http://www.expertreviews.org/

expert reviews in molecular medicine

Genomic imprinting in fetal growth and development

Megan P. Hitchins and Gudrun E. Moore

Each somatic cell of the human body contains 46 chromosomes consisting of two sets of 23; one inherited from each parent. These chromosomes can be categorised as 22 pairs of autosomes and two sex chromosomes; females are XX and males are XY. Similarly, at the molecular level, two copies of each autosomal gene exist; one copy derived from each parent. Until the mid-1980s, it was assumed that each copy of an autosome or gene was functionally equivalent, irrespective of which parent it was derived from. However, it is now clear from classical experiments in mice and from examples of human genetic disease that this is not the case. The functional activity of some genes or chromosomal regions is unequal, and dependent on whether they have been inherited maternally or paternally. This phenomenon is termed 'genomic imprinting' and the activity or silence of an imprinted gene or chromosomal region is set during gametogenesis. Genomic imprinting involving the autosomes appears to be restricted to eutherian mammals, and has most likely evolved as a result of the conflicting concerns of the parental genomes in the growth and development of their offspring. When the normal pattern of imprinting is disrupted, the phenotypes observed in humans and mice are generally associated with abnormal fetal growth, development and behaviour, illustrating its importance for a normal intrauterine environment. The characteristics of imprinted genes, their regulation and the phenotypes associated with altered imprinting are discussed.

Megan P. Hitchins
Postdoctoral Research Associate, Department of Fetal and Maternal Medicine, Institute of Reproductive and Developmental Biology, Imperial College Faculty of Medicine, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK. Tel: +44 (0)207 594 2120; Fax: +44 (0)207 594 2129; E-mail: mhitchin@hgmp.mrc.ac.uk

Gudrun E. Moore (corresponding author)
Reader in Molecular Biology, Department of Fetal and Maternal Medicine, Institute of Reproductive and Developmental Biology, Imperial College Faculty of Medicine, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK. Tel: +44 (0)207 594 2120; Fax: +44 (0)207 594 2129; E-mail: gemoore@ic.ac.uk

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

Genomic imprinting is defined as the differential expression of a gene or chromosomal region according to the parental origin of inheritance. Both the maternal and paternal alleles are present, but while one is functionally active, the other is silenced (inactive) in somatic cells (Fig. 1a). Genomic imprinting is reversible through successive generations. Inherited maternal and paternal 'imprints' are erased during gametogenesis (gamete production) and new imprints established according to the sex of the parent. Genomic imprinting is an epigenetic phenomenon (not dependent on the DNA sequence itself, but rather on factors that regulate DNA activity). These factors include attachments of methyl groups to the DNA, which are set in the gamete and serve to distinguish the parental alleles in somatic cells post-fertilisation (Ref. 1).

Evidence for genomic imprinting of the maternal and paternal genomes

The first evidence for genomic imprinting was provided by classical mouse experiments using the technique of pronuclear transplantation (Ref. 2). Mouse embryos that were diploid but with the nuclear material derived solely from the maternal (gynogenetic) or paternal (androgenetic) genomes were created, but failed to develop post-implantation. In gynogenotes, development of the extraembryonic tissues was poor, although an embryo was present. Conversely, embryonic development in androgenotes was considerably retarded but substantial growth of the trophoblast and yolk sac was evident (Refs 2, 3). These experiments demonstrated that diploidy alone is not sufficient for normal embryonic development, but that both the maternal and paternal genomes are required. Furthermore, they showed that the maternal genome appears to be biased towards fetal development, whereas the paternal genome contributes more towards the development of extraembryonic structures (Ref. 2).

Evidence for the differential contribution of the maternal and paternal genomes is also provided by the reciprocal phenotypes observed in ovarian teratomas and complete hydatidiform moles in humans. These are naturally occurring parthenogenotes and androgenotes, respectively. Ovarian teratomas are composed of a disorganised mass of differentiated embryonic tissues, but do not contain any placental tissue (Ref. 4). Complete hydatidiform moles are

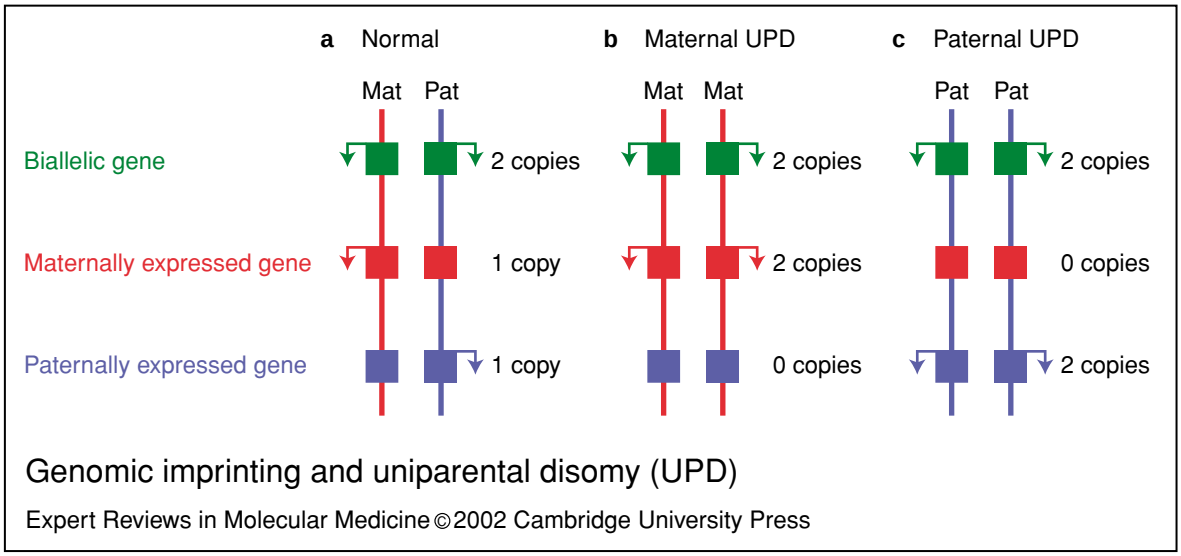


Figure 1. Genomic imprinting and uniparental disomy (UPD). A hypothetical imprinted region is depicted for the maternal (red line, labelled 'Mat') and paternal (blue line, labelled 'Pat') homologues of a chromosome pair. Genes are represented by boxes, and arrows indicate transcriptional activity. (a) Normal state. The biallelic gene is expressed from both parental copies, as are most genes. The imprinted genes are functionally hemizygous, expressed specifically from the maternal allele and silenced on the paternal allele (red), or vice versa (blue). (b) In cases of maternal UPD, there are two copies of the maternal allele, with a consequent double dose of maternally expressed transcripts, and an absence of paternally expressed RNA. (c) In cases of paternal UPD, there is an absence of maternally expressed products, and those genes that are active specifically on the paternal allele are over-expressed **(fig001gml)**.

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994 ©2002 Cambridge University Press

characterised by extensive growth of the trophoblast in the absence of an embryo (Ref. 5).

Uniparental disomy

Uniparental disomy (UPD) is the inheritance of both homologues of a particular chromosome from a single parent (Ref. 6) (Fig. 1b and 1c). In UPD for the whole chromosome, the individual has a balanced chromosome number and, in humans, appears cytogenetically normal. Nevertheless, human clinical disorders associated with UPD for individual chromosomes or chromosomal regions have provided evidence for genomic imprinting at the chromosomal and subchromosomal level. Mice with artificially created UPD have been bred in order to study this phenomenon.

Types of UPD and causative mechanisms

There are different types of UPD, which might arise owing to gametal aneuploidies resulting from mal-segregation of the chromosomes or chromatids during meiosis, or owing to post-fertilisation errors. The mechanism causing UPD can be determined from the combination of the uniparental disomic chromosomes remaining. Four mechanisms are apparent, as described below.

Heterodisomy is the inheritance of two different homologues (both grandparental copies) of a particular chromosome from one parent (Fig. 2a). This can arise when a trisomic conceptus, resulting from the fusion of a normal monosomic gamete (a sperm) with a disomic gamete (a non-disjoined ovum), is corrected by post-zygotic loss of one of the extra homologues. This is referred to as 'trisomic rescue'. For example, maternal heterodisomy is identified by heterozygosity for polymorphic maternal alleles on the chromosome, together with the absence of a paternal allele. Fetuses that are heterodisomic are frequently accompanied by trisomic mosaicism of the placenta, whereby cell populations of different chromosomal constitutions (yet derived from a single zygote) make up the placenta, and this can be detected through chorionic villus sampling (Ref. 7).

Complete isodisomy is the inheritance of two identical copies of a chromosome homologue from one parent, and occurs when a normal

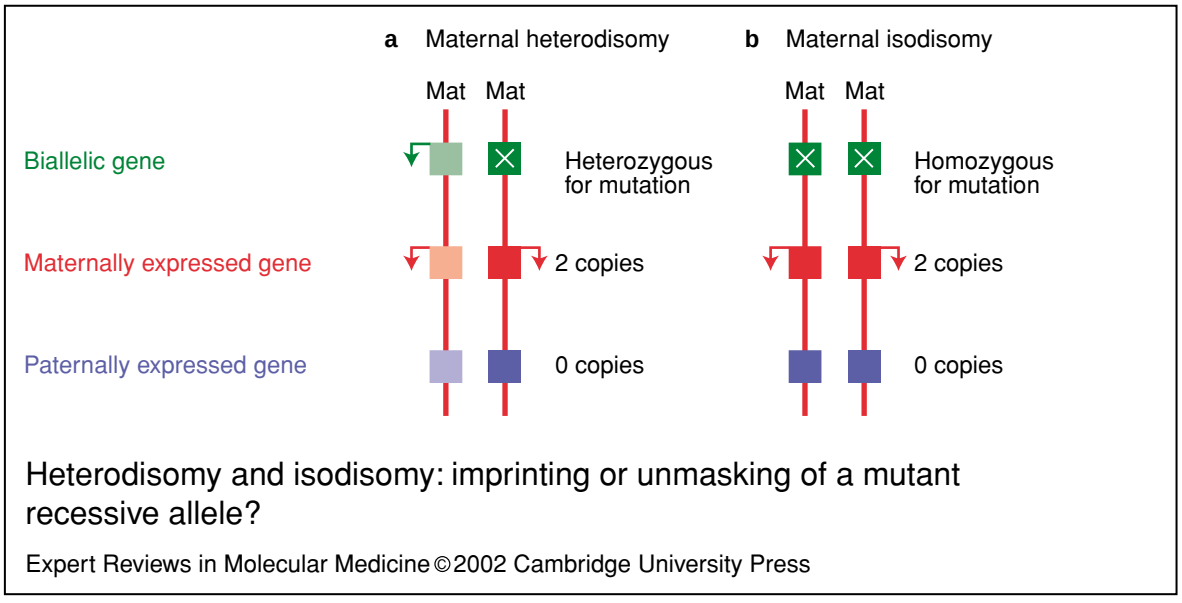


Figure 2. Heterodisomy and isodisomy: imprinting or unmasking of a mutant recessive allele? The two main types of uniparental disomy (UPD) are represented, using maternal UPD7 as an example. (a) Heterodisomy; two different copies of the maternal chromosome 7 (inherited from both maternal grandparents). A recessive mutation (labelled 'X') present in a biallelically expressed gene is masked by the second maternal homologue. (b) Isodisomy; two replica copies of a maternal chromosome 7 homologue. If the mother is a carrier of a recessive mutation on this homologue, it will be 'unmasked' and cause a recessive genetic disease. Imprinting effects are seen in both heterodisomy and isodisomy, but demonstration of complete heterodisomy can rule out aetiology due to mutation of a recessive gene **(fig002gml)**.

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994 ©2002 Cambridge University Press

monosomic gamete fuses with a nullisomic gamete (Fig. 2b). In this case, the homologue that is present within the conceptus duplicates mitotically to form an exact replica, which shows homozygosity for DNA markers along the full length of the chromosome (Ref. 8).

Segmental UPD can occur either as a result of the unbalanced inheritance of reciprocal translocations or a mitotic error post-fertilisation. Segmental UPD following somatic recombination usually results in a conceptus mosaic for disomic and normal cells (Ref. 9).

UPD together with mosaicism for a partial supernumerary chromosome, such as a ring chromosome (a chromosome in which the ends of each arm have been lost and reunited in ring formation), can occur by heterochromosomal substitution. Here, an abnormal chromosome is removed from some of the cells. The remaining normal chromosome endoreduplicates to compensate for the loss of its homologue. Thus, some cells demonstrate UPD whereas others contain both a normal chromosome and a cytogenetically abnormal chromosome (Ref. 10).

UPD in mice

Mice that are heterozygous for reciprocal translocations have been crossed to create mice with segmental UPD. Mice with partial UPD for chromosomes 2, 6, 7, 9, 11, 12, 17 and 18 have demonstrated imprinting effects, whereby disomy or duplication from one parent fails to complement a corresponding nullisomy from the other parent. The imprinting phenotypes generally involve early embryonic, fetal or neonatal lethality, and alterations in fetal and placental growth (reviewed in Ref. 11). Opposite imprinting phenotypes have been observed for proximal chromosome 11. Mice with maternal disomy or duplication and paternal deficiency for this region have a low birth weight (70%) compared with their normal littermates, whereas mice with paternal disomy and maternal deficiency for the same region are larger than normal (130%) (Ref. 12). Through the examination of individual segments of the mouse autosomes, a map of imprinted regions has been produced (Refs 11, 13, 14, 15, 16, 17, 18, 19). Refinement of these regions to identify candidate imprinted genes and mouse models for human imprinted disorders is ongoing. The mouse imprinting map may be accessed via the website for the Mammalian Genetics Unit at Harwell (http://www.mgu.har.mrc.ac.uk/research/imprinted/imprin.html).

UPD as a cause of genetic disease in humans

The first observation of UPD in humans was maternal UPD (mUPD) for chromosome 7 in two individuals suffering from cystic fibrosis (CF) and severe growth restriction. Both patients were isodisomic, and consequently homozygous for a *CFTR* mutation carried by their mothers. However, disrupted genomic imprinting was suggested as the aetiological basis for the severe growth retardation also observed (Refs 8, 20). The disease phenotypes associated with UPD in humans might be due to three distinct factors (Ref. 21), as described below.

Homozygosity of a recessive mutation inherited from one carrier parent

Unmasking of a recessive disease mutation can occur in isodisomy if the transmitting parent is a carrier (Fig. 2). In addition to its association with CF, isodisomy has been associated with several autosomal recessive diseases, including congenital chloride-loss diarrhoea in paternal UPD for chromosome 7 (pUPD7) (Ref. 22).

The effects of trisomy on the placenta in cases of 'trisomic rescue'

Intrauterine growth retardation (IUGR) in cases of mUPD for chromosome 16 (mUPD16) has been shown to be related to the level of trisomic mosaicism of the placenta as opposed to UPD itself, because cases with biparental inheritance were also growth restricted (Ref. 23).

Imprinting effects

Genetic diseases due to imprinting effects that are associated with UPD in humans have been confirmed for chromosomes 7, 11, 14 and 15 (reviewed in Ref. 21) (Table 1).

Interestingly, the imprinted regions on these human chromosomes share homology with regions of non-complementation in the mouse, showing evolutionary conservation of the imprinting status (Refs 13, 14, 15, 17, 18, 19). In some human disorders that are associated with UPD, additional causative mechanisms, such as deletions occurring consistently on one parental allele in some patients, further indicated that imprinting underlies the phenotype. In the absence of additional cytogenetic evidence,

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

Table. 1 Genetic diseases caused by imprinting effects in humans (tab001gml)

Imprinted region	Disease	Refs
mUPD7	Silver–Russell syndrome	76, 77, 78
Segmental pUPD11p15.5	Beckwith–Wiedemann syndrome	9, 101, 102
mUPD14	MatUPD14 syndrome	93, 94
pUPD14	PatUPD14 syndrome	96
mUPD15; chromosomal region 15q11-13	Angelman syndrome	103, 104
pUPD15; chromosomal region 15q11-13	Prader–Willi syndrome	105, 106

Abbreviations: mUPD, maternal uniparental disomy; pUPD, paternal uniparental disomy.

phenotypes that are caused by imprinting effects can be distinguished from uniparental inheritance of a recessive allele by the demonstration of heterodisomy for the full length of the chromosome involved (Ref. 24) (Fig. 2).

Imprinted genes and their characteristics

It has been estimated that there are ~200 imprinted genes in the mammalian genome, and ~50 have been identified in human and mouse autosomes to date (Table 2). The list of imprinted genes is constantly being updated and can be found at: the University of Otago's Imprinted Gene Catalogue (http://www.otago.ac.nz/IGC).

Imprinted genes show three primary characteristics: monoallelic expression; clustering in evolutionarily conserved imprinted domains and an association with parental-allele-specific methylation. The elucidation of these characteristics provides a better understanding of how imprinting is controlled, why disorders of growth and development occur when imprinting is disturbed, and a means with which to identify novel imprinted genes.

Monoallelic expression

Monoallelic expression refers to the transcription of a gene from a single parental allele and is the fundamental characteristic of imprinted genes (Fig. 1a). The *SNRPN* (small nuclear ribonucleoprotein-associated polypeptide N) gene, implicated in Prader–Willi syndrome (PWS), is a classic example of an imprinted gene. *SNRPN* is expressed solely from the paternal allele in pre-implantation embryos (Ref. 25) and continues to be expressed in this manner throughout gestation in all major tissues, into adulthood (Ref. 26). The murine equivalent, *Snrpn*, is also paternally expressed in the mouse (Ref. 14).

The expression patterns of imprinted genes can be complex. Some imprinted genes are monoallelically expressed only in a particular organ or tissue, and can be expressed from both parental alleles in other parts of the body. The imprinting profile of the gene coding for ubiquitin protein ligase (*Ube3a*) has been intricately studied in mice with pUPD and mUPD for central chromosome 7, and found to be highly tissue specific. *Ube3a* is maternally expressed in specific regions of the brain, but is biallelically expressed in other regions of the brain, and all other tissues and organs (Ref. 27). Imprinted genes can also be monoallelically expressed during a specific developmental stage. Expression of the gene coding for insulin-like growth factor 2 (*IGF2*) occurs specifically from the paternal allele in most fetal tissues, including the fetal liver. However, *IGF2* expression becomes biallelic during infancy, and expression from both parental alleles is maintained in the mature liver (Ref. 28). In fact, the imprinted expression of *IGF2* is particularly complex, as it is also promoter dependent. *IGF2* has four promoters in humans, namely P1, P2, P3 and P4. Transcripts that are derived from promoters P2, P3 and P4 are specific

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

Table 2. Human imprinted genes and their mouse orthologues[a] (tab002gml)

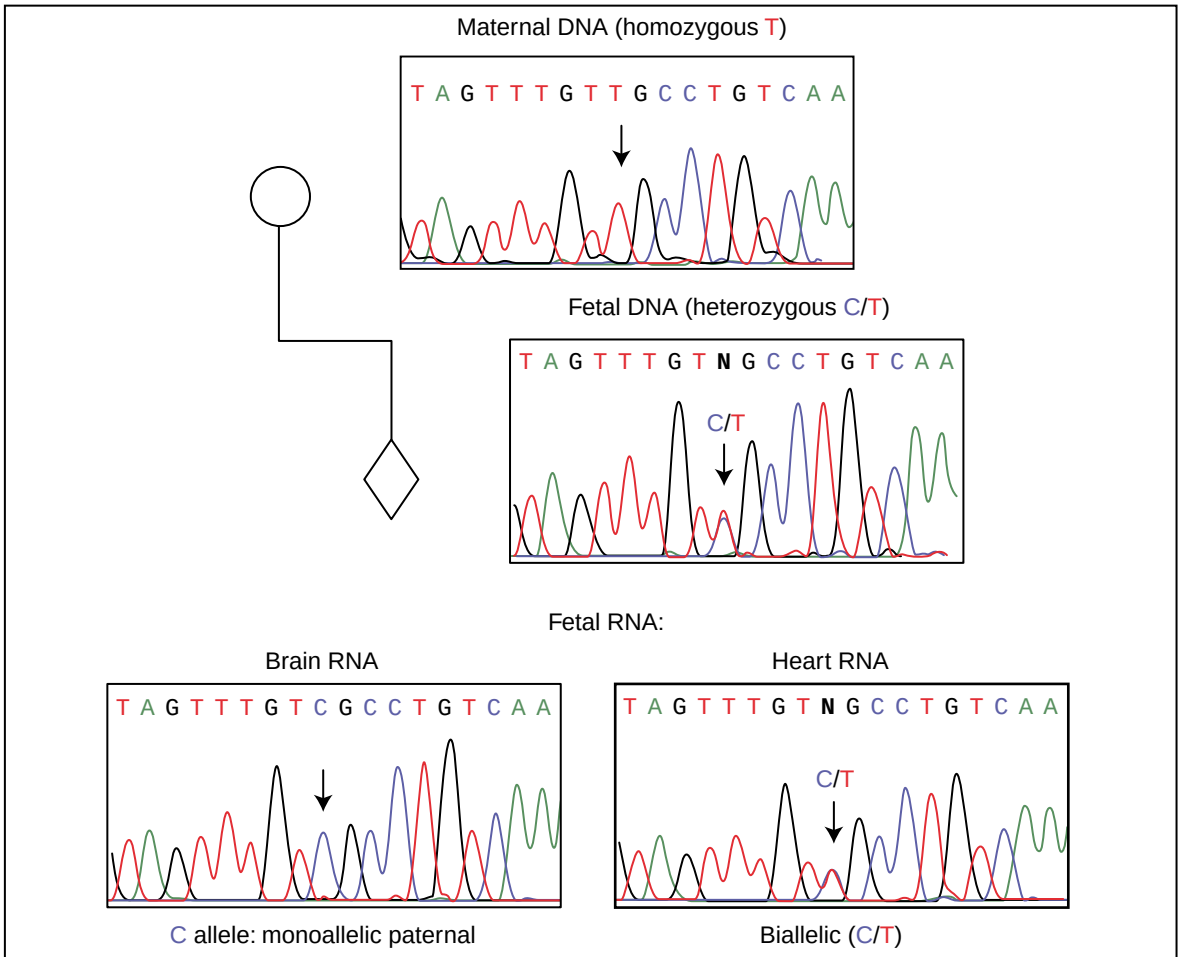
Human gene	Human chromosome	Mouse gene	Mouse chromosome
NOEY2, ARH1	1p31		
p73	1p36.33		
ZAC, PLAGL1	6q24	*Zac1, Lot1*	10
HYMA1	6q24.1-q24.3		
IGF2R, M6PR[b]	6q25.3	*Igf2r*	17
GRB10, MEG1	7p11.2-p12	*Grb10, Meg1*	11
MEST, PEG1	7q32	*Peg1, Mest*	6
COPG2[b]	7q32	*Copg2*	6
WT1[b]	11p13		
H19	11p15.5	*H19*	7
IGF2	11p15.5	*Igf2*	7
INS	11p15.5	*Ins2, insulin II*	7
ASCL2, HASH2	11p15.5		
LTRPC5, MTR1	11p15.5		
KCNQ1, KVLQT1	11p15.5	*Kcnq1, Kvlqt1*	7
CDKN1C, p57^{KIP2}	11p15.5	*Cdnk1c, p57, Kip2*	7
TSSC5, SLC22A1L	11p15.5	*Orct12, Impt1, Itm, Tssc5, Bwscr1a*	7
IPL, TSSC3	11p15.5	*Tssc3*	7
ZNF215	11p15.5		
2G3-8	11p15.5		
SDHD	11q22.3-q23		
HTR2A	13q4	*Htr2a*	14
MEG3, GTL2	14q32	*Meg3, Gtl2*	12
DLK1, PEG9	14q32	*Dlk1, pref1, Ly107, FA1, SCP1, Zog, Peg9*	12
MKRN, ZNF127	15q11-q13		
NDN	15q11-q13	*Ndn, nectin*	7
MAGEL2, NDNL1	15q11-q13		
SNURF-SNRPN	15q11-q13	*Snrpn*	7
PAR-SN	15q11-q13		
HBII-13	15q11-q13		
HBII-85, PWCR1	15q11-q13		
HBII-52	15q11-q13		
PAR5	15q11-q13		
PAR1	15q11-q13		
IPW	15q11-q13	*Ipw*	7
UBE3A	15q11-q13	*Ube3a*	7
ATP10C	15q11-q13		
GABRB3	15q11-q13	*Gabrb3*	7
GABRA5	15q11-q13	*Gabra5*	7
GABRG3	15q11-q13	*Gabrg3*	7
PEG3	19q13.4	*Peg3, Pw1*	7
GNAS1	20q13.11	*Gnas*	2
XIST	X	*Xist, Tsix*	X

[a] Adapted from http://www.otago.ac.nz/IGC
[b] Imprinting status disputed. Antisense transcripts have not been included.

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

to the paternal allele, whereas expression from P1 occurs from both parental alleles in adult liver (Ref. 29). The gene coding for human growth factor receptor-bound 10 (*GRB10*) is oppositely imprinted in different tissues within the same individual. *GRB10* is paternally expressed in the fetal brain, yet a maternally expressed isoform has been identified in skeletal muscle, and biallelic expression occurs in all other tissues (Refs 30, 31).

Imprinted expression can be detected by several methods, including exploitation of an expressed polymorphism occurring within an exon of a gene (Fig. 3). Because imprinting is important for normal fetal development, and



Detection of imprinted expression during fetal development using an exonic polymorphism

Figure 3. Detection of imprinted expression during fetal development using an exonic polymorphism. An expressed polymorphism within the gene encoding growth factor receptor-bound 10 (*GRB10*) on human chromosome 7 is used to demonstrate tissue-specific imprinting by sequence analysis. The fetal DNA is heterozygous for a C/T polymorphism in the 3' untranslated exon. The maternal DNA is homozygous for the T allele, indicating that the C allele was paternally inherited in this fetus, and enabling the allelic origin of expression to be traced. In the heart RNA, both the C and T were detected, showing that expression of *GRB10* is biallelic in this tissue. In the brain RNA, only the C allele was visualised, indicating that *GRB10* is expressed exclusively from the paternal allele in this tissue. Abbreviations: A, adenosine; C, cytosine; G, guanosine; N, unspecified nucleotide; T, thymine **(fig003gml)**.

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994 ©2002 Cambridge University Press

might occur only during gestation, fetal tissue samples are needed to determine which parental allele a gene is transcribed from (Refs 26, 30, 31). If the fetal genomic DNA is heterozygous for an exonic polymorphism within the gene under study, then imprinted expression from one parental allele can be detected by visualisation of a single allele in the RNA. If a corresponding maternal DNA sample is also available for study, then the parental origin of the active allele can be determined. If the gene is not imprinted, that is biallelic in some tissues, then both alleles will be represented in the RNA (Fig. 3).

Clustering of imprinted genes into evolutionarily conserved domains

Imprinted genes tend to occur in discrete clusters in the genome. This is most probably because the allelic expression, or silencing, of imprinted genes within a cluster is co-ordinately regulated by a *cis*-acting element (or elements) referred to as an 'imprinting centre' or 'imprinting control element'.

Imprinted genes and regions are often highly conserved between mice and humans. This includes the gene sequence, the allelic origin of expression, the gene order and regulation within the cluster. This degree of species conservation illustrates the importance of correct maintenance of imprinting in mammals; moreover, it is fortuitous for the study of imprinting processes in mouse models of human imprinted disease. For example, the 15q11-13 imprinted region that is involved in PWS and Angelman syndrome (AS) is homologous to central mouse chromosome 7 (Refs 15, 32). Mice with paternal disomy spanning the imprinted region have a PWS-like phenotype (Ref. 14), and conversely mice with maternal disomy have an AS-like phenotype (Ref. 15). The human and mouse gene homologues are imprinted in the same way in the two species, and are located in the same order on the chromosome, but in the opposite orientation (Refs 32, 33, 34).

Parental-allele-specific methylation

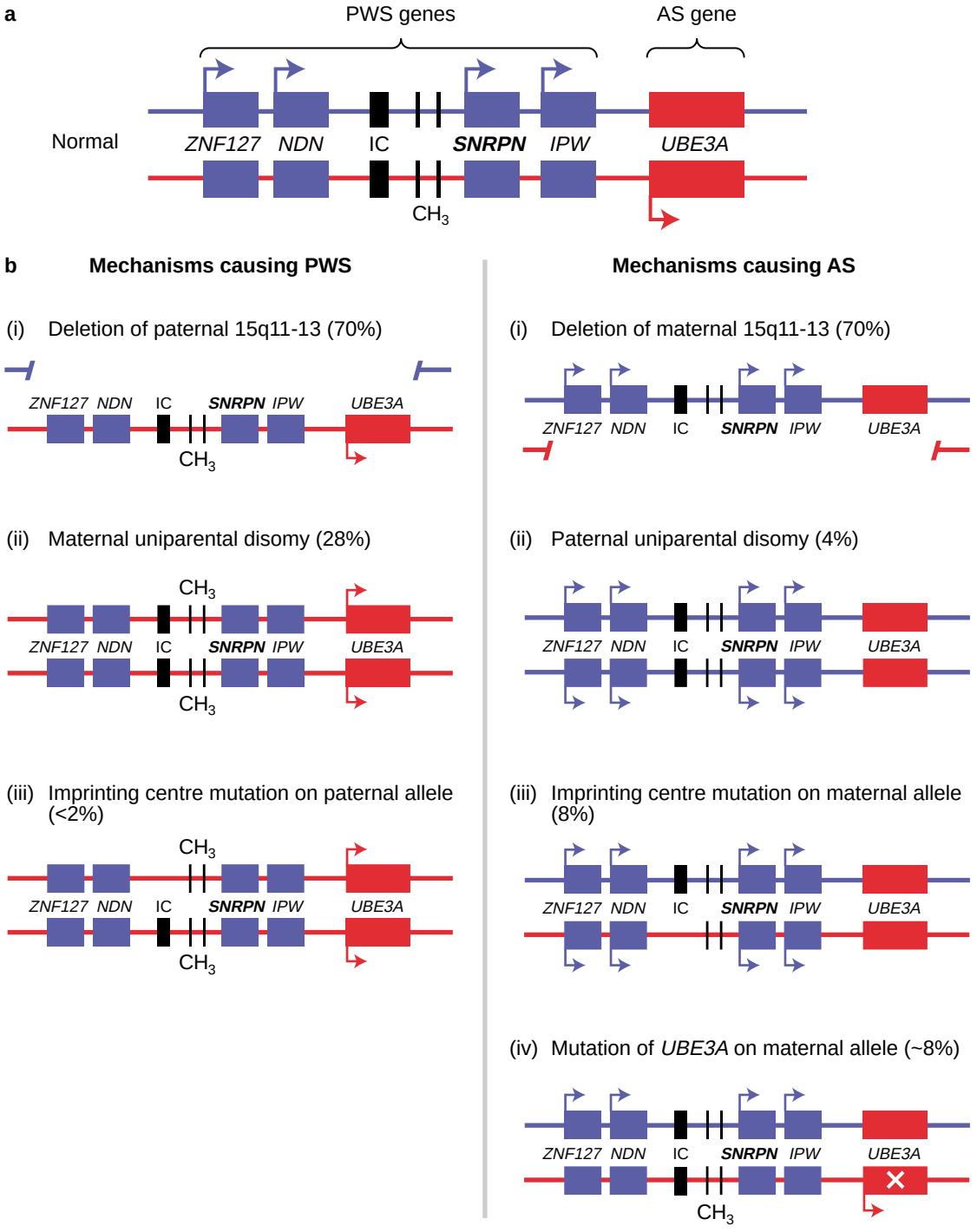
DNA can be modified by methyl groups that attach to cytosine residues within specific CpG (cytosine phosphate diester guanine) dinucleotide pairs. CpG islands at the 5′ end of genes are generally unmethylated to allow constitutive expression of the genes. Methylation of a single parental allele is a hallmark of imprinted genes (Ref. 35). This usually occurs across the 5′ CpG islands of imprinted genes, and methylation of an allele usually correlates with its transcriptional inactivation. For example, the *H19* (Ref. 36) and *Igf2r* (Ref. 37) promoters are methylated on the paternal allele and expressed exclusively from the maternal allele. *SNRPN* (Ref. 38) and *MEST* (Ref. 39) are methylated on the maternal allele and transcribed from the paternal allele. However, there are exceptions to this generalisation. *IGF2* is methylated on the active paternal copy (Ref. 40), and the maternally expressed *Mash2* gene is unmethylated on both alleles (Ref. 41).

Parental-allele-specific methylation is the primary candidate for the gametic imprint. Biallelic expression has been demonstrated for the imprinted genes *Snrpn*, *Igf2r* and *Igf2* in mouse primordial germ cells (germ cells that are at the earliest stage of development), suggesting that imprint erasure occurs during gametogenesis (Ref. 1). In the case of *Snrpn*, the methylation imprint is reset in the mature gametes and is inherited stably throughout somatic cell division. *SNRPN* has two differentially methylated sites in humans: at the 5′ promoter, which is unmethylated on the active paternal copy (Ref. 38), and at a reciprocally methylated site in intron 9 (Ref. 42) (Fig. 4). Studies of the *Snrpn* gene in mice, in which this pattern is conserved, have shown that the 5′ CpG island is methylated in oocytes, and the downstream intron is methylated in sperm. This methylation pattern is maintained on the respective parental alleles throughout embryogenesis and adulthood, serving to distinguish them (Ref. 43).

Epigenetic regulation of imprinting

Imprinting is regulated by the interplay of different epigenetic components, including chromatin structure, replication timing, and degree of histone acetylation and methylation of the DNA, between the two parental alleles. Allelic differences in chromatin compaction and replication timing were first observed between the two X chromosomes in mammalian female cells, in which one of the X chromosomes needed to be inactivated to compensate for two copies of the X chromosome in females and only one in males. The active X chromosome had an open euchromatin conformation, and replicated earlier in the S-phase of the cell cycle than did the inactivated X (Ref. 44). In imprinted regions, the active allele has a euchromatin-like structure, which is more accessible to DNA-modifying

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994



Diagrammatic representation of the mechanisms causing Prader–Willi syndrome (PWS) and Angelman syndrome (AS)

Figure 4. Diagrammatic representation of the mechanisms causing Prader–Willi syndrome (PWS) and Angelman syndrome (AS) *(see next page for legend)* **(fig004gml).**

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994 ©2002 Cambridge University Press

Figure 4. Diagrammatic representation of the mechanisms causing Prader–Willi syndrome (PWS) and Angelman syndrome (AS). (a) The paternal (blue line) and maternal (red line) homologues of the human 15q11-13 region are shown. Paternally expressed genes involved in PWS are represented by blue boxes, and the *UBE3A* gene, which is maternally expressed in brain, is represented by a red box. Arrows denote functional activity. The imprinting centre (IC) is shown as a black box. The parental epigenotype is represented by vertical black lines; methylated loci are labelled CH_3. (b) The mechanisms causing PWS and AS are similar, involving the same region, but occur on opposite alleles. Either disorder is caused by absence [see parts (i) and (ii)] or loss of transcription [see part (iii)] of imprinted genes on the respective alleles. AS is also caused by mutations of *UBE3A* [see part (iv)]. PWS is a multigene disorder. The frequency (%) of each mechanism among patients is given **(fig004gml)**.

enzymes, as measured by increased sensitivity to nucleases. This is generally associated with hyperacetylation of the histones H3 and H4 and lack of CpG methylation. By contrast, the silenced allele has a heterochromatin-like conformation, which is more resistant to nuclease activity, and is characterised by hypoacetylation of the histones and hypermethylation of the gene promoters (Refs 45, 46). Asynchronous replication between the parental alleles extends along the entire length of the imprinted domain, as observed for chromosomal region 15q11-13 (Ref. 47).

Correct DNA methylation is essential for normal gene function. This fact is demonstrated by the finding that a homozygous mutation of the DNA methyltransferase gene (*Dnmt1*), which maintains the DNA methylation patterns, causes embryonic lethality in mice (Ref. 48). The importance of allele-specific methylation in maintaining monoallelic expression of imprinted genes is well documented, but is best illustrated by erroneous imprinting due to altered methylation status. Loss of methylation in the mutant *Dnmt1* mouse embryos caused biallelic expression or 'loss of imprinting' of the *H19*, *Igf2* and *Igf2r* genes (Ref. 48), but not of the *Mash2* gene, which is unmethylated on both alleles (Ref. 41). In humans, the biallelic expression of the gene coding for growth-promoting *IGF2* can occur owing to aberrant methylation of nearby sites in patients suffering from somatic overgrowth (Ref. 49), Beckwith–Wiedemann syndrome (BWS) (Ref. 50) or Wilms' tumour of the kidney (Ref. 51).

Within the imprinted region 15q11-13, an imprinting centre, which encompasses the *SNPRN* promoter and first exon, controls the methylation and monoallelic expression of the imprinted genes along the entire region (Refs 38, 52). The imprinting centre is unmethylated and associated with acetylated histones on the paternal allele (Refs 38, 53). Mutation of the imprinting centre results in the incorrect setting of the methylation patterns within 15q11-13 during gametogenesis, as well as the reversal of allele-specific expression of imprinted genes on the affected homologue in the offspring. This is one cause of PWS and AS, depending on whether the imprinting centre is mutated on the paternal or maternal allele, respectively (Refs 52, 54) (Fig. 4).

Why does imprinting occur in mammals?

Several reasons to explain the evolution of imprinting have been proposed (reviewed in Ref. 55). These include a host-defence mechanism to protect the mammalian genome from the integration of foreign DNA (Ref. 56), protection against parthenogenesis and aneuploidy (Ref. 57), and protection of the female from invasive trophoblastic tumours (Ref. 58). However, there are several arguments disputing each of these hypotheses. The most widely accepted explanation for genomic imprinting is the 'parental conflict hypothesis' put forward in 1989 by Haig and Westoby (Ref. 59).

This parental conflict hypothesis is founded on the conflicting interests of the maternal and paternal genomes during the growth and development of offspring, especially in promiscuous mammals, or where superfecundation occurs. The father is concerned with the development of his offspring at the expense of other littermates or subsequent offspring that do not share his genes. Conversely, the mother is concerned with allocating equal resources to each of her littermates, while ensuring her own survival and future ability to reproduce. Because autosomal genomic imprinting seems to be limited to eutherian (i.e. placental) mammals, and the role of the placenta is to allocate fetal resources from the mother, this model seems to be the most likely. Indeed, most imprinted genes are monoallelically expressed in the placenta, supporting this theory (Ref. 60).

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

The Haig and Westoby model predicts that the paternal genome promotes fetal growth, whereas the maternal genome limits it. Compared with normal mice, androgenetic chimaeras are large, whereas parthenogenetic chimaeras are small (Refs 61, 62). The imprinting profiles of several genes involved in the promotion or inhibition of growth support this model. The *Igf2* gene, which encodes an embryonic growth factor, is paternally expressed. This gene is oppositely imprinted to the maternally expressed Igf2 receptor gene (*Igf2r*), whose product inhibits Igf2 function (Ref. 63). Loss of function of *Igf2* results in a 40% reduction in birth weight (Ref. 64), whereas mutation of *Igf2r* on the maternal allele produces inviable, over-sized mice (Ref. 65). Although parental conflict might not be the sole reason for the evolution of imprinting, it does appear to explain many examples of imprinting, and it is possible that those that it does not explain are a result of other evolutionary pressures.

Genomic imprinting renders a gene functionally hemizygous, which potentially endangers the mammal to mutation, because the silent copy is incapable of masking a mutation of the active copy. However, the importance of controlling the expression of some genes by imprinting is illustrated by the disorders of growth and development that are incurred when normal imprinting is disturbed.

Clinical disorders caused by imprinting defects in humans

The congenital disorders that result from the disruption of imprinting commonly involve a growth phenotype and a varying degree of developmental problems. Behavioural abnormalities are also apparent in some imprinted disorders. Individual genes that cause, or are implicated in, some of these disorders have now been identified and their regulation better understood.

PWS, AS and 15q11-13

PWS is a disorder of growth and development. Severe hypotonia (reduced skeletal muscle tone) and feeding problems related to poor suck during infancy, and hyperphagia (ingestion of more than optimum amounts of food) leading to obesity, are cardinal features of this disorder. Additional variable manifestations include characteristic facial dysmorphology, hypogonadism (retardation of growth and sexual development caused, or characterised, by abnormally decreased functional activity of the gonads), mental retardation, IUGR (the failure of a fetus to attain its expected growth potential at any gestational stage), short stature, small hands and feet, and behavioural problems (reviewed in Ref. 66). The vast majority of cases are sporadic, and there are only a limited number of reports describing familial cases, in which more than one sibling is affected (Refs 52, 54).

AS is primarily a neurobehavioural disorder that is characterised by mental retardation, jerky movements, seizures, ataxia (impairment of the ability to perform smoothly co-ordinated voluntary movements), frequent outbursts of laughter, absence of speech, abnormal electroencephalograms and characteristic facial dysmorphisms (reviewed in Ref. 67). AS is generally sporadic, although up to 20% of cases are familial, with more than one affected sibling (Ref. 68).

AS and PWS have become a paradigm of genomic imprinting in humans. Not only did these two distinct disorders provide the first definitive example of so-called imprinting mutations in humans, but also similar genetic defects involving the same chromosomal location of 15q11-13 give rise to both syndromes. The factor determining the phenotypic outcome is the parental origin of the chromosome defect (Fig. 4). Through the analysis of the genetic aetiology of AS and PWS in 15q11-13, much has been learned about genomic imprinting and its processes.

PWS is caused by the loss of function of imprinted genes on the paternal allele of region 15q11-13. This might result from deletion of the paternally derived 15q11-13, mUPD15 or mutation of the imprinting centre. In the latter mechanism, the paternally inherited allele bears the maternal methylation pattern, and consequently the imprinted genes that are normally active on this allele are silenced. The mechanisms resulting in PWS are depicted in Figure 4. PWS is most probably a contiguous gene syndrome involving several or all of the paternally expressed genes, including *ZNF127*, *NECDIN*, *SNRPN* and *IPW*, because each mechanism affects all of these genes and no mutations have been identified in only one of these genes in PWS patients (reviewed in Ref. 69).

AS results from the lack of a functional maternal copy of the *UBE3A* gene on 15q12. However, sequence mutations of *UBE3A* itself

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

have been identified in only a small number of AS patients, including familial cases (Refs 70, 71, 72). Loss of *UBE3A* in most cases results from a deletion of the maternal 15q11-13 allele, pUPD15 or imprinting centre mutations on the maternal allele; these are similar to the mechanisms leading to PWS (reviewed in Ref. 69) (Fig. 4). In imprintor mutations, the maternal allele has the paternal methylation imprint, effectively imposing a functional pUPD on the 15q11-13 allele (Ref. 54). *UBE3A* is expressed solely from the maternal allele in the brain, and is active on both parental alleles in all other tissues (Ref. 73), which is consistent with the neurobehavioural manifestations of AS patients.

Silver–Russell syndrome and chromosome 7

Silver–Russell syndrome (SRS) is a growth disorder that is characterised by both prenatal and postnatal growth retardation, a small, triangular face and a spectrum of other dysmorphic features. This disorder is clinically heterogeneous, but is most frequently associated with fifth-finger clinodactyly (incurving) or brachydactyly (short fingers and toes), relative macrocephaly (abnormally large head) due to sparing of cranial growth, skeletal asymmetry, muscular hypotrophy (progressive degeneration caused by loss of cells) or hypotony (lower than normal intraocular pressure) and down-slanting corners of the mouth (reviewed in Refs 74, 75).

SRS is genetically heterogeneous, which probably reflects the clinical variation associated with this syndrome. However, mUPD7 occurs in 7–10% of cases (Refs 76, 77, 78). In any case of UPD with heterodisomy, some regions of isodisomy might exist owing to prior recombinational activity at the first meiotic division. To rule out the possibility that SRS was due to unmasking of a mutant recessive allele within a pocket of isodisomy, Preece and colleagues analysed the entire length of the maternal homologues in five SRS cases with mUPD7 (Ref. 24). Although the probands showed mixed heterodisomy and isodisomy for chromosome 7, no common region of isodisomy was found, indicating that SRS is due to an imprinting effect in mUPD7 cases. SRS might be caused by the absence of a functional growth-promoting gene that is active on the paternal allele, or by the over-expression of a growth inhibitor that is active on the maternal chromosome 7.

Two separate imprinted regions on chromosome 7 appear to give rise to SRS. Two cases of SRS with a maternal duplication of the region 7p11.2-p13 have been reported (Refs 79, 80). The 7p11.2-p13 region in humans is homologous to the mouse proximal chromosome 11 imprinted region, for which mice with maternal disomy have IUGR and mice with paternal disomy are overgrown (Refs 12, 16). Although no human growth phenotype is associated with pUPD7 that is equivalent to that seen in mice, it is likely that the mUPD11 mice with low birth weight represent a model for SRS. The *Grb10* gene lies in the imprinted region and is expressed from the maternal allele in mice (Ref. 81). Human *GRB10*, which codes for a potent growth inhibitor, is the only imprinted gene to have been identified in the 7p11.2-p13 region that is duplicated in two SRS patients. However, it has a more-complex imprinting profile than that observed in mice, and there is no evidence from mutation screening in patients indicating a role for *GRB10* in SRS (Refs 30, 31, 82).

To date, only one patient with segmental mUPD for the region 7q31-qter has been identified (Ref. 83). The disomic region in this patient encompasses the imprinted region at 7q32, which contains the imprinted genes *MEST* (Ref. 39) and *gamma-2 COP* (Ref. 84). This region is homologous to an imprinted region on mouse chromosome 6, which is associated with both prenatal and postnatal growth restriction in mice with maternal disomy (Ref. 18). *MEST* is expressed from the paternal allele, and so a lack of the transcript might contribute to SRS (Ref. 39). However, there is no further evidence to suggest that *MEST* is involved in SRS in patients without mUPD7 (Ref. 85).

BWS and 11p15.5

BWS is an overgrowth disorder that is characterised in most cases by prenatal or postnatal gigantism, macroglossia (tongue enlargement), anterior abdominal wall defects, ear anomalies and characteristic facial dysmorphisms. Organomegaly (abnormal enlargement of an organ), renal anomalies, facial naevus flammeus ('port wine stain' birth mark), hypoglycaemia and hemihypertrophy (one side of the body seems to grow faster than the other) also commonly occur. Wilms' tumour of the kidney occurs in 5% of BWS cases (reviewed in Ref. 86).

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

The genetics of BWS is particularly complex, but imprinting defects are implicit in each causative mechanism (reviewed in Ref. 87). Up to 15% of cases are familial. In 20% of sporadic cases, mosaic segmental pUPD11p15.5 is seen, owing to post-zygotic mitotic recombination. Some patients have cytogenetic alterations with parent-of-origin effects, including duplication of the paternal allele, or inversions and translocations involving the maternal allele. Within the BWS imprinted region of 11p15.5, there are not only paternally expressed genes that are involved in growth promotion, including *IGF2* and the insulin gene, but also maternally expressed genes that encode growth suppressors, including *H19*, *KVLQT1* (*KCNQ1*) and *CDKN1C* ($p57^{KIP2}$) (Ref. 87).

The embryonic growth factor gene *IGF2* is strongly implicated in BWS, as shown by the finding that it is expressed from both the maternal and paternal alleles in some patients. Interestingly, overgrowth in BWS occurs only in those tissues in which *IGF2* is expressed. This loss of imprinting of *IGF2* has been shown to be due to an altered epigenotype at differentially methylated sites within the closely linked *H19* or *KVLQT1* genes. The *H19* and *IGF2* genes are co-ordinately regulated, most probably through interaction of either promoter with a common 'enhancer element', and the action of a further 'insulator'. In this model, the *H19* promoter is unmethylated on the maternal allele and has access to the enhancer element, which drives expression from this allele. At the same time, a DNA-binding protein, CTCF, attaches to the unmethylated *H19* promoter and, in so doing, prevents *IGF2* transcription. On the paternal allele, *H19* is methylated, which blocks the insulating CTCF protein, allowing the *IGF2* promoter access to the enhancer element. This, in turn, drives *IGF2* expression from the paternal allele, while *H19* is silenced (reviewed in Ref. 88). However, in a subgroup of patients, *H19* is completely silenced owing to aberrant methylation of the maternal allele, which causes biallelic expression of *IGF2* (Ref. 50). In another group of patients with loss of imprinting of *IGF2*, the *H19* methylation pattern and expression were normal, but maternal methylation had been lost at a differentially methylated site within the *KVLQT1* gene instead (Ref. 89). This suggests that there are two separate imprinting centres within the BWS region, which independently control *IGF2* imprinting (Ref. 87).

Maternally inherited mutations of *CDKN1C* have also been identified in 40% of BWS families and 5% of sporadic cases (Ref. 90). This gene codes for a cyclin-dependent kinase inhibitor, and mutation in BWS patients has been shown to cause the loss of cell-cycle inhibition (Ref. 91). The loss of methylation at the *KVLQT1* differentially methylated site might be associated with silencing of the expression of maternal *CDKN1C*.

Some genotype–phenotype correlations are evident in BWS (reviewed in Ref. 92). For instance, there is a strong association of hemihypertrophy in BWS cases with mosaic pUPD11p15.5, most probably reflecting a differing ratio of disomic to normal cells on the two sides of the body. Moreover, in cases with *CDKN1C* mutations, there is a high incidence of exomphalos (the formation of some internal organs outside the body in a protective sac at the umbilical cord) (Ref. 92). This does not occur in cases with UPD or *H19* inactivation and *IGF2* over-expression, although Wilms' tumour tends to occur in the latter category of patients.

mUPD14 and pUPD14 syndromes

Approximately 22 cases with mUPD14 have been reported. These patients have a variable phenotype. In a few UPD cases that were due to trisomic rescue, accompanied by trisomic mosaicism of the placenta, the phenotype included IUGR, short stature, small hands and feet, and precocious puberty (Refs 93, 94). In one case, the characteristics were poor suck, obesity in childhood and mild developmental delay (Ref. 95). These cases included patients with heterodisomy, suggesting imprinting as the genetic aetiology. However, most of the cases of mUPD14 that are reported are caused by meiotic Robertsonian translocations (translocations in which the two long arms of chromosomes that have their centromeres very close to one end fuse at the centromeres such that the two short arms are lost) in both parents, and have additional manifestations including arrested hydrocephalus (abnormal accumulation of cerebrospinal fluid in the brain) and scoliosis (side-to-side spinal curves) (reviewed in Ref. 93). These features might be a result of the other chromosomes involved in the translocations. IUGR and small hands and feet are also observed in cases with trisomy for distal 14q, suggesting that a double dose of a maternally expressed imprinted gene might be responsible.

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

Only four cases of pUPD14 have been described, although the phenotype has been consistent in each patient, warranting a specific pUPD14 syndrome. The clinical features observed were polyhydramnios (excessive amniotic fluid surrounding the unborn infant), oedema (excess of fluid within a tissue), skeletal abnormalities including small thorax, hypoplastic ribs, elongated clavicle, short neck and short long-bones of the limbs, and facial dysmorphisms including depressed nasal bridge, short palpebral fissures and protruding philtrum, and severe mental retardation (reviewed in Ref. 96).

In both mUPD14 and pUPD14, the phenotype might be modulated by trisomic mosaicism of the placenta. However, the 14q32 region is homologous to an imprinted region on distal mouse chromosome 12, which results in embryonic lethality and a growth phenotype (Ref. 19). Furthermore, two imprinted genes, *GTL2* and *DLK1*, have been identified within 14q32 in humans, suggesting that the phenotypes associated with UPD14 are caused by imprinting effects (Refs 97, 98). *DLK1*, which is paternally expressed, encodes a transmembrane protein that is likely to be involved in cellular signalling, and therefore represents a good candidate for involvement in the UPD14 phenotypes (Ref. 98).

Conclusions and future work

Imprinted genes play an important role in the regulation of fetal growth and development in mammals. Although only some imprinted genes have been identified to date, this fact is certainly true of those that are known. The detrimental effects on growth and development that occur in humans and mice when normal imprinting processes are disrupted best illustrate the role of genomic imprinting. Particularly notable imprinting disorders include the growth phenotypes of both SRS (growth restriction), with mUPD7, and BWS (overgrowth), with disrupted imprinting within 11p15.5. Imprinting effects that are associated with chromosomes 14 and 15q11-13 have drastic developmental consequences, including some growth aspects. Many cancers are also attributable to the loss of imprinting of genes that are involved in growth and cell-cycle regulation in given cells (Ref. 99), including Wilms' tumour of the kidney (Ref. 51). It is now becoming apparent that some imprinted genes also affect behaviour. AS is categorised as a neurobehavioural disorder, and PWS has a behavioural component including skin picking, temper tantrums, obsessive–compulsive disorder and stubbornness (Ref. 66). The *MEST*-knockout mouse shows defective maternal behaviour, characteristically impaired placentophagia (ingestion of the afterbirth) and poor nurturing (Ref. 100).

There is still some debate as to why imprinting has evolved in placental mammals. The parental conflict theory, which states that imprinting is due to the tug-of-war between the differing maternal and paternal requirements in mammalian reproduction, is the current tenet, but does not fit the imprinting profile of all genes. There is still much work to do before genomic imprinting is fully understood. Dissection of the various molecular mechanisms causing BWS has revealed that different mechanisms are associated with particular manifestations of the phenotype, enabling the roles of individual genes in chromosomal region 11p15.5 to be better understood (Ref. 87). An estimated 150 imprinted genes are as yet unidentified, and their roles not yet understood. Several modern techniques can be used to identify imprinted genes, each of which exploits the characteristics of the gene, including monoallelic expression or allele-specific methylation. Sequencing of the entire human and mouse genomes, and availability of SNP (single-nucleotide polymorphism) databases, will contribute significantly to the speed at which the remaining imprinted genes are identified.

Acknowledgements and funding

Megan P. Hitchins is a Postdoctoral Research Associate funded by the Dunhill Medical Trust. We thank Dr Anne Ferguson-Smith (Department of Anatomy, University of Cambridge, UK) and Professor Eamonn Maher (Department of Paediatrics and Child Health, Medical School, Birmingham, UK) for their peer review of this article.

References

1 Szabo, P.E. and Mann, J.R. (1995) Biallelic expression of imprinted genes in the mouse germ line: implications for erasure, establishment, and mechanisms of genomic imprinting. Genes Dev 9, 1857-1868, PubMed ID: 95377637

2 McGrath, J. and Solter, D. (1984) Completion of mouse embryogenesis requires both the maternal and paternal genomes. Cell 37, 179-183, PubMed ID: 84205639

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

3 Barton, S.C, Surani, M.A. and Norris, M.L. (1984) Role of paternal and maternal genomes in mouse development. Nature 311, 374-376, PubMed ID: 85012678
4 Linder, D. et al. (1975) Origin of extragonadal teratomas and endodermal sinus tumours. Nature 254, 597-598, PubMed ID: 75156442
5 Kajii, T. and Ohama, K. (1977) Androgenetic origin of hydatidiform mole. Nature 268, 633-634, PubMed ID: 77255101
6 Engel, E. (1980) A new genetic concept: uniparental disomy and its potential effect, isodisomy. Am J Med Genet 6, 137-143, PubMed ID: 81083290
7 Kalousek, D.K. et al. (1996) Trisomy 7 CVS mosaicism: pregnancy outcome, placental and DNA analysis in 14 cases. Am J Med Genet 65, 348-352, PubMed ID: 97082712
8 Spence, J.E. et al. (1988) Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 42, 217-226, PubMed ID: 88131039
9 Henry, I. et al. (1993) Somatic mosaicism for partial paternal isodisomy in Wiedemann-Beckwith syndrome: a post-fertilization event. Eur J Hum Genet 1, 19-29, PubMed ID: 94348893
10 Miyoshi, O. et al. (1999) 47,XX,UPD(7)mat,+r(7)pat/46,XX,UPD(7)mat mosaicism in a girl with Silver-Russell syndrome (SRS): possible exclusion of the putative SRS gene from a 7p13-q11 region. J Med Genet 36, 326-329, PubMed ID: 99241942
11 Cattanach, B.M. and Beechey, C.V. (1990) Autosomal and X-chromosome imprinting. Dev Suppl 1990, 63-72, PubMed ID: 91216054
12 Cattanach, B.M. and Kirk, M. (1985) Differential activity of maternally and paternally derived chromosome regions in mice. Nature 315, 496-498, PubMed ID: 85213883
13 Ferguson-Smith, A.C. et al. (1991) Embryological and molecular investigations of parental imprinting on mouse chromosome 7. Nature 351, 667-670, PubMed ID: 91270376
14 Cattanach, B.M. et al. (1992) A candidate mouse model for Prader-Willi syndrome which shows an absence of Snrpn expression. Nat Genet 2, 270-274, PubMed ID: 93265158
15 Cattanach, B.M. et al. (1997) A candidate model for Angelman syndrome in the mouse. Mamm Genome 8, 472-478, PubMed ID: 97341108
16 Cattanach, B.M. et al. (1998) Association of a redefined proximal mouse chromosome 11 imprinting region and U2afbp-rs/U2af1-rs1 expression. Cytogenet Cell Genet 80, 41-47, PubMed ID: 98341473
17 Williamson, C.M. et al. (1998) Localisation of the imprinted gene neuronatin, Nnat, confirms and refines the location of a second imprinting region on mouse chromosome 2. Cytogenet Cell Genet 81, 73-78, PubMed ID: 98358150
18 Beechey, C.V. (2000) Peg1/Mest locates distal to the currently defined imprinting region on mouse proximal chromosome 6 and identifies a new imprinting region affecting growth. Cytogenet Cell Genet 90, 309-314, PubMed ID: 20573859
19 Georgiades, P. et al. (2000) Parental origin-specific developmental defects in mice with uniparental disomy for chromosome 12. Development 127, 4719-4728, PubMed ID: 20480563
20 Voss, R. et al. (1989) Isodisomy of chromosome 7 in a patient with cystic fibrosis: could uniparental disomy be common in humans? Am J Hum Genet 45, 373-380, PubMed ID: 89371744
21 Ledbetter, D.H. and Engel, E. (1995) Uniparental disomy in humans: development of an imprinting map and its implications for prenatal diagnosis. Hum Mol Genet 4, 1757-1764, PubMed ID: 96121571
22 Hoglund, P. et al. (1994) Paternal isodisomy for chromosome 7 is compatible with normal growth and development in a patient with congenital chloride diarrhea. Am J Hum Genet 55, 747-752, PubMed ID: 95029375
23 Kalousek, D.K. et al. (1993) Uniparental disomy for chromosome 16 in humans. Am J Hum Genet 52, 8-16, PubMed ID: 93167295
24 Preece, M.A. et al. (1999) An analysis of the distribution of hetero- and isodisomic regions of chromosome 7 in five mUPD7 Silver-Russell syndrome probands. J Med Genet 36, 457-460, PubMed ID: 20332807
25 Huntriss, J. et al. (1998) Imprinted expression of SNRPN in human preimplantation embryos. Am J Hum Genet 63, 1009-1014, PubMed ID: 98431784
26 Reed, M.L. and Leff, S.E. (1994) Maternal imprinting of human SNRPN, a gene deleted in Prader-Willi syndrome. Nat Genet 6, 163-167, PubMed ID: 94214496
27 Albrecht, U. et al. (1997) Imprinted expression of the murine Angelman syndrome gene, Ube3a, in

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

hippocampal and Purkinje neurons. Nat Genet 17, 75-78, PubMed ID: 97434215
28 Davies, S.M. (1994) Developmental regulation of genomic imprinting of the IGF2 gene in human liver. Cancer Res 54, 2560-2562, PubMed ID: 94221578
29 Vu, T.H. and Hoffman, A.R. (1994) Promoter-specific imprinting of the human insulin-like growth factor-II gene. Nature 371, 714-717, PubMed ID: 95021742
30 Blagitko, N. et al. (2000) Human GRB10 is imprinted and expressed from the paternal and maternal allele in a highly tissue- and isoform-specific fashion. Hum Mol Genet 9, 1587-1595, PubMed ID: 20320688
31 Hitchins, M.P. et al. (2001) Maternal repression of the human GRB10 gene in the developing central nervous system; evaluation of the role for GRB10 in Silver-Russell syndrome. Eur J Hum Genet 9, 82-90, PubMed ID: 21214710
32 Nicholls, R.D. et al. (1993) Evaluation of potential models for imprinted and nonimprinted components of human chromosome 15q11-q13 syndromes by fine-structure homology mapping in the mouse. Proc Natl Acad Sci U S A 90, 2050-2054, PubMed ID: 93189635
33 Watrin, F. et al. (1997) The mouse Necdin gene is expressed from the paternal allele only and lies in the 7C region of the mouse chromosome 7, a region of conserved synteny to the human Prader-Willi syndrome region. Eur J Hum Genet 5, 324-332, PubMed ID: 98074270
34 Wevrick, R. and Francke, U. (1997) An imprinted mouse transcript homologous to the human imprinted in Prader-Willi syndrome (IPW) gene. Hum Mol Genet 6, 325-332, PubMed ID: 97217793
35 Neumann, B. and Barlow, D.P. (1996) Multiple roles for DNA methylation in gametic imprinting. Curr Opin Genet Dev 6, 159-163, PubMed ID: 96279969
36 Ferguson-Smith, A.C. et al. (1993) Parental-origin-specific epigenetic modification of the mouse H19 gene. Nature 362, 751-755, PubMed ID: 93226046
37 Stoger, R. et al. (1993) Maternal-specific methylation of the imprinted mouse Igf2r locus identifies the expressed locus as carrying the imprinting signal. Cell 73, 61-71, PubMed ID: 93214996
38 Sutcliffe, J.S. et al. (1994) Deletions of a differentially methylated CpG island at the SNRPN gene define a putative imprinting control region. Nat Genet 8, 52-58, PubMed ID: 95078923
39 Riesewijk, A.M. et al. (1997) Monoallelic expression of human PEG1/MEST is paralleled by parent-specific methylation in fetuses. Genomics 42, 236-244, PubMed ID: 97336048
40 Reik, W. et al. (1994) Allelic methylation of H19 and IGF2 in the Beckwith-Wiedemann syndrome. Hum Mol Genet 3, 1297-1301, PubMed ID: 95078831
41 Caspary, T. et al. (1998) Multiple mechanisms regulate imprinting of the mouse distal chromosome 7 gene cluster. Mol Cell Biol 18, 3466-3474, PubMed ID: 98252933
42 Glenn, C.C. et al. (1993) Modification of 15q11-q13 DNA methylation imprints in unique Angelman and Prader-Willi patients. Hum Mol Genet 2, 1377-1382, PubMed ID: 94061032
43 Shemer, R. et al. (1997) Structure of the imprinted mouse Snrpn gene and establishment of its parental-specific methylation pattern. Proc Natl Acad Sci U S A 94, 10267-10272, PubMed ID: 97439853
44 Morishima, A, Grumbach, M.M. and Taylor, J.H. (1962) Asynchronous duplication of human chromosomes and the origin of sex chromatin. Proc Natl Acad Sci USA 48, 756-763
45 Schweizer, J, Zynger, D. and Francke, U. (1999) In vivo nuclease hypersensitivity studies reveal multiple sites of parental origin-dependent differential chromatin conformation in the 150 kb SNRPN transcription unit. Hum Mol Genet 8, 555-566, PubMed ID: 99172063
46 Grandjean, V. et al. (2001) Relationship between DNA methylation, histone H4 acetylation and gene expression in the mouse imprinted Igf2-H19 domain. FEBS Lett 488, 165-169, PubMed ID: 21099852
47 Knoll, J.H, Cheng, S.D. and Lalande, M. (1994) Allele specificity of DNA replication timing in the Angelman/Prader-Willi syndrome imprinted chromosomal region. Nat Genet 6, 41-46, PubMed ID: 94184363
48 Li, E, Bestor, T.H. and Jaenisch, R. (1992) Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. Cell 69, 915-926, PubMed ID: 92298390
49 Morison, I.M. et al. (1996) Somatic overgrowth associated with overexpression of insulin-like growth factor II. Nat Med 2, 311-316, PubMed ID:

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

96197733
50 Reik, W. et al. (1995) Imprinting mutations in the Beckwith-Wiedemann syndrome suggested by altered imprinting pattern in the IGF2-H19 domain. Hum Mol Genet 4, 2379-2385, PubMed ID: 96177675
51 Steenman, M.J. et al. (1994) Loss of imprinting of IGF2 is linked to reduced expression and abnormal methylation of H19 in Wilms' tumour. Nat Genet 7, 433-439, PubMed ID: 95004614
52 Buiting, K. et al. (1995) Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting centre on human chromosome 15. Nat Genet 9, 395-400, PubMed ID: 95315990
53 Fulmer-Smentek, S.B. and Francke, U. (2001) Association of acetylated histones with paternally expressed genes in the Prader—Willi deletion region. Hum Mol Genet 10, 645-652, PubMed ID: 21153104
54 Saitoh, S. et al. (1996) Minimal definition of the imprinting center and fixation of chromosome 15q11-q13 epigenotype by imprinting mutations. Proc Natl Acad Sci U S A 93, 7811-7815, PubMed ID: 96353900
55 Bartolomei, M.S. and Tilghman, S.M. (1997) Genomic imprinting in mammals. Annu Rev Genet 31, 493-525, PubMed ID: 98105116
56 Barlow, D.P. (1993) Methylation and imprinting: from host defense to gene regulation? Science 260, 309-310, PubMed ID: 93227039
57 Thomas, J.H. (1995) Genomic imprinting proposed as a surveillance mechanism for chromosome loss. Proc Natl Acad Sci U S A 92, 480-482, PubMed ID: 95132623
58 Varmuza, S. and Mann, M. (1994) Genomic imprinting—defusing the ovarian time bomb. Trends Genet 10, 118-123, PubMed ID: 94302673
59 Haig, D. and Westoby, M. (1989) Parent-specific gene expression and the triploid endosperm. Am Naturalist 134, 147-155
60 Tilghman, S.M. (1999) The sins of the fathers and mothers: genomic imprinting in mammalian development. Cell 96, 185-193, PubMed ID: 99140713
61 Fundele, R.H. et al. (1990) Temporal and spatial selection against parthenogenetic cells during development of fetal chimeras. Development 108, 203-211, PubMed ID: 90276237
62 Barton, S.C. et al. (1991) Influence of paternally imprinted genes on development. Development 113, 679-687, PubMed ID: 92146278
63 Willison, K. (1991) Opposite imprinting of the mouse Igf2 and Igf2r genes. Trends Genet 7, 107-109, PubMed ID: 91297745
64 DeChiara, T.M, Robertson, E.J. and Efstratiadis, A. (1991) Parental imprinting of the mouse insulin-like growth factor II gene. Cell 64, 849-859, PubMed ID: 91146004
65 Lau, M.M. et al. (1994) Loss of the imprinted IGF2/cation-independent mannose 6-phosphate receptor results in fetal overgrowth and perinatal lethality. Genes Dev 8, 2953-2963, PubMed ID: 95095080
66 Holm, V.A. et al. (1993) Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics 91, 398-402, PubMed ID: 93141302
67 Williams, C.A. et al. (1995) Angelman syndrome: consensus for diagnostic criteria.Angelman Syndrome Foundation. Am J Med Genet 56, 237-238, PubMed ID: 95351380
68 Meijers-Heijboer, E.J. et al. (1992) Linkage analysis with chromosome 15q11-13 markers shows genomic imprinting in familial Angelman syndrome. J Med Genet 29, 853-857, PubMed ID: 93124475
69 Nicholls, R.D, Saitoh, S. and Horsthemke, B. (1998) Imprinting in Prader-Willi and Angelman syndromes. Trends Genet 14, 194-200, PubMed ID: 98276151
70 Kishino, T, Lalande, M. and Wagstaff, J. (1997) UBE3A/E6-AP mutations cause Angelman syndrome. Nat Genet 15, 70-73, PubMed ID: 97141921
71 Matsuura, T. et al. (1997) De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. Nat Genet 15, 74-77, PubMed ID: 97141922
72 Malzac, P. et al. (1998) Mutation analysis of UBE3A in Angelman syndrome patients. Am J Hum Genet 62, 1353-1360, PubMed ID: 98254455
73 Vu, T.H. and Hoffman, A.R. (1997) Imprinting of the Angelman syndrome gene, UBE3A, is restricted to brain. Nat Genet 17, 12-13, PubMed ID: 97434201
74 Wollmann, H.A. et al. (1995) Growth and symptoms in Silver-Russell syndrome: review on the basis of 386 patients. Eur J Pediatr 154, 958-968, PubMed ID: 96255819
75 Price, S.M. et al. (1999) The spectrum of Silver-Russell syndrome: a clinical and molecular genetic study and new diagnostic criteria. J Med Genet 36, 837-842, PubMed ID:

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

20013054
76 Kotzot, D. et al. (1995) Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. Hum Mol Genet 4, 583-587, PubMed ID: 95359961
77 Eggermann, T. et al. (1997) Molecular studies in 37 Silver-Russell syndrome patients: frequency and etiology of uniparental disomy. Hum Genet 100, 415-419, PubMed ID: 97418128
78 Preece, M.A. et al. (1997) Maternal uniparental disomy 7 in Silver-Russell syndrome. J Med Genet 34, 6-9, PubMed ID: 97184872
79 Joyce, C.A. et al. (1999) Duplication of 7p12.1-p13, including GRB10 and IGFBP1, in a mother and daughter with features of Silver-Russell syndrome. Hum Genet 105, 273-280, PubMed ID: 20441964
80 Monk, D. et al. (2000) Duplication of 7p11.2-p13, including GRB10, in Silver-Russell syndrome. Am J Hum Genet 66, 36-46, PubMed ID: 20100607
81 Miyoshi, N. et al. (1998) Identification of the Meg1/Grb10 imprinted gene on mouse proximal chromosome 11, a candidate for the Silver-Russell syndrome gene. Proc Natl Acad Sci U S A 95, 1102-1107, PubMed ID: 98115881
82 Mergenthaler, S. et al. (2001) Conflicting reports of imprinting status of human GRB10 in developing brain: how reliable are somatic cell hybrids for predicting allelic origin of expression? Am J Hum Genet 68, 543-545, PubMed ID: 21090523
83 Hannula, K. et al. (2001) A narrow segment of maternal uniparental disomy of chromosome 7q31-qter in Silver-Russell syndrome delimits a candidate gene region. Am J Hum Genet 68, 247-253, PubMed ID: 21063158
84 Blagitko, N. et al. (1999) gamma2-COP, a novel imprinted gene on chromosome 7q32, defines a new imprinting cluster in the human genome. Hum Mol Genet 8, 2387-2396, PubMed ID: 20025747
85 Riesewijk, A.M. et al. (1998) Evidence against a major role of PEG1/MEST in Silver-Russell syndrome. Eur J Hum Genet 6, 114-120, PubMed ID: 98454339
86 Elliott, M. and Maher, E.R. (1994) Beckwith-Wiedemann syndrome. J Med Genet 31, 560-564, PubMed ID: 95055607
87 Maher, E.R. and Reik, W. (2000) Beckwith-Wiedemann syndrome: imprinting in clusters revisited. J Clin Invest 105, 247-252, PubMed ID: 20141351
88 Allshire, R. and Bickmore, W. (2000) Pausing for thought on the boundaries of imprinting. Cell 102, 705-708, PubMed ID: 20483530
89 Smilinich, N.J. et al. (1999) A maternally methylated CpG island in KvLQT1 is associated with an antisense paternal transcript and loss of imprinting in Beckwith-Wiedemann syndrome. Proc Natl Acad Sci U S A 96, 8064-8069, PubMed ID: 99324189
90 Hatada, I. et al. (1996) An imprinted gene p57KIP2 is mutated in Beckwith-Wiedemann syndrome. Nat Genet 14, 171-173, PubMed ID: 96438852
91 Bhuiyan, Z.A. et al. (1999) Functional analysis of the p57KIP2 gene mutation in Beckwith-Wiedemann syndrome. Hum Genet 104, 205-210, PubMed ID: 99254822
92 Engel, J.R. et al. (2000) Epigenotype-phenotype correlations in Beckwith-Wiedemann syndrome. J Med Genet 37, 921-926, PubMed ID: 20558896
93 Healey, S. et al. (1994) Distinct phenotype in maternal uniparental disomy of chromosome 14. Am J Med Genet 51, 147-149, PubMed ID: 94379083
94 Sanlaville, D. et al. (2000) Maternal uniparental heterodisomy of chromosome 14: chromosomal mechanism and clinical follow up. J Med Genet 37, 525-528, PubMed ID: 20341813
95 Hordijk, R. et al. (1999) Maternal uniparental disomy for chromosome 14 in a boy with a normal karyotype. J Med Genet 36, 782-785, PubMed ID: 99456128
96 Cotter, P.D. et al. (1997) Paternal uniparental disomy for chromosome 14: a case report and review. Am J Med Genet 70, 74-79, PubMed ID: 97275984
97 Miyoshi, N. et al. (2000) Identification of an imprinted gene, Meg3/Gtl2 and its human homologue MEG3, first mapped on mouse distal chromosome 12 and human chromosome 14q. Genes Cells 5, 211-220, PubMed ID: 20223871
98 Kobayashi, S. et al. (2000) Mouse Peg9/Dlk1 and human PEG9/DLK1 are paternally expressed imprinted genes closely located to the maternally expressed imprinted genes: mouse Meg3/Gtl2 and human MEG3. Genes Cells 5, 1029-1037, PubMed ID: 21110711
99 Rainier, S. et al. (1993) Relaxation of imprinted genes in human cancer. Nature 362, 747-749, PubMed ID: 93226044
100 Lefebvre, L. et al. (1998) Abnormal maternal

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994

behaviour and growth retardation associated with loss of the imprinted gene Mest. Nat Genet 20, 163-169, PubMed ID: 98442652
101 Henry, I. et al. (1991) Uniparental paternal disomy in a genetic cancer-predisposing syndrome. Nature 351, 665-667, PubMed ID: 91270375
102 Slatter, R.E. et al. (1994) Mosaic uniparental disomy in Beckwith-Wiedemann syndrome. J Med Genet 31, 749-753, PubMed ID: 95139045
103 Malcolm, S. et al. (1991) Uniparental paternal disomy in Angelman's syndrome. Lancet 337, 694-697, PubMed ID: 91163210
104 Nicholls, R.D. et al. (1992) Paternal uniparental disomy of chromosome 15 in a child with Angelman syndrome. Ann Neurol 32, 512-518, PubMed ID: 93089882
105 Nicholls, R.D. et al. (1989) Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. Nature 342, 281-285, PubMed ID: 90044101
106 Robinson, W.P. et al. (1991) Molecular, cytogenetic, and clinical investigations of Prader-Willi syndrome patients. Am J Hum Genet 49, 1219-1234, PubMed ID: 92081768

Further reading, resources and contacts

The UK Medical Research Council Mammalian Genetics Unit at Harwell incorporates the Mouse Genome Centre and comprises 'an integrated campus for mouse genetics research'. The Unit's website provides information on mouse genomic sequencing and chromosomal maps and references relating to imprinted genes in the mouse.

http://www.mgu.har.mrc.ac.uk/

The Imprinted Gene Catalogue website, collated by the University of Otago (New Zealand), contains over 200 entries and can be searched by species name, chromosome or gene.

http://www.otago.ac.nz/IGC

Features associated with this article

Figures

Figure 1. Genomic imprinting and uniparental disomy (UPD) (fig001gml).
Figure 2. Heterodisomy and isodisomy: imprinting or unmasking of a mutant recessive allele? (fig002gml).
Figure 3. Detection of imprinted expression during fetal development using an exonic polymorphism (fig003gml).
Figure 4. Diagrammatic representation of the mechanisms causing Prader–Willi syndrome (PWS) and Angelman syndrome (AS) (fig004gml).

Tables

Table 1. Genetic diseases caused by imprinting effects in humans (tab001gml).
Table 2. Human imprinted genes and their mouse orthologues (tab002gml).

Citation details for this article

Megan P. Hitchins and Gudrun E. Moore (2002) Genomic imprinting in fetal growth and development. Exp. Rev. Mol. Med. 9 May, http://www.expertreviews.org/0200457Xh.htm

Accession information: (02)00457-Xa.pdf (short code: txt001gml); 9 May 2002
ISSN 1462-3994