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Review

The role of imprinted genes in humans

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ABSTRACT

Genomic imprinting, a process of epigenetic modification which allows the gene to be expressed in a parent-of-origin specific manner, has an essential role in normal growth and development. Imprinting is found predominantly in placental mammals, and has potentially evolved as a mechanism to balance parental resource allocation to the offspring. Therefore, genetic and epigenetic disruptions which alter the specific dosage of imprinted genes can lead to various developmental abnormalities often associated with fetal growth and neurological behaviour. Over the past 20 years since the first imprinted gene was discovered, many different mechanisms have been implicated in this special regulatory mode of gene expression. This review includes a brief summary of the current understanding of the key molecular events taking place during imprint establishment and maintenance in early embryos, and their relationship to epigenetic disruptions seen in imprinting disorders. Genetic and epigenetic causes of eight recognised imprinting disorders including Silver–Russell syndrome (SRS) and Beckwith–Wiedemann syndrome (BWS), and also their association with Assisted reproductive technology (ART) will be discussed. Finally, the role of imprinted genes in fetal growth will be explored by investigating their relationship to a common growth disorder, intrauterine growth restriction (IUGR) and also their potential role in regulating normal growth variation.

Contents

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1. Introduction

In diploid mammalian cells, most autosomal genes are expressed equally from the paternal and maternal alleles, resulting in biallelic expression. There is, however, a small subset of genes that show monoallelic or highly biased expression, according to the parental origin of the allele. This phenomenon is termed genomic imprinting, controlled by epigenetic marks set differently in the parental germline, without changing the DNA sequence.

Although early evidence of parent-of-origin effects was noted almost 40 years ago through studies of insects, plants and mammals, definitive evidence of genomic imprinting in mammals was provided by a set of seminal mouse experiments involving pronuclear transplantation in the early 1980s (McGrath and Solter, 1984; Surani et al., 1984). In these studies, diploid mouse embryos were created with either two female pronuclei (gynogenotes) or two male pronuclei (androgenotes). As neither conceptuses were viable post implantation, these experiments demonstrated that both maternal and paternal genomes are essential for normal embryonic development and that they are not functionally equivalent.

Subsequent observations in mice which were uniparental disomy (UPD) for specific chromosomes or sub-chromosomal regions, created by interbreeding mice heterozygous for known Robertsonian and reciprocal translocations, revealed that the parental origin effect was not prevalent throughout the genomes, but localised to specific chromosomal regions (Cattanach and Kirk, 1985; Searle and Beechey, 1990). Further studies in mice narrowed down the regions containing parent-of-origin effects to clusters of genes, and in some cases to single genes, with the first mouse imprinted gene insulin-like growth factor 2 receptor (*Igf2r*) identified in 1991 (Barlow et al., 1991).

At present, over 100 genes have been confirmed to be imprinted in mice and approximately 50 of these maintain their imprinted status in humans. Although recent transcriptome sequencing studies have reported more than 1000 potential imprinted genes in the mouse brain (Gregg et al., 2010a, b), the vast majority of these findings were not verified by another independent study (Deveale et al., 2012). In addition, other studies using similar approaches identified only 3–6 new putative imprinted genes (Babak et al., 2008; Wang et al., 2008). Thus, the evidence so far suggests that the total number of imprinted genes is likely to be around the initial estimate of a few hundred genes (Barlow, 1995). A regularly updated list of mammalian imprinted genes can be obtained from University of Otago's Catalogue of Parent of Origin Effects (http://igc.otago.ac.nz/) and at the Harwell mouse database (http://www.har.mrc.ac.uk/).

The diploid state confers on organisms increased protection against the effects of any exposure to deleterious mutations and/or epimutations occurring on one allele. Selection for monoallelic expression of imprinted genes, therefore, seems paradoxical and its evolutionary benefits must outbalance the vulnerability associated with functional haploidy. Remarkably, the phenomenon of genomic imprinting is observed predominantly in eutherian mammals (mammals with long-lived placenta), but not in prototherians (egg-laying mammals), birds or reptiles (Hore et al., 2007). Imprinting has also evolved independently in flowering plants where the endosperm has a placenta-like function (Scott and Spielman, 2006). The close association between the acquisition of imprinting and placenta during the course of evolution has led to several hypotheses to explain the reason for the emergence of genomic imprinting. The kinship theory, also commonly referred to as the parental conflict theory (Moore and Haig, 1991), is considered the most widely accepted theory. It predicts that paternally expressed genes are driven to promote fetal growth by extracting maximal resources from the mother, especially in a polygamous population. In contrast, the maternal genome discourages offspring growth by limiting its share of her resources, and ensures her survival and the equal allocation of nutrients among her offspring, both to the common aim of producing the maximum number of viable offspring carrying their genes. Consistently, imprinting is observed to occur predominantly in genes influencing fetal growth, particularly through placental growth, suckling and nutrient metabolism (reviewed in Frost and Moore, 2010; Piedrahita, 2011).

The conflict theory is supported by the example of the prototypical mouse imprinted gene *Igf2* and its receptor *Igf2r*. *Igf2* is a paternally expressed potent growth enhancer, whereas maternally expressed *Igf2r* products suppress growth by mediating the degradation of IGF-II proteins (Scott and Weiss, 2000). Mouse knockouts of these genes exhibited opposite growth phenotypes; *Igf2*-null mice are growth deficient whilst *Igf2r*-null mice show overgrowth phenotypes (Lau et al., 1994). Additionally, consistent with the conflict theory, mice lacking paternally expressed *Peg3* (paternally expressed gene 3) and *Mest* (mesoderm specific transcript) genes result in IUGR (Lefebvre et al., 1998; Li et al., 1999), whereas mice being null for maternally expressed genes *H19* and *Grb10* exhibit fetal overgrowth (Charalambous et al., 2003; Leighton et al., 1995). It is now argued that paternally expressed genes tend to promote fetal growth whereas maternally expressed genes restrict fetal growth.

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2. Mechanisms of genomic imprinting

With the exception of individual sequence polymorphisms which are unrelated to imprinting status, the DNA sequences of the two parental alleles of imprinted genes are identical. Thus, in order to achieve parental specific expression, the homologous chromosomes have to be distinguished by some kind of epigenetic mark. Imprinted gene regions studied so far predominantly show differences in DNA methylation between the parental alleles. A sequence contributing to this epigenetic contrast is known as a differently methylated region (DMR). At imprinted loci, two types of DMR have been described; one of them acquires methylation during gametogenesis (germline DMR) and the other one becomes methylated after fertilisation (somatic DMR), which is dependent on the presence of the germline DMR (Lewis and Reik, 2006).

Imprinted genes tend to be organised in clusters, many of which are under the control of key *cis*-acting loci called imprinting control regions (ICRs), or sometimes imprinting centers (ICs) or imprinting control elements (ICEs). These are normally differentially methylated in the germline (Lewis and Reik, 2006). Some of the germline DMRs have been established as definitive ICRs by targeted deletion experiments in mice, where the appropriate expression of imprinted genes within the cluster relied upon the ICR (Fitzpatrick et al., 2002; Lin et al., 2003; Shiura et al., 2009; Thorvaldsen et al., 1998; Williamson et al., 2006; Wutz et al., 1997; Yang et al., 1998). Although the regulation of imprinted expression is cluster specific, several common features shared by imprinting clusters have been described, including enrichment of CpG sites which are normally

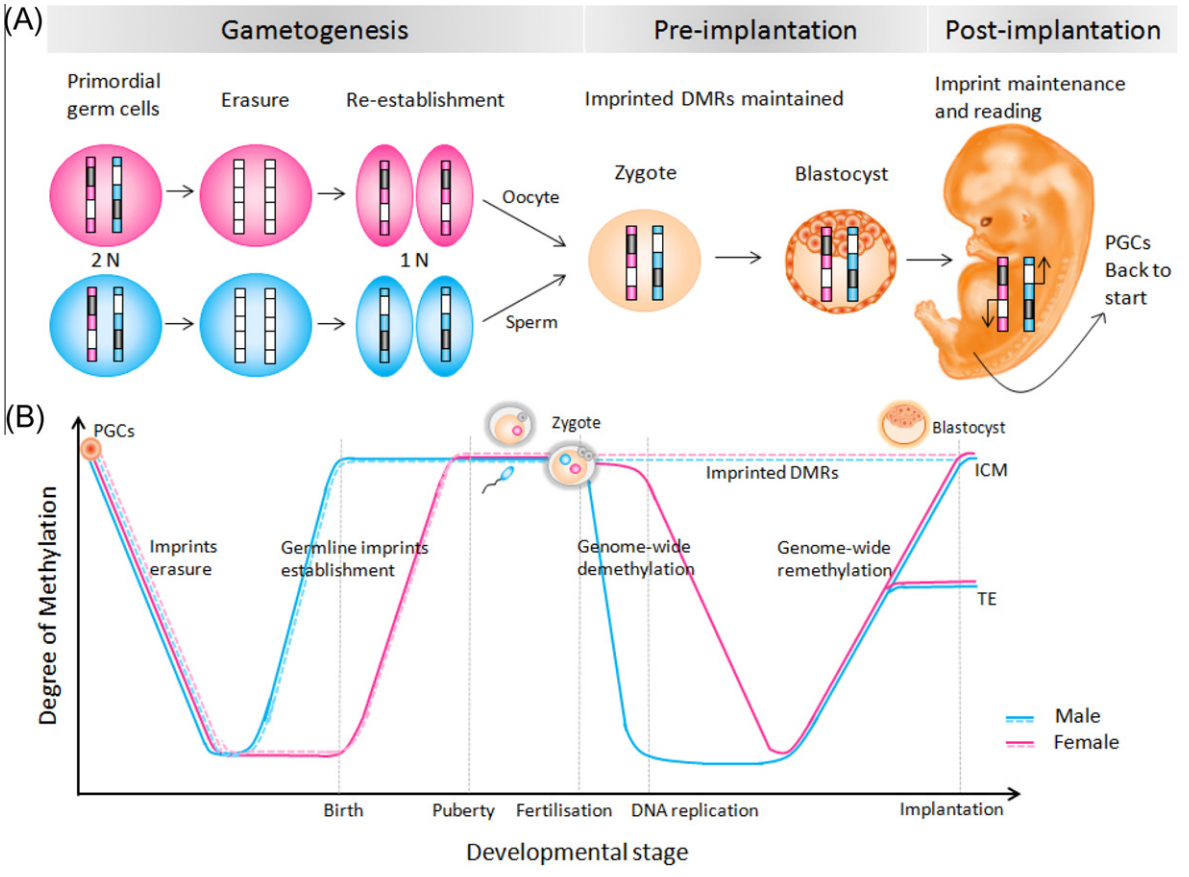

Fig. 1. DNA methylation during gametogenesis and early embryonic development. (A) Methylation imprint erasure, re-establishment and maintenance at the germline differentially methylated regions (gDMRs) during gametogenesis and early embryonic development. Maternal and paternal chromosomes are represented in pink and blue bars, respectively. The black and white filled boxes on the chromosomes indicate the presence or absence of allelic modifications, respectively. The black arrows indicate expression from the unmethylated alleles. (B) Genome-wide and imprint methylation programming during early development (based on mice). The time of the events depicted in the graph corresponds approximately to the events of Fig. 1A. As primordial germ cells (PGCs) of the developing embryo enter the genital ridge, genome-wide (solid lines) demethylation occurs which erases the imprint marks (dashed lines) present on the maternal and paternal chromosomes, and *de novo* methylation follows to establish the new sex-specific imprints during gametogenesis. Following fertilisation, global demethylation occurs. The paternal pronucleus undergoes active demethylation which is completed before the first DNA replication while the maternal chromosome is demethylated by a DNA replication-dependent passive mechanism. The imprint marks established in the parental gametes resist the demethylation and are maintained. Genome-wide remethylation takes place around the time of implantation, and these marks are faithfully propagated to the daughter cells throughout the development of individuals. The inner cell mass (ICM; giving rise to the foetus) have been found to carry higher methylation than the trophectoderm (TE; giving rise to the placenta) (adapted from Dean et al. (2003), Reik and Walter (2001)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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subject to allelic DNA methylation, allelic histone modifications associated with repressive or active chromatin conformation, high concentration of tandem repeat sequence, presence of CTCF and YY1 transcription factor binding sites and non-coding RNA transcriptional units (Kim et al., 2009; Lewis and Reik, 2006; McEwen and Ferguson-Smith, 2010; Neumann et al., 1995; Peters and Robson, 2008).

2.1. The imprinting cycle

The parental allele-specific epigenetic marks are heritable to the daughter cells, but must be reset in each successive generation to establish parental specific imprints. In mammals, two major genome-wide epigenetic reprogramming events take place during gametogenesis and early embryogenesis (Reik et al., 2001). The parental-specific imprints must be 'erased' and new imprints reflecting the sex of the embryo are 'established' during germ cell development. Following fertilisation, these imprint marks are 'maintained' as the cell propagates, except in the germ cells where the imprints are erased and re-established for the next generation (see Fig. 1).

2.1.1. Imprint erasure and establishment in the germline

Genome-wide demethylation occurs as the primordial germ cells (PGCs) of the developing embryo enter the genital ridge, followed by *de novo* DNA methylation to establish the new sex-specific imprints during gametogenesis. In the male germline, the *de novo* methylation at each ICR begins to be established during late fetal development (Hajkova et al., 2008). In contrast, imprint acquisition in the female germline starts postnatally and occurs throughout reproductive life. Maternal specific imprints are laid down as the developing oocyte, arrested at the diplotene stage of meiosis, is recruited into folliculogenesis for further maturation and ovulation (Hiura et al., 2006; Lucifero et al., 2004).

In mammals, three functional DNA (cytosine-5) methyltransferase (DNMT) enzymes have been described, which are DNMT1, DNMT3a and DNMT3b. Both DNMT3a and DNMT3b have been shown to be essential for *de novo* methylation and for mouse development (Okano et al., 1999), with DNMT3b specifically required for methylation of minor satellite repeats at the centromeric regions and DNMT3a for methylation of imprinted loci in conjugation with non-enzymatic cofactor Dnmt3-like protein (DNMT3L) (Hata et al., 2002; Kaneda et al., 2004). However, disruption of the *Dnmt3l* gene in perinatal male germ cells leads to the meiotic failure to establish the *de novo* methylation of retrotransposons. Isolating sufficient material to examine the role of *Dnmt3l* in male germline imprinting is challenging however, and the data remain inconclusive (Bourc'his and Bestor, 2004; Webster et al., 2005).

How DMRs of the imprinting clusters are specifically recognised and targeted for sex-specific acquisition of DNA methylation imprint is still poorly understood. Periodic arrangement of CpGs at distances of eight to ten base pairs has been shown to be enriched at the maternal germline DMRs examined, and has been suggested to provide a favourable environment for methylation by the DNMT3a/3L tetramer complex in the female germline (Jia et al., 2007). The histone modification profile at imprinted loci has been suggested as another instructive signal for DNA methylation machinery. DNMT3L recognises and interacts specifically with the unmethylated histone H3 lysine 4 (H3K4), and can recruit DNMT3a to its target DNA sequences (Ooi et al., 2007). Therefore, H3K4 methylation may give the unmethylated allele of imprinted loci protection from *de novo* methylation by DNMT3a/3L complex (Jia et al., 2007; Ooi et al., 2007). Furthermore, transcription has been suggested to be important for establishment of DNA methylation imprints during oogenesis. At the *Gnas* (guanine nucleotide binding protein, alpha stimulating complex locus) imprinting domain, transcription of the protein-coding *Nesp* (neuroendocrine secretory protein) gene which originates from the furthest upstream promoter and traverses the entire cluster including two downstream maternal germline DMRs, has been shown to be required for normal establishment of DNA methylation at these DMRs (Fig. 2E) (Chotalia et al., 2009). Similar transcripts from different imprinted loci crossing the prospective maternal germline DMRs have also been detected in oocytes. The authors suggest that transcription may create an open chromatin environment to allow access of the DNA methylation complex to the DMRs.

2.1.2. Maintenance of imprinting marks

Upon fertilisation, the egg cytoplasm contains two pronuclei that are epigenetically distinct. The paternal pronucleus rapidly undergoes an active genome-wide demethylation, possibly through a mechanism involving a 5-hydroxymethylcytosine (5hmC) intermediate (reviewed in (Branco et al., 2012), which completes prior to the DNA replication (Reik et al., 2001). In contrast, the maternal genome becomes demethylated by a passive mechanism which depends on the subsequent DNA replications (Reik et al., 2001). However, the parental specific DNA methylation imprints are retained, despite otherwise global demethylation. One potential mechanism for this is through protection by a maternal protein DPPA3 (also known as PGC7 or Stella) (Nakamura et al., 2007).

Around the time of implantation, genome-wide re-methylation occurs (Reik et al., 2001). The methylation marks at imprinted loci are then faithfully maintained by DNMT1, which preferably methylates hemimethylated CpGs (Pradhan et al., 1999). In the pre-implantation embryo, this is carried out by DNMT1o, an isoform of *Dnmt1* expressed from the oocyte-specific promoter which enters the nuclei at the eight-cell stage (Dean and Ferguson-Smith, 2001; Howell et al., 2001), and later by somatic DNMT1, in conjugation with ZFP57 (zinc finger protein 57) (Hirasawa et al., 2008; Li et al., 2008). This basic methylation reprogramming pattern is also conserved in other eutherian mammals such as bovines, rats and pigs, with some variable timing with respect to their developmental stage (Dean et al., 2001), but not in other vertebrates such as zebrafish (Macleod et al., 1999) or *Xenopus* (Stancheva et al., 2002).

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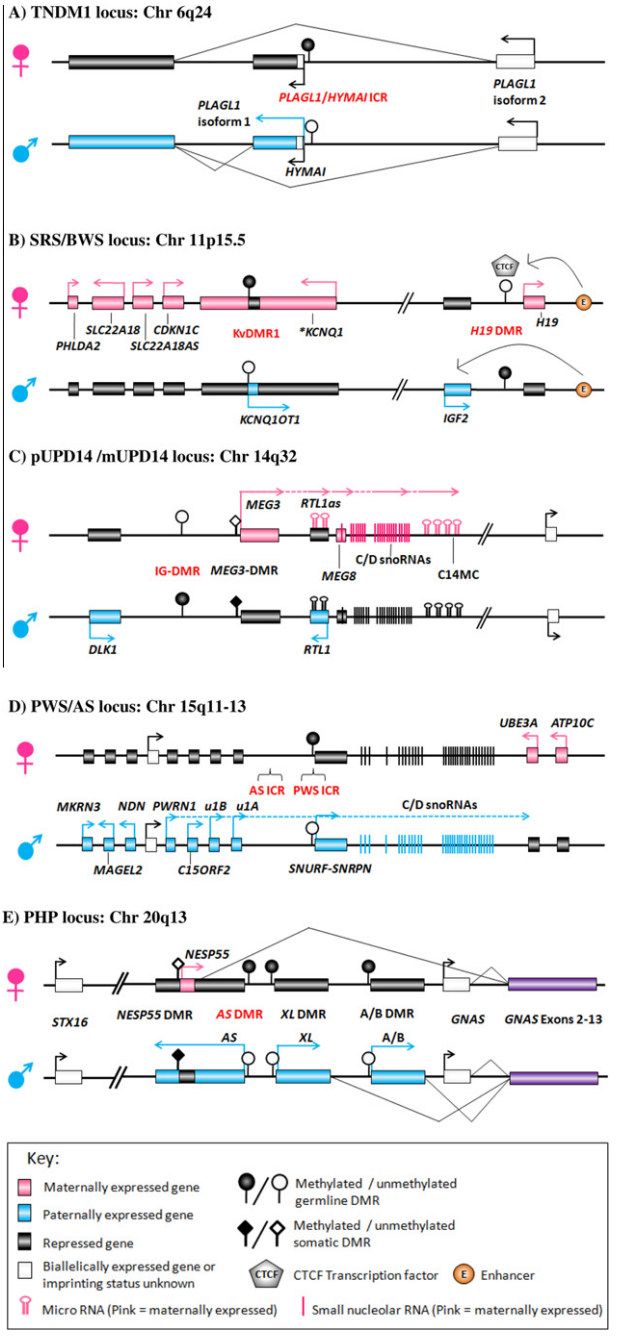

Fig. 2. Human imprinted clusters associated with imprinting disorders. Schematic representations of the human imprinted clusters related to imprinting disorders (A–E; figures not drawn to scale). The DMRs described in red letters have been established as ICRs of each cluster by targeted deletion in mice. Biallelic (black), paternal (blue) and maternal (pink) specific and the direction of transcription are indicated by arrows. Figure orientations: left = centroemric and right = telomeric. (A) *PLAGL1* imprinted cluster implicated in transient neonatal diabetes mellitus 1 (TNDM1). *PLAGL1* isoform 1 is imprinted and expressed from the unmethylated paternal allele. (B) The centromeric *KCNQ1* (potassium voltage-gated channel, KQT-like subfamily, member 1) and the telomeric *IGF2*/*H19* imprinted domains are associated with Silver–Russell syndrome (SRS) and Beckwith–Wiedemann syndrome (BWS). **KCNQ1* shows polymorphic maternal expression in term placenta (Monk et al., 2006). KvDMR1 (potassium voltage-gated channel differentially methylated region 1) located in intron 10 of *KCNQ1* acts dually as an ICR for the *KCNQ1* cluster and a promoter for the paternally expressed ncRNA *KCNQ1OT1* (*KCNQ1* overlapping transcript 1). The CTCF protein binds to the unmethylated *H19* DMR which blocks the access of *IGF2* promoters to the enhancers downstream of *H19* and activates *H19* expression. The methylated *H19* DMR prevents the CTCF from binding, allowing the enhancers to interact with *IGF2* promoters. (C) The *DLK1-DIO3* locus implicated in paternal and maternal uniparental disomy 14 syndromes (pUPD14/mUPD14). Dotted lines indicate the possible extension of the transcripts. (D) The *SNRPN* cluster implicated in Prader–Willi syndrome (PWS) and Angelman syndrome (AS). (E) The *GNAS* locus associated with Pusedohypoparathyroidism (PHP). The first exons of *GNAS*, *A/B*, *GNASXL* and *NESP55* are all spliced onto the *GNAS* downstream exons 2–13 (purple) to produce different transcripts. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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3. Human imprinting disorders

In humans, the physiological importance of genomic imprinting can be demonstrated by the imprinting disorders caused by disruptions or epimutations of imprinted genes. Types of disruptions found in imprinting disorders vary but are mostly associated with altered dosage of imprinted genes, such as UPDs, chromosomal duplication and deletions. Aberrant DNA methylation pattern at ICRs is also a common finding, which could be a defect introduced during gametogenesis resulting in a failure of erasure and re-establishment of new imprints or post-fertilisation due to ineffective imprint maintenance. Imprinting diseases are very rare, but are often severe, indicating that appropriate expressions of this small subset of genes is indispensable for normal human development. The clinical phenotypes of imprinting disorders are diverse, but primarily involve growth or neurological development. Some of the well-characterised imprinting disorders are described in the following paragraphs.

3.1. Prader–Willi syndrome and Angelman syndrome

The first human imprinting disorders to be reported were Prader–Willi syndrome (PWS) [OMIM ID: 176270] and Angelman syndrome (AS) [OMIM ID: 105830], each occurring with an estimated frequency of one in 15,000 to 25,000 live births (Buiting, 2010). PWS is characterised by mild intellectual disability, low birth weight, poor suckling and hypotonia before weaning but followed by voracious appetite, leading to obesity after weaning (Cassidy and Driscoll, 2009). Approximately 70% of PWS patients are found to have *de novo* interstitial deletion of chromosome 15q11-13 on the paternal chromosome and about 25% have maternal UPD of chromosome 15 (mUPD15) (Fig. 2D) (Buiting, 2010). It is not yet clear which genes in this region contribute to PWS; however, paternally expressed *SNORD116* snoRNAs (small nucleolar RNA, C/D box 116 cluster), hosted within the *SNURF*/*SNRPN* (*SNRPN* upstream reading frame/small nuclear ribonucleoprotein polypeptide N) locus, have been suggested to have a prominent role in the aetiology of PWS (de Smith et al., 2009; Ding et al., 2008; Sahoo et al., 2008; Skryabin et al., 2007). The clinical phenotypes of AS include severe intellectual disability, microcephaly, delayed weaning by prolonged suckling period, and frequent laughter and smiling (Buiting, 2010). Chromosomal deletion at 15q11-13 accounts for approximately 70% of AS patients but unlike PWS, the deletion is always on the maternal chromosome. Approximately 2–5% of AS patients have pUPD15, and about 10% have a mutation in the maternally expressed imprinted gene *UBE3A* (ubiquitin protein ligase E3A) (Buiting, 2010). Epimutations in PWS and AS are rare, with a frequency of about 1–3% and 2–4%, respectively, found to have DNA methylation defects throughout the imprinted domain (Buiting et al., 1994; Glenn et al., 1993; Reis et al., 1994). A small fraction of these patients were found to carry microdeletions which defined a bipartite ICR controlling the parental-specific expression of the entire cluster. PWS-ICR, overlapping the *SNURF*/*SNRPN* exon1/promoter region, is differentially methylated in the maternal germline whereas AS-ICR mapping to 35 kb upstream of *SNURF-SNRPN* exon 1, is thought to help establish the maternal imprint on PWS-ICR (Horsthemke and Wagstaff, 2008). The majority of PWS (85%) and AS (92%) patients with an imprinting defect, however, represent primary epimutation and the defective imprinting has been suggested to occur during maternal imprint establishment or imprint maintenance in AS patients whilst failure to erase grandmaternal imprint in the paternal germline may be responsible for these PWS patients (Buiting, 2010).

3.2. Silver–Russell syndrome

Silver–Russell syndrome (SRS) [OMIM ID: 180860] is a disorder characterised by pre- and/or postnatal growth restriction with additional features such as a small triangular shaped face and skeletal asymmetry. The incidence of SRS has been estimated to be from 1 in 3000 to 100,000 (Abu-Amero et al., 2008). Both the genetic and epigenetic aetiologies of SRS have been investigated, revealing its heterogeneous nature. Currently, mUPD7 accounts for 10%, and hypomethylation of the paternally methylated *H19* DMR at chromosome 11p15.5 contributes about 35–65% of SRS cases (reviewed in Abu-Amero et al., 2008, 2010) (Fig. 2B). In addition, SRS patients with *H19* DMR hypomethylation have been reported to exhibit hypo- and hypermethylation at other imprinted loci (multilocus methylation defects, MLMD), suggestive of general defects in establishment or post-fertilisation imprint maintenance (Azzi et al., 2009; Begemann et al., 2011; Kannenberg et al., 2012; Turner et al., 2010). Of the SRS patients with *H19* DMR epimutations, approximately 8% were found to have MLMD by direct investigations of the selected imprinted loci (Azzi et al., 2009; Begemann et al., 2011; Turner et al., 2010), whilst a recent genome-wide study detected MLMD in about 73% of SRS patients with *H19* DMR epimutations (Kannenberg et al., 2012). The latter study also noted the lack of recurrent methylation defect patterns outside the *H19* DMR, suggesting a specific involvement of *IGF2*/*H19* locus in the development of SRS (Kannenberg et al., 2012). Hypomethylation of *H19* DMR leads to deregulation of maternally expressed *H19* and paternally expressed *IGF2* genes, possibly by permitting the CTCF to bind to normally methylated paternal *H19* DMR (see Fig. 2B). This results in reduced *IGF2* expression and potentially growth restriction (Gicquel et al., 2005). However, IGF-II serum levels are not decreased in SRS children with *H19* DMR hypomethylation, although this observation does not exclude the role of IGF-II in the prenatal period (Binder et al., 2006). Two regions within chromosome 7, 7q32 containing *MEST* and 7p12.2-3 containing *GRB10*, have been delineated as candidate areas for SRS, though there have not been any conclusive reports to support this (Abu-Amero et al., 2008; Mergenthaler et al., 2001).

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3.3. Beckwith–Wiedemann syndrome

Chromosome 11p15.5 is also a critical region for Beckwith–Wiedemann syndrome (BWS) [OMIM ID: 130650] which is phenotypically and genotypically opposite to SRS, with an estimated prevalence of approximately one in 13,700 live births (Engstrom et al., 1988; Gicquel et al., 2005; Thorburn et al., 1970). The clinical features of BWS include pre- and/or postnatal overgrowth, placental overgrowth, macroglossia (enlarged tongue) and predisposition to embryonal tumours (e.g. Wilms' tumour) (Choufani et al., 2010). Deregulation of 11p15.5 imprinting region has been associated with about 85% cases of BWS (Weksberg et al., 2005). Around 50% of BWS patients are reported to have hypomethylation at the KvDMR1 (potassium voltage-gated channel differentially methylated region 1), which is the ICR of the centromeric *KCNQ1* imprinting domain at 11p15.5, normally methylated on the maternal germline (Fig. 2B), and 5% are associated with hypermethylation at *H19* DMR, possibly leading to CTCF binding inhibition and reduced *H19* and increased *IGF2* expressions (Fig. 2B). Approximately 22% of BWS patients with KvDMR1 hypomethylation have been shown to exhibit MLMD through investigation of the selected imprinted loci (Azzi et al., 2009; Bliek et al., 2009; Rossignol et al., 2006). Moreover, *NALP2* (NLR family, pyrin domain containing 2) has been suggested to act *in trans* to establish or maintain imprints at KvDMR1, from an observation that the mother of two BWS affected siblings with KvDMR1 hypomethylation was shown to carry homozygous mutation at *NLRP2* (Meyer et al., 2009). Mutations found in *CDKN1C* (cyclin-dependent kinase inhibitor 1C), one of the maternally expressed genes in the *KCNQ1* domain, have been reported for 10% of BWS patients (Choufani et al., 2010). BWS cases are mostly sporadic but approximately 15% are familial, 40% of which are associated with *CDKN1C* mutation. About 20% of BWS cases show pUPD involving both *IGF2*/*H19* and *KCNQ1* clusters (Catchpoole et al., 1997;Choufani et al., 2010), whilst chromosomal rearrangements such as inversions/translocation at the 11p15 locus are rarely observed (<1%) (Weksberg et al., 2005).

3.4. pUPD14/mUPD14

Deregulation of the genes within the *DLK1-MEG3* imprinting cluster on chromosome 14q32 are thought to be responsible for the distinct phenotypes observed in the patients of maternal and paternal UPD14 syndromes (mUPD14 and pUPD14, respectively) (Fig. 2C). Clinical phenotypes of mUPD14 include a pre- and postnatal growth restriction, premature puberty and obesity (Kotzot, 2004). In contrast, pUPD14 is characterised by facial anomaly, small bell-shaped thorax, abdominal wall defects, placentomegaly (enlarged placenta) and polyhydramnios (excessive amniotic fluid) (Kagami et al., 2008). The *DLK1-MEG3* domain harbours two well characterised paternally methylated DMRs; the intergenic (IG)-DMR, one of the very few paternal germline methylated DMRs located between *DLK1* and *MEG3* (Takada et al., 2000; Wylie et al., 2000), and a somatic *MEG3*-DMR, which overlaps the *MEG3* promoter, as well as its first exon and intron (Kagami et al., 2010; Murphy et al., 2003; Rosa et al., 2005). Patients with mUPD14-like and pUPD14-like phenotypes have been reported to have epimutations and microdeletions at 14q32 on the paternal and maternal chromosomes, respectively, suggesting an important contribution for normal pre- and postnatal development from this locus (Kagami et al., 2008, 2010). Observation of patients with pUPD14-like phenotype who carry either microdeletions of the IG-DMR with affected body and placenta, or a *MEG3*-DMR microdeletion with affected body only, suggested that the IG-DMR and *MEG3*-DMR may act as the placenta and the body ICRs, respectively, with the methylation status of the *MEG3*-DMR in the body being controlled by that of IG-DMR (Kagami et al., 2010).

3.5. Transient neonatal diabetes mellitus type 1

Transient neonatal diabetes mellitus type 1 (TNDM1) [OMIM ID: 601410], is characterised by severe IUGR and hyperglycaemia which initiates in the neonatal period and resolves by 18 months of age (Temple and Shield, 2010). This results from overexpression of paternally expressed genes at chromosome 6q24 imprinting cluster including *PLAGL1* (pleiomorphic adenoma gene-like 1) and *HYMAI* (hydatidiform mole associated and imprinted) (Kamiya et al., 2000; Mackay et al., 2002) (Fig. 2A). pUPD6 and paternal duplication of 6q24 account for about 40% and 32% of TNDM1, respectively (Mackay and Temple, 2010). Approximately 28% of TNDM1 patients show hypomethylation at normally maternally methylated ICR which acts as a promoter for the imprinted isoform 1 of *PLAGL1* and also overlaps the exon 1 of *HYMAI* (Mackay et al., 2002; Mackay and Temple, 2010). More than half of these patients with the hypomethylation at 6q24 have been shown to be hypomethylated at other imprinted loci, some of which have been associated with mutations in *ZFP57* gene involved in post-fertilisation maintenance of imprints in mice (Li et al., 2008; Mackay et al., 2008).

3.6. Pseudohypoparathyroidism type Ib

Pseudohypoparathyroidism type Ib (PHP-Ib) [OMIM ID: 603233] represents a condition characterised by end organ resistance to parathyroid hormone (PTH), leading to hypocalcemia and hyperphosphatemia. The majority of PHP-Ib patients show epigenetic defects in the imprinted *GNAS* cluster on chromosome 20q13 (Fig. 2E), mostly associated with hypomethylation at the maternal germline methylated *GNAS* exon A/B DMR (also called A1 DMR), and sometimes additionally at the *GNAS XL* (extra-large), *AS* (*NESP* antisense, known as *Nespas* in mice) and *NESP55* DMRs (reviewed in Mantovani, 2011). Both familial (autosomal dominant; AD-PHP-Ib) and sporadic forms of PHP-Ib have been reported. In AD-PHP-Ib patients, maternal microdeletions disrupting the non-imprinted *STX16* (syntaxin-16) gene located ~220 kb upstream of the exon A/B have

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Table 1
Genetic variants associated with fetal growth.

Chr	Associated genes	Genetic variant	Type of cohort	Type of analysis	Effect of the genetic variant	Notes	References
3q25	*LEKR1* and *CCNL1*	rs900400	Europeans (n = 27,591)	Meta-analysis of 13 GWAS	30 g reduction in BW per C allele was observed. The C allele is also associated with reduced PW and EFW, AC, FL and HC in late gestation	Being C/C homozygote at both rs900400 and rs9883204 (9% of Europeans) is associated with 113 g reduction in birth weight relative to the 24% carrying 0 or 1 of the C allele	Freathy et al. (2010), Mook-Kanamori et al. (2011)
3q21	*ADCY5*	rs9883204	Europeans (n = 27,591)	Meta-analysis of 13 GWAS	40 g reduction in BW per C allele was observed. The C allele is also associated with reduced PW, EFW, AC, FL but not with HC in late gestation	C allele of rs9883204 is in strong LD with the allele A of rs11708067 which is associated with higher risk of type 2 diabetes	Freathy et al. (2010), Mook-Kanamori et al. (2011)
		rs11708067	Danish (n = 6784)	T2D associated SNPs	33 g reduction in BW per A allele was observed using an additive model		(Andersson et al., 2010)
6q25.3	***IGF2R**	rs8191754	Japanese (n = 884; mother-baby pairs)	SNPs selected within *IGF2R*	Babies homozygous for the minor G allele had lower BW than CC homozygotes, with heterozygotes having the intermediate BW	This association was not found in the Greek cohort (n = 97 babies). In African-American and Caucasian mix cohort (n = 342 mother–baby pairs), BW was associated only with maternal genotypes, where babies with GG homozygous mothers being the heaviest	Adkins et al. (2010), Kaku et al. (2007), Kukuvitis et al. (2004)
11p15.5	***IGF2***	rs680	Japanese (n = 884 mother–baby pairs)	SNPs selected within *IGF2*	Babies homozygous for the minor A allele had lower BW than GG homozygotes, with heterozygotes having the intermediate BW	This associations was not replicated in Belgian (n = 2235 adults), Brazilian (n = 294 adults) or African-American and Caucasian mix (n = 342 mother–baby pairs) cohorts	Adkins et al. (2010), Gomes et al. (2005), Heude et al. (2007), Kaku et al. (2007)
		rs3741205	African-American and Caucasian mix (n = 342 mother–baby pairs)	SNPs selected within *IGF2*	Presence of the G allele was associated with 74 g increase in BW both in an additive and a recessive model, but not in a parent-of-origin model		Adkins et al. (2010)
	H19	rs217727	British cohort (ALSPAC) (n = 1696 babies, 822 mothers and 661 fathers)	SNPs selected within *H19*	TT homozygous babies were 56 g heavier than CC homozygotes, and babies with TT homozygous mothers are 138 g heavier than the babies with CC homozygous mothers in additive and dominant models. No evidence of parent-of-origin effects in T versus C allele transmission was found	Maternal genotypes were also associated with cord blood IGF-II level. The association between maternal genotype and BW was replicated in Cambridge birth cohort (n = 646 mother–baby pairs) but not in the African-American and Caucasian mixed (n = 342 mother–baby pairs) population	Adkins et al. (2010), Petry et al. (2005)
		rs2071094	Two independent UK birth cohorts (n = 845 trios and n = 315 trios)	SNPs selected within *H19*	Maternally inherited A allele was associated with increased BW, HC, length and sum of skinfold thickness, in a parent-of-origin model		Petry et al. (2011)
11p15.5	***H19/IGF2***	rs4929984	American-African and Caucasian mix cohorts (n = 342 mother–baby	SNPs selected near *H19*	Maternal transmission of the A allele results in an 89 g decrease whereas paternal transmission of the same allele results in a	rs4929984 is tagged by rs2071094	Adkins et al. (2010)

Table 1 (*continued*)

Chr	Associated genes	Genetic variant	Type of cohort	Type of analysis	Effect of the genetic variant	Notes	References
			pairs and $n = 527$ trios)		78 g increase in BW in a parent-of-origin model		
	INS	Class III VNTR allele	British (ALSPAC) ($n = 758$ mother–baby pairs)	VNTR genotype–phenotype	Class III/III genotype was associated with increased birth weight among babies who did not show catch-up growth within two years of birth	This association was not replicated in Finnish ($n = 5646$) and British ($n > 1000$ trios) cohorts	Bennett et al. (2004), Dunger et al. (1998), Mitchell et al. (2004)
	PHLDA2	15 bp repeat sequence	Three independent British cohorts (total $n = 9433$)	Repeat variants genotype–phenotype	Maternal inheritance of repeat sequence 1 (RS1) in *PHLDA2* promoter results in 93 g and 0.2 cm increase in BW and HC, respectively. When the mother is RS1/RS1 homozygous, the effect on birth weight is + 155 g	The rare RS1 allele is conserved in monkeys while the common RS2 allele seems specific to humans	Ishida et al. (2012)
12q23.2	*IGF1*	192 bp allele	Dutch cohort ($n = 463$ adults)	CA repeat genotype–phenotype	Absence of the common 192 bp allele was associated with 215 g reduction in BW compared to 192 bp allele homozygotes	This association was not replicated in the British cohort ($n = 640$)	Frayling et al. (2002), Vaessen et al. (2002)

Chr, chromosome; BW, birth weight; PW, placental weight; EFW, estimated fetal weight; AC, abdominal circumference; FL, femur length; HC, head circumference; VNTR, variable number tandem repeat. Imprinted genes are represented in bold. **IGF2R* is polymorphically imprinted in human term placenta (Monk et al., 2006).

been identified, which appear to cause hypomethylation mostly confined to A/B DMR (Bastepe et al., 2003; Linglart et al., 2005). Furthermore, maternal transmission of the microdeletions overlapping the exons of *NESP55* and *AS*, *AS* only and *NESP55* only, have also been shown to cause hypomethylation at A/B DMR in AD-PHP-Ib patients, suggestive of additional control regions for A/B DMR (Bastepe et al., 2005; Chillambhi et al., 2010; Richard et al., 2012). In addition to A/B DMR, the former two deletions have been shown to result in hypomethylation of the rest of *GNAS* DMRs (AS and XL), implying a critical region for an imprinting control of the whole maternal *GNAS* allele where the deletions overlap. In mice, *Nespas* promoter DMR has been shown to act as the principle ICR of this cluster (Williamson et al., 2006). The majority of sporadic PHP-Ib patients exhibits methylation defects at multiple *GNAS* DMRs, although the underlying mechanism for this is currently unknown (Liu et al., 2005). Unlike other imprinted disorders, few cases of UPD20 have been reported, with only one case of pUPD20q found in a patient with PHP-Ib-like features (Bastepe et al., 2001).

3.7. Assisted reproductive technology

It has been suggested that children conceived with assisted reproductive technology (ART), have a greater risk of having imprinting disorders. To date, of the imprinting disorders mentioned in this review, BWS, SRS and AS have been observed in ART-conceived offspring. So far, the reported evidence of association between imprinting disorders and various types of ART including *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), have been confined to epimutations (reviewed in Amor and Halliday, 2008; Eroglu and Layman, 2012). Since ART is performed during the critical periods of epigenetic reprogramming, it is possible that proper regulation of epigenetic modification is susceptible to change under external influences. For example, superovulated oocytes from mice and infertile women exhibited methylation defect at several ICRs; hypomethylation at *MEST* in humans and *Snrpn*, *Peg3* and *Kcnq1ot1* in mice, and hypermethylation at *H19* both in humans and mice have been observed (Market-Velker et al., 2010; Sato et al., 2007). Moreover, embryo culture conditions have been shown to result in variable effects on methylation patterns in mice (Doherty et al., 2000; Fauque et al., 2007). However, infertility/subfertility itself could confer an increased risk of epigenetic abnormality, as patients who receive ART may differ from the general population with respect to parental age and fertility (Doornbos et al., 2007). Abnormal DNA methylation patterns at imprinted loci have been observed in sperm of infertile patients with oligospermia (Kobayashi et al., 2007; Marques et al., 2008). Therefore, further studies are required to establish the ART-associated risk of imprinting disorders.

4. The role of imprinted genes in IUGR

It is evident from mouse studies that imprinted genes have a critical role in fetal and placental growth and development, and imprinting disorders often cause growth abnormalities. Imprinting disorders, however, are rare and are accompanied with several other phenotypes. Therefore, the role of imprinted genes in human fetal growth can be further investigated by studying more common growth disorders such as intrauterine growth restriction (IUGR). IUGR is described as a

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pathologically reduced fetal growth rate, as observed by serial ultrasound examinations, resulting in failure to achieve their growth potential (Pollack and Divon, 1992). IUGR is the second leading cause of perinatal morbidity and mortality affecting approximately 6% of pregnancies, and those who survive this complication will face increased risk of chronic adult diseases such as type 2 diabetes and cardiovascular diseases (Brodsky and Christou, 2004). Fetal growth is a complex, dynamic process dependent on the balanced interactions between mother, placenta and foetus. Any deviation from this balance will have a detrimental effect, often resulting in the IUGR phenotype.

Several studies have reported differential expression of imprinted genes between control and IUGR placental samples. According to the kinship theory, maternally expressed and paternally expressed genes may be expected to be up- and down-regulated in IUGR placenta, respectively (Moore and Haig, 1991). However, their role in IUGR may be more complex since altered expressions of imprinted genes in the IUGR-associated placenta can be interpreted as causative or protective of fetal growth. In other words, some may act to reduce fetal growth, resulting in IUGR (negative effectors), while others may act to enhance fetal growth in a compensatory manner to save a pathogenically growth restricted foetus (positive effectors) (Piedrahita, 2011).

Gene expression studies in IUGR placentas using either microarray for global transcriptome and/or real-time PCR for specific imprinted genes, have, without correlation to their imprinting status, demonstrated upregulation of some imprinted genes including *PHLDA2*, *PEG3*, *PEG10* and *IGF2*, and downregulation of others such as *MEST*, *MEG3*, *GATM* (glycine amidinotransferase), *GNAS* and *PLAGL1* (Abu-Amero et al., 1998; Diplas et al., 2009; Kumar et al., 2012; McMinn et al., 2006; Piedrahita, 2011). Of these, consistent results have been found for *PHLDA2*, *PEG3*, *PEG10* and *PLAGL1* in more than one study. Therefore, upregulation of the maternally expressed gene *PHLDA2*, and downregulation of the paternally expressed *PLAGL1* may imply their role as negative effectors of growth, whilst upregulation of the paternally expressed genes *PEG10* and *PEG3* allows them to act as positive effectors in response to IUGR (Piedrahita, 2011). Microarray gene expression studies have also detected differential expression of many other non-imprinted genes in IUGR placentas including the elevated expression of *LEP* (leptin), *IGFBP1* (insulin-like growth factor binding protein 1) and *CRH* (corticotropin releasing hormone) which are thought to be involved in appetite control, IGF-I and IGF-II regulation and stress response, respectively (Habib et al., 2000; McCarthy et al., 2007; McMinn et al., 2006; Piedrahita, 2011; Struwe et al., 2010).

Overall, these findings suggest that imprinted genes are likely to be involved in the aetiology of IUGR, along with a number of non-imprinted genes. Although these observations do not suggest a strong role of imprinted genes in the development of IUGR, it may reflect the complex, and multifactorial nature of IUGR where it can be caused by fetal (e.g. infection, congenital abnormalities), placental (e.g. abnormal cord insertion, vascular system) and maternal (e.g. smoking, malnutrition, hypoxic condition) factors. Moreover, the absence of universal diagnostic criteria for IUGR may also limit the study. Further grouping of the IUGR patients into type I (symmetric) and type II (asymmetric) which results from different causes, would be more informative.

5. The role of imprinted genes in normal growth

Imprinted genes are good candidates as factors controlling individual birth size variation in healthy populations. As both low and high birth weights have been associated with perinatal and life-long complications (Simmons, 2009), increasing numbers of studies have been carried out to try to identify major genetic factors associated with birth size (summarised in Table 1). The effect of genetic variants on fetal growth can be analysed by using different models including dominant, recessive and additive models. The effects of variants associated with imprinted genes, however, can be further analysed by a parent-of-origin model, where the influence of variants on a silenced or active parental allele is expected to contribute differently to the phenotype, i.e. to find the effect of the G allele of the G/C SNP, the effects of transmission of paternal G versus maternal G or paternal G versus paternal C, for example, can be investigated. Types of studies included genome-wide association study (GWAS) or direct association between genotypes of selected SNPs or repeat variants and fetal growth parameters. The reported genetic variants associated with birth size are summarised in Table 1.

SNPs within or in the vicinity of imprinted genes such as paternally expressed *IGF2* and maternally expressed *H19* have been shown to be associated with birth size (Adkins et al., 2010; Lindsay et al., 2002; Petry et al., 2005, 2011). We have recently identified that maternal inheritance of a minor 15 bp repeat sequence variant (RS1) in the promoter region of maternally expressed gene *PHLDA2* is associated with increased birth weight (Ishida et al., 2012). RS1 allele is associated with lower transcriptional efficiency and RS1/RS1 homozygous mothers were found to have on average 155 g heavier babies, an influence equivalent to the scale of reduction caused by maternal smoking (Ishida et al., 2012). Interestingly, while the minor RS1 allele is conserved in monkeys, a common duplicated RS2 allele, which should not promote fetal growth, seems to be specific to humans, suggesting selection of the RS2 allele for human reproductive success. This is because although larger size at birth may be advantageous for the baby, it could be detrimental for the mother during the birth process. Therefore, genes controlling the optimal birth size will be under a strong selection pressure. In addition, these variants associated with imprinted genes have not been identified in GWAS, although this study did not look for parent-of-origin effect (Freathy et al., 2010).

Importantly, of the imprinted genes whose genetic variants showed association with normal birth weight variation, *PHLDA2* expression have been found to be up-regulated in the term placenta of the lower birth weight babies in the healthy cohort, consistent with the growth-suppressing role of maternally expressed genes suggested by the conflict theory (Moore

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and Haig, 1991), while *IGF2* and *H19* (unpublished data) showed no association (Apostolidou et al., 2007). Overall, these findings suggest that imprinted genes are important regulators of normal birth weight variation, and these genetic variants may be useful as a biomarker to predict birth sizes.

6. Conclusions

Genomic imprinting represents a special case of epigenetic modification where one of the alleles is silenced according to their parental origin, which resets in every generation, and precise control of this expression balance is absolutely essential for normal mammalian growth and development. Imprinting disorders are caused by genetic and epigenetic disruptions that alter the correct dosage of imprinted genes, exhibiting various phenotypes, particularly affecting growth. Expression analyses on IUGR-associated placenta have provided further insight into the role of imprinted genes in acting to cause and/or in response to the development of growth phenotypes. In terms of diagnostics or monitoring purposes, production of expression and methylation profiles in placental cells from early stages of pregnancy using cells isolated from chorionic villus sampling (CVS) would be of interest. Also, methylation profiles may be further annotated by the recently introduced oxidative bisulfite sequencing (oxBS-seq) method which can distinguish the 5′-methylcytosine from 5′-hyroxymethylcytosine in single-base resolution (Booth et al., 2012). Some of the genetic variants associated with imprinted genes have been shown to be important regulators of individual fetal growth variation, with their effects controlled under the layer of parental specific expression. Recent genome-wide studies have found parental-origin-specific associations between variants with common diseases such as breast cancer, type 1 and type 2 diabetes (Kong et al., 2009; Wallace et al., 2010), widening the functional role of imprinted genes in humans. Finally, understanding the effects of imprinted genes on fetal growth, and the nature of genomic imprinting itself, will help unravelling the mechanisms of normal and abnormal growth in humans, and could lead to better *in utero* therapeutic options in the future.

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