprint acquisition (Ciccone *et al.* 2009; Wasson *et al.* 2016). Methylation of H3K4 repels DNMT3A-DNMT3l complex and prevent DNA methylation and hence has to be removed before the acquisition of DNA methylation (Ciccone *et al.* 2009). In line with this hypothesis, it has been observed that KDM1B/LSD2 (histone demethylase) is highly expressed in growing oocytes and its ablation led to the accumulation of H3K4me2/3 and loss of imprint acquisition at several maternal ICR (*Mest*, *Zac1, Impact, Peg3,* and *Snrpn;* (Ciccone *et al.* 2009). Hypomorphic maternal KDM1A (LSD1) led to partial perinatal lethality and disruption of genomic imprinting and decreased DNA methylation at ICR and altered transcription of imprinted genes (Wasson *et al.* 2016). Thus histone methylation at ICR plays a critical role on both imprint establishment as well as imprint maintenance.

Transcription of imprinted genes is not always affected by the histone modifications at the ICRs. Histone modifications at the promoters of the imprinted gene also affect its transcription. In case of *Igf2-H19* locus, H4 hyperacetylation (H4K8Ac, H4K16Ac, H4K12Ac, and H4K5Ac) was found to be enriched on the active promoters of the *H19* and *Igf2* genes but differential H4 hyperacetylation was not observed on its ICR. But trichostatin A treatment of the fibroblast cells led to decreased expression of *H19* with a concomitant change of H4 acetylation level at its ICR without affecting the DNA methylation levels in the same region. At *Igf2r* imprinted locus, H4 hyperacetylation was associated only with active promoters. Trichostatin A treatment of the fibroblast cells, induced partial relaxation of the imprinted expression along with decreased DNA methylation at the promoters. *Grb10*, a tissue-specific imprinted gene with promoter-specific expression is maternally expressed only from the major promoter in most tissues however, in the brain, *Grb10* is paternally expressed from a promoter specific to the brain (Yamasaki-Ishizaki *et al.* 2007; Sanz *et al.* 2008). The major type promoter is biallelically hypomethylated regardless of its transcription status whereas the brain-specific promoter is a DMR and maintains the methylated status in the brain (Yamasaki-Ishizaki *et al.* 2007; Sanz *et al.* 2008). Histone modification analysis at the locus revealed the transcription at the major type promoter was controlled by H3K27me3 marks (Yamasaki-Ishizaki *et al.* 2007). Brain-specific promoter carries bivalent mark (H3K4me2 and H3K27me3) in the embryos that are resolved only in the brain during development (Sanz *et al.* 2008). Moreover, a transcriptionally silent allele of maternal ICRs is enriched for bivalent marks (Maupetit-Méhouas *et al.* 2016).

A recent paper has established the role of H3K27me3 in DNA methylation-independent genomic imprinting (Inoue *et al.* 2017b). 76 candidate genes were identified to be imprinted by maternal H3K27me3 several of which are involved in placental development

(Inoue *et al.* 2017b). These genes are characterized by allele-specific DNase I hypersensitivity site and biallelic expression upon KDM6B (demethylates H3K27me3) knockdown in embryos (Inoue *et al.* 2017b). These genes are found to be imprinted transiently in pre-implantation embryo, with only a few genes maintaining imprinted expression in post-implantation embryo and placenta (Inoue *et al.* 2017b).

2.1.3 *Non-coding RNA:* As mentioned earlier most of the imprinted genes are found to be clustered together and can span 80–3700 kb of DNA sequences. The most common feature of such imprinted clusters is presence of at least one lncRNA. This lncRNAs are either antisense-lncRNA or intergenic lncRNA and are always expressed from the allele on which the protein-coding gene is repressed (Barlow 2011). Mostly the promoters of antisense lncRNA within an imprinted locus are a gDMR (methylated on the maternal allele) and ICR of the imprinted loci (Barlow 2011). Methylation of the antisense lncRNA promoter represses its expression whereas the protein-coding gene within the locus is expressed. When unmethylated, the promoter of ncRNA is active and there is repression of the protein-coding genes. *Igf2r, Kcnq1, Gnas, Pws* are well defined imprinted locus with maternal ICR at the promoter of antisense lncRNA (Thakur *et al.* 2004; Williamson *et al.* 2006; Nagano *et al.* 2008; Barlow 2011). When the ICRs of these genes are deleted from the allele on which it is unmethylated, it leads to biallelic expression of the protein-coding genes within the imprinted loci. Given below are few examples by which ncRNA are involved in the establishment of ICR and transcription fine-tuning of imprinted loci. Apart from lnc RNA, enhancer RNA (eRNA) and piRNA were also found to be involved in imprint establishment and maintenance.

Igf2r imprinted loci codes for a 108kb *Airn* lncRNA that is paternally expressed and three other maternally expressed protein-coding genes (*Igf2r*, *Slc22a2,* and *Slc22a3*) (Nagano *et al.* 2008; Latos *et al.* 2012). *Airn* lncRNA is transcribed antisense to *Igf2r* and represses all three protein-coding genes (Nagano *et al.* 2008; Latos *et al.* 2012). *Airn* lncRNA transcripts overlap with the *Igf2r* promoter and prevent RNA polII recruitment (Latos *et al.* 2012). *Slc22a3* promoter is silenced by *Airn* lncRNA by recruiting G9a and subsequent enrichment of H3K9me3 (Nagano *et al.* 2008).

Kcnq1/Cdkn1c imprinted locus contains 10–12 imprinted genes and is located on the distal end of chromosome 7. Some of the protein-coding genes are ubiquitously expressed whereas some expressed only in placenta. All the genes in this locus that code for proteins are expressed from the maternal allele. *Kcnq1ot1,* the only lncRNA in this locus, is transcribed from the paternal allele. The promoter of *Kcnq1ot1* also known as KvDMR1 was identified as the ICR of *Kcnq1/Cdkn1c* imprinted locus and is methylated on the maternal allele (Mancini-DiNardo *et al.* 2003; Cerrato *et al.* 2005). The bidirectional silencing property of KvDMR1 was shown to be regulated by *Kcnq1ot1* (Thakur *et al.* 2004). *Kcnq1ot1*establishes lineage-specific transcriptional silencing by recruiting G9a and PRC2 complex to the paternal allele in placenta (Pandey *et al.* 2008). *Kcnq1ot1* lncRNA contain an 890bp region that interacts with *Dnmt1* and helps in the maintenance of sDMRs at *Kcnq1/Cdkn1c* imprinted loci without affecting the histone modifications (Mohammad *et al.* 2010).

Dlk1-Dio3 locus consists of three paternally expressed protein-coding genes, *Dlk1, Dio3* and *Rtl1/Mart1* and several maternally expressed non-protein coding RNA including miRNAs and C/D small nucleolar RNA gene (Edwards *et al.* 2008). The ICR of the *Dlk1-Dio3* locus has been identified as an intergenic differentially methylated region (IG-DMR) located 75bp downstream of *Dlk1* (Luo *et al.* 2016). The IG-DMR is methylated on the paternal allele and its deletion when inherited from the mother results in maternal to paternal epigenetic switching (Luo *et al.* 2016). The IG-DMR has been identified as an enhancer region capable of transcribing bidirectional eRNA (Kota *et al.* 2014). The IG-DMR includes enhancer marks such as H3K4me2 and H3K27ac and DNaseI hypersensitivity site on the active maternal allele (Kota *et al.* 2014). The bidirectional eRNA was transcribed from the maternal allele in ESCs and neuronal cells (Kota *et al.* 2014). The IG-DMR ncRNA transcription from the maternal allele was linked to early DNA replication of the maternal allele as well as subnuclear localization of the same (Kota *et al.* 2014). The IG-DMR ncRNA was found to act in *cis* and shRNA knockdown of the same led to the loss of IG-DMR enhancer activity and aberrant DNA methylation and H3K9me3 marks (Kota *et al.* 2014).

Rasgrf1 locus comprises of protein-coding gene *Rasgrf1* and several ncRNA like A19 expressed predominantly from the paternal allele (Yoon *et al.* 2002; Ratajczak *et al.* 2011; Watanabe *et al.* 2011). *Rasgrf1* is expressed exclusively from the paternal allele in neonatal brain whereas in other organs *Rasgrf1* expression is biallelic but predominantly from the paternal allele (Yoon *et al.* 2002). The ICR of *Rasgrf1* constitutes a binary switch 30kb upstream of the

Rasgrf1 TSS, which includes a repeated sequence element of 41-mer repeated 40 times and upstream DMR methylated on the paternal allele (Yoon *et al.* 2002, 2005). Methylation of the upstream DMR is controlled by the 41mer repeat unit (Yoon *et al.* 2002). Repeat sequence, when deleted from the paternal allele, led to the loss of DNA methylation as well as expression of *Rasgrf1* (Yoon *et al.* 2002). The DMR was found to be an enhancer blocker that binds to CTCF on the unmethylated maternal allele and thus repress the expression of *Rasgrf1* (Yoon *et al.* 2005). Moreover, *Rasgrf1* is the only imprinted known so far that need DNMT3B for imprint establishment (Watanabe *et al.* 2011). Many piRNAs derived from chromosome 7 was targeted to ncRNA(pit-RNA) derived from the retrotransposon sequence RMER4B, mapped upstream of the direct repeat (Watanabe *et al.* 2011). The transcription of the pit-RNA is initiated within the direct repeat sequence (Watanabe *et al.* 2011). The pit-RNA is targeted by the piRNA derived from chromosome 7, which then recruits DNA methyltransferase complex to the DMR to methylate the *Rasgrf1* DMR (Watanabe *et al.* 2011).

Thus various epigenetic marks such as DNA methylation, Histone modifications, and ncRNA are involved in the establishment as well as maintenance of imprint marks or ICR at imprinted loci. These marks either independently or by recruiting each other fine-tune the expression of imprinted genes.

3. Role of genomic imprinting in development

Assisted reproductive techniques (ART) including ICSI (Intracytoplasmic sperm injection) and IVF (*In vitro* fertilization) have helped in the treatment of infertile people. However, there is an increased realization that many children born using ART have genomic imprinting disorders. Imprint establishment occurs in the gametes and these imprints are faithfully maintained after fertilization. Imprint establishment and maintenance being an epigenetic process is vulnerable and hence can be influenced by the external environment as any other epigenetic process. Since the process of ART includes several procedures like *in vitro* culturing, cryopreservation etc., it has the potential to change the environmental cues for the developing embryo and hence can influence the canonical establishment and maintenance of genomic imprints. The problems associated with ART emphasize the role of imprinted genes in the development of the embryo especially during earlt embryogenesis and placental development. Therefore, below we have explored the role of imprinted genes in fetal and placental development.

3.1 *Role of genomic imprinting in fetoplacental growth and development*

Several experimental pieces of evidence point out to the importance of imprinted genes in fetoplacental development regulating placenta implantation, growth, and embryogenesis (Lambertini *et al.* 2012).

Many imprinted genes have been associated with fetal-growth-promoting pathway and fetal-growth restricting pathways (table 1). Major imprinted genes involved in fetal growth-promoting pathway include *Igf2, Igf2r*, and *Dlk1*, whereas major imprinted gene involved in fetal growth-restricting pathway involve *Grb10, Cdkn1c* (Cassidy and Charalambous 2018). Table 1 gives a list of imprinted genes involved in fetal developmental pathways. Apart from individual imprinted genes, an imprinted gene network (IGN) consisting of a group of imprinted genes that influence the expression of each other is shown to affect fetal development. *Zac1* is a zinc finger transcription factor that induces apoptosis and cell-cycle arrest. *Zac1* binds to the H19/Igf2 enhancer and alter its expression as well as alter the expression of *Cdkn1c,* and *Dlk1* involved in IGN (Varrault *et al.* 2006). *Zac1* was found to target 22% of genes that make up IGN and coordinates regulation of a subset of IGN genes and extracellular matrix composition (Varrault *et al.* 2017). *H19* has been hypothesized as trans-factor that fine-tune IGN (Gabory *et al.* 2009). Apart from the direct effect of these imprinted genes in the growth and development of the fetus, genomic imprinting in placenta also plays an important role in controlling fetal development.

The success of mammalian reproduction depends on specialized organ called placenta that mediates nutrient transfer, thermos-regulation, waste elimination and gas exchange between the mother and fetus (Fowden *et al.* 2011). All eutherian mammals rely on chorioallantoic placenta derived from the trophoblast lineage (John and Hemberger 2012; Rai and Cross 2014). Placenta also prepares the maternal physiology for changes that allocates and increases nutrient supply to offspring both during pregnancy and immediately after birth (John 2017). These changes in maternal physiology are mediated partly by placental hormones: placental prolactin (in mice and humans) and placental growth hormone (in humans) (John 2017). Placental lactogen

Table 1. Imprinted genes and function in fetal development

Imprinted gene	Biallelic expression phenotype	Loss of expression phenotype	Associated Signaling pathway	References
Igf2	Embryonic overgrowth	Growth restriction	The rate of cellular proliferation that increases total cell number	Dechiara *et al.* (1991); Ferguson-Smith *et al.* (1991); Leighton *et al.* (1995)
Igf2r	Viable	Overgrowth generalized organomegaly, kinky tail, postaxial polydactyly, heart abnormalities, and edema die perinatally	Turnover of *Igf2* by receptor-mediated endocytosis	Ludwig *et al.* (1996)
Grb10	Significant undergrowth	Overgrowth	Insulin signaling	
H19	Postnatal growth reduction	Overgrowth	The regulation of several genes of the IGN	Gabory *et al.* (2009)
Peg1		Embryonic growth retardation and behavioral changes in maternal mice decreased reproductive fitness	Maternal behavior	Gabory *et al.* (2009)
Cdkn1c	Embryonic growth retardation reduction in the expression of embryonic growth factor, *Igf1*	11% heavier embryo a two-fold increase in *Igf1*	Regulate cell proliferation	Andrews *et al.* (2007)
Zac1		Intrauterine growth restriction and neonatal lethality	Regulates expression of Cdkn1c and Dlk1, and it directly regulates the H19/Igf2 locus through binding of its shared enhancer	Varrault *et al.* (2006, 2017)
Dlk1	Overgrowth	Growth retardation, accelerated adiposity, eyelid and skeletal deformations	Prevents premature Notch-dependent differentiation, Soluble DLK1 acts as an inhibitor of adipogenesis	Falix *et al.* (2013); Cleaton *et al.* (2016)

plays an important role in stimulating mammary glands for milk production as well as triggering maternal care (John 2017). The mice placenta can be divided into three major layers, with the outermost maternal layer of decidua basalis containing glycogen cells, secondary parietal trophoblast giant cells (TGCs), a single layer of cells with giant nuclei, a junctional zone formed of glycogen cells and spongiotrophoblast with endocrine functions and the labyrinth zone consisting of two types of syncytiotrophoblast cells that are important for nutrient and gas supply and form the fetal-maternal interface (John and Hemberger 2012; Rai and Cross 2014).

One of the most interesting facts is the presence of genomic imprinting only in placental mammals (Cassidy and Charalambous 2018). Several genes have been found to be specifically imprinted only in the placenta (table 2, Cassidy and Charalambous 2018). Expression of genes from placenta-specific promoter results in placenta-specific mRNA splice variant. Imprinting status of various genes was found to be conserved between species even though spatiotemporal expression pattern may vary with species (Cassidy and Charalambous 2018). Genomic imprinting in the placenta is regulated developmentally and is highly sensitive to external environmental cues (Cassidy and Charalambous 2018). Abnormal placental weights were observed in human infants with imprinting disorders such as Beckwith-Weidemann and Silver Russell syndromes (Õunap 2016). Targeted deletion of imprinted genes, uniparental duplications, loss of imprinting induced either by deletion of ICR or by administration of 5-azacytidine resulted in small placentae with abnormalities in proliferation, apoptosis and trophoblast differentiation (Fowden *et al.* 2011). Changes in dosage of imprinted genes both overexpression as well as loss of expression led to gross morphological changes including zonal

Table 2. Imprinted genes and function in placental development

Imprinted gene	Knockout phenotype	References
Peg10	Early placental development	Ono *et al.* (2006)
Igf2	Decreased labyrinth size Decreased trophoblast surface area surface Decreased glycogen cells Altered placental efficiency Poor passive permeability Slc38a2, System XAG and System Y+ amino acid transporter is down regulated	Matthews *et al.* (1999); Constância *et al.* (2002); Sibley *et al.* (2004); Constancia *et al.* (2005)
IGF2 P0	Reduced placental weight Reduction in passive diffusion Affects small, neutral amino acids via System A Transporters	Constância *et al.* (2002); Sibley *et al.* (2004); Angiolini *et al.* (2006)
Grb10	Increase in labyrinth size and the surface area for exchange Altered placental efficiency	Charalambous *et al.* (2010)
Aquaporin	Vascular branching density	Guo *et al.* (2016)
Mash2	Early placental development	Guo *et al.* (2016)
Phlda2	Absolute increases in labyrinthine Larger spongiotrophoblast 2-fold increase in expression of the placental lactogens Altered placental efficiency	Tunster *et al.* (2010, 2016)
Dkl1-Dio3	ltered placental efficiency	Prats-Puig *et al.* (2017)
H19	Absolute increases in labyrinthine trophoblast Altered placental efficiency Poor passive permeability Slc38a2 is down regulated	Ying *et al.* (2010); Bourque *et al.* (2010); Koukoura *et al.* (2011); Gao *et al.* (2012)
Peg1	Growth restriction of the placenta Impaired angiogenesis	Mayer *et al.* (2000)
Rtl1	Fetal vascular abnormalities Impaired basement membrane	Sekita *et al.* (2008)
Cdknlc/ p57Kip2	Increased spongiotrophoblast Decreased labyrinthine trophoblast	Takahashi (2000)
Peg3	Growth restriction of the placenta Changes in the expression of a number of placental lactogens	Li (1999)
Ascl2	Spogiotrophoblast development	Li (1999)
Slc22a3	Inhibition of Monoamine transfer	Zwart *et al.* (2001)
Sfmbt2 miRNA	Severely impaired spongiotrophoblast layer,	Inoue *et al.* (2017a)
Sfmbt2	Reduction of all trophoblast cell types	Miri *et al.* (2013)
Kcnq1	Trophoblast giant cell (TGC) expansion	Koppes *et al.* (2015)

disorganization, changes in proportions of junctional zone and labyrinth zone, number of glycogen cells and trophoblast cells, underdevelopment of spongiotrophoblast cells, barrier thickness and vascularity of labyrinth zone and altered placental efficiency measured as the ratio of fetal to placental weight (Fowden *et al.* 2011; John 2017; Cassidy and Charalambous 2018). Imprinting defects that affect spongiotrophoblast and parietal TGCs can interfere with endocrine functioning of the placenta (John 2017). Changes in placenta morphology might or might not affect nutrient uptake. Aberrant expression of the certain imprinted gene also affects glucose transporters, System A amino acid transporters and hence nutrient uptake by the fetus (John 2017). Table 2 provides a list of imprinted genes and its role in placental development and function. Disrupted imprinted gene expression can also affect fetal growth.

Aberrant expression of imprinted genes within placenta can affect the fetal development and behavior. A

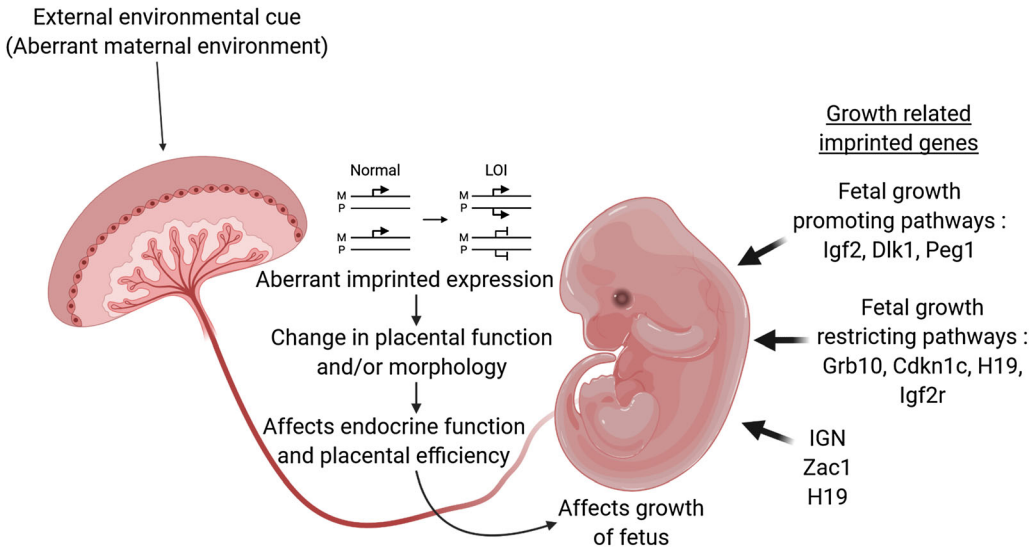

Figure 2. Imprinted genes can directly influence the fetal development as several imprinted genes are either a part of fetal growth promoting or growth restricting pathways as well as a part of the imprinted gene network. Aberrant maternal environment profoundly effect the expression of imprinted genes in the placenta in due course leading to changes in placental function and/or morphology and thereby altering placenta efficiency and endocrine function in turn affecting the fetal development. Aberrant maternal environment leading to loss of imprinting (LOI) can cause abnormal expression of the imprinted gene from the paternal copy (P) or repression of the normally expressed maternal copy (M) as indicated by the raised arrows.

study conducted in 677 term human pregnancy, found 2-fold increased expression 9 imprinted genes (*BLCAP, DLK1, H19, IGF2, MEG3, MEST, NNAT, NDN,* and *PLAGL1*) in placenta to be positively correlated to the Large for Gestational Age (LGA) status of fetus (Kappil *et al.* 2015). A study by Green *et al*. reported 10 imprinted genes (*DLX5, DHCR24, VTRNA2-1, PHLDA2, NPAP1, FAM50B, GNAS-AS1, PAX8-AS1, SHANK2,* and *COPG2IT1*) associated with infant neurobehavioral development in humans (Green *et al.* 2015). One of the Rhode Island Child Health Study (RICHS) identified two clusters of imprinted genes deregulated in human placenta that affect the growth of fetus measured by birth weight, newborn head circumference and size for gestational age. The first cluster of imprinted genes involved in cell growth and tissue development and the second cluster in coordinating theses process (Lambertini *et al.* 2012).

Importance of imprinted genes in placental development and in effect the development of the fetus is underlined by the fact that imprinting status is more sensitive to early environmental cues in placenta than in fetus (Hamada *et al.* 2016). It was found that many of the transient maternal gDMRs lost in embryonic tissues after implantation persisted in human placenta and correlated with imprinted gene expression indicating that the germline DNA methylation is incompletely erased in the human placenta (Hamada *et al.* 2016). Exposure of mother to endocrine disruptors such as BPA and phthalates, residential air pollutants, alcohol consumption resulted in imprinting defects in placenta (Kingsley *et al.* 2017; Strakovsky and Schantz 2018; Carter *et al.* 2018).

Imprinted genes can thus control fetal development directly through various growth- promoting or growth-restricting pathway as well as by modulating the expression of other gene involved in development and differentiation. Fetal development is also affected by the efficiency of placenta which expresses a lot of imprinted genes whose expression patterns are much more sensitive to early environmental cues. Thus proper imprinting in the placenta is not only vital for fetal development but acts as a mediator that can pass on the effects of the early maternal environment to offspring (figure 2).

3.2 *Role of genomic imprinting in the brain and neuronal development*

Differential role of parental genes in brain development was first observed with gynogenic (Gg)/parthenogenetic (Pg) and androgenetic (Ag) mouse chimeras. Ag chimeras have a smaller brain size in spite of heavier body weight. Gg/Pg chimeras have enhanced brain development relative to smaller body weight

Table 3. Imprinted genes and function in neuronal and brain development

Imprinted gene	Function in neuronal and brain development	References
Zac1	Induce expression of *Cdkn1c* and promote NSC cell cycle arrest Promotes differentiation of GABAergic interneurons and Golgi cells	Valante *et al.* (2005); Chung *et al.* (2011)
Igf2	Self-renewal of neuroepithelial progenitor cells and NSCs Memory consolidation and retrieval	Lehtinen *et al.* (2011); Ouchi *et al.* (2013); Ferrón *et al.* (2015)
Ndn	Decreased proliferation of Intermediate Progenitor Cell Inhibit the expression of *Cdkn1c* Protection of neurons by promoting mitochondrial biogenesis, protection of embryonic motoneurons and sensory neurons from apoptosis Proper functioning of the cortical GABAergic system and gonadotropin-releasing hormone (GnRH) neurons Neuronal migration – tangential migration of neocortical interneurons from basal forebrain, migration of serotonin (5-HT) neuronal precursors and expression of 5-HT Transporter (SERT/Slc6a4) ultimately leading to respiratory disease Control LepR sorting and degradation in hypothalamic pro-opiomelanocortin neurons implicated in feeding behavior and obesity phenotype Modulates thyroid axis through acetylation of *Foxo1* in hypothalamic arcuate neurons Axonal outgrowth Prevents apoptosis in cerebellar granule cells Spatial memory	Muscatelli (2000); Lee *et al.* (2005); Kuwako (2005); Andrieu *et al.* (2006); Kurita *et al.* (2006); Tennese *et al.* (2008); Miller *et al.* (2009); Kuwajima *et al.* (2010); Aebischer *et al.* (2011); Hasegawa *et al.* (2012); Minamide *et al.* (2014); Matarazzo *et al.* (2017); Wijesuriya *et al.* (2017)
Dlk1	NSC self-renewal in the adult brain Cerebellar development Survival of midbrain dopaminergic neurons Proper thermoregulation Post-natal development of hypothalamic functions Knockout results in anxiety-like behaviors and increased alcohol consumption The determinant of motor neuron functional diversification	Labialle *et al.* (2008); Jacobs *et al.* (2009); Ferrón *et al.* (2011); Villanueva *et al.* (2012); Hiraoka *et al.* (2013); Müller *et al.* (2014); García-Gutiérrez *et al.* (2018)
Grb10	Survival of midbrain dopaminergic neurons Involved in social interactions (hyper-aggression and social dominance)	Garfield *et al.* (2011); Hoekstra *et al.* (2013); Cowley *et al.* (2014); Plasschaert and Bartolomei (2015)
Ube3a	Survival of midbrain dopaminergic neurons Antiapoptotic role in brain Normal action potentials and synaptic plasticity Proper pre-synaptic and post-synaptic function Synaptic localization of AMPA receptors Promotes long-term-potentiation (synaptic plasticity) Hippocampal-related memory and learning Contextual memory Motor system behavior Sleep induction and REM sleep Proper circadian rhythm Involved in social interactions Involved in anxiety and depression	Mishra and Jana (2008); Heck *et al.* (2008); Yashiro *et al.* (2009); Greer *et al.* (2010); Sato and Stryker (2010); Jiang *et al.* (2010); Smith *et al.* (2011); Wallace *et al.* (2012); Shi *et al.* (2015); Noor *et al.* (2015); Sun *et al.* (2015)
Cdkn1c	Actin polymerization critical for cell motility Promote NSC cell cycle arrest Antiapoptotic role in brain	Joseph *et al.* (2009); Matsumoto *et al.* (2011); Furutachi *et al.* (2013); Peña *et al.* (2014)

Table 3 (continued)

Imprinted gene	Function in neuronal and brain development	References
Kcnk9	Resting potentials and neuronal excitability Induces granule cell death through Proper resting membrane potential Sustained high-frequency firing in cerebellar granule neurons Proper REM and non-REM sleep Proper working memory	Patel and Lazdunski (2004); Musset *et al.* (2006); Linden *et al.* (2007); Pang *et al.* (2009); Bista *et al.* (2015)
MAGEL2	Axonal outgrowth Proper oxytocin level Regulates normal circadian rhythm Involved in social interactions Proper melanocortin and dopamine pathway function Proper POMC neuron activity	Kozlov *et al.* (2007); Schaller *et al.* (2010); Mercer *et al.* (2013); Meziane *et al.* (2015); Pravdivyi *et al.* (2015); Oncul *et al.* (2018); Ates *et al.* (2019)
Pcdhβ20	Dendritic self-avoidance and neuronal wiring	Perez *et al.* (2015)
Pcdhβ12, Pcdhβ10	Dendritic self-avoidance and neuronal wiring	Perez *et al.* (2015)
Peg3	Control of apoptosis in brain Proper thermoregulation Proper circadian rhythm Proper maternal care Proper hypothalamic functions (suckling ability in pups and milk letdown in mums) Maternal care behavior Expression of Oxytocin receptor in the hypothalamus	Li (1999); Johnson *et al.* (2002); Curley *et al.* (2005); Broad *et al.* (2009); Frey *et al.* (2018)
MEG3	Proapoptotic role in the brain Modulates AMPA receptor surface expression in primary Cortical neurons	Yan *et al.* (2017); Liang *et al.* (2018)
Rasgrf1	Differentiation of neurons in mouse dentate gyrus Post-synaptic regulation Contextual memory Proper hypothalamic function especially hypothalamic secretion of growth hormone (GH)-releasing hormone (GHRH) and somatostatin	Brambilla *et al.* (1997); Giese *et al.* (2001); Li (2006); Drake *et al.* (2009); Ye and Carew (2010); D'ISA, Clapcote SJ, Voikar V, Wolfer DP, Giese KP, Brambilla R (2011); D'ISA *et al.* (2011); Darcy *et al.* (2014); Gómez *et al.* (2017)
Gnas	Regulation of Schwann cell proliferation and myelination Proper REM and non-REM sleep Contextual memory and exploration behavior Proper feeding behavior in neonates	Chen *et al.* (2005, 2012); Kuwako (2005); Lassi *et al.* (2012); Deng *et al.* (2017)
Dio3	Inactivates the thyroid hormone T3 thus affecting the feeding behavior of neonates Proper thermoregulation Social interactions (aggression and maternal behavior)	Peeters *et al.* (2013); Martinez *et al.* (2014); Stohn *et al.* (2018)
Snord116	Proper feeding behavior of neonates Proper circadian rhythm Feeding behavior Proper sleep	Ding *et al.* (2008); Duker *et al.* (2010); Zhang *et al.* (2012); Powell *et al.* (2013); Lassi *et al.* (2016); Qi *et al.* (2016)

(Barton *et al.* 1991). Moreover, there was specific and reciprocal localization of the uniparental cells within the chimeric mice. Pg/Gg cells are found to be accumulated in the frontal cortex, striatum, and hippocampus whereas Ag cells are enriched in the hypothalamus and pre-optic area (Keverne *et al.* 1996). Transcriptome sequencing analysis by Gregg *et al* identified more proportion of imprinted genes in the brain particularly the hypothalamus and hindbrain when compared to a control gene set in the cerebral cortex. Most of the imprinted genes were for gene functions such as feeding, maternal care, with feeding and metabolism, and motivational behaviors. It was also found that in the early embryonic development, there was an

enrichment in maternally expressed genes whereas in adult brain regions there was more paternally expressed genes (Gregg *et al.* 2010). These observations imply the developmental regulation of imprinted genes in the brain. Certain imprinted genes such as Dlk1 and Igf2 (imprinted in other tissues) were found to be biallelically expressed in brain implying the importance of transcriptional dosage in neuronal and brain development whereas certain genes such as *Ube3a* is imprinted only in brain (Albrecht *et al.* 1997). The *Grb10* is expressed from the paternal allele in a subset of neurons whereas it is expressed from the maternal allele in other adult mouse tissues. This diversity in allelic bias was also reflected in the transcriptome sequence analysis by Gregg *et al.* There were several genes that display significant bias in parental allele expression rather than absolute silencing of one allele (Gregg *et al.* 2010).

It has been hypothesized that the neocortical expansion in mammalian evolution is influenced by genomic imprinting in neocortex. Imprinted genes are found to influence various neurodevelopmental processes from self- renewal of neural stem cells, to cell proliferation, differentiation as well as neuronal migration, axonal and dendritic outgrowth (table 3). In the adult brain, imprinted genes are found to influence synaptic plasticity through controlling synaptic transmission, action potentials, pre, and post synaptic regulation. Imprinted genes have very complex spatiotemporal gene regulation. This has resulted in having an impact on phenotypes influenced by brain such as learning, memory, energy homeostasis and social behaviors including mother-pup interactions (Perez *et al.* 2016).

4. Closing remarks

This review explores the mechanisms underlying the phenomenon of genomic imprinting and its role during early embryogenesis and placental development. Imprint establishment in gametes and its maintenance in early developing embryo are the hall marks of genomic imprinting and are important for the proper development of the embryo. Incorrect dosage of imprinted genes can have subtle but serious consequences on the growth and development of embryo, its metabolism, and the social behavior of the new born and adult mammals. Importantly and as discussed in this review, the epigenetic marks are established in the germ cells of the parent and passed on to the progeny. The phenomenon of genomic imprinting, thus, is a classic case of intergenerational epigenetic inheritance. Epigenetic modifications are dynamic and are influenced by developmental and environmental cues. Therefore, any aberrant environmental cues (including those from the maternal environment) causing change in the epigenetic imprints in the germ cells would have transgenerational effects. With emphasis these days on the impact of environment changes, studies on genomic imprinting would help us in understanding the mechanisms behind epigenetic inheritance and its role in shaping the evolutionary processes working on the mammalian population in particular and the living organisms in general.

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