Human Molecular Genetics, 1998, Vol. 7, No. 10 Review 1599–1609

A catalogue of imprinted genes and parent-of-origin effects in humans and animals

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Received April 28, 1998

Parent-of-origin effects were first recorded >3000 years ago by mule breeders in Asia Minor. There are now several different types of evidence suggesting the presence of a large number of imprinted genes, many of which have not yet been identified. Here, we catalogue a wide range of evidence and phenomena which indicate or suggest the presence of genomic imprinting in animals. This evidence includes: the direct documentation of parent-of-origin-specific gene transcription; human disease inheritance patterns which suggest the involvement of imprinted genes; and older, less well studied animal models which may show parent-of-origin effects.

INTRODUCTION

Although parent-of-origin effects were clearly recognized by the mule breeders in Asia Minor >3000 years ago (1), formal demonstration of genomic imprinting was not achieved until 1991 when the selective maternal expression of *Igf2r*, the paternal expression of *Igf2* and the maternal expression of *H19* in mice were reported (2–4). Since this time, numerous genes have been shown to be subject to genomic imprinting, a process through which the expression of a gene is dependent on the sex of the parent from which it was inherited. Additionally, we now recognize several phenotypes in humans, mice and other animals which show a pattern of inheritance consistent with the involvement of imprinted genes. In retrospect, past writers clearly described parental effects some of which are attributable to genomic imprinting. For example, in 1937 Reed observed parental effects on the Fused phenotype in mice (5), in 1938 Walton and Hammond reported marked and persistent differences in the size of offspring from reciprocal Shire horse–Shetland pony crosses (6), while even Mendel clearly recognized 'non-Mendelian' inheritance patterns in some plant crosses when '[t]he hybrids had the greatest similarity to the pollen parent...' (7).

During the last year, the rapid increase in the number of imprinted genes has continued. Significant recent additions to the list of human imprinted genes include: *p73*, a putative tumour suppressor gene involved in neuroblastoma; *KvLQT1*, *IPL* and *IMPT1* in the imprinted cluster of genes on 11p15; necdin (*NDN*) and *UBE3A* in the Prader–Willi/Angelman disease locus on 15q; and genes on the X chromosome which influence the phenotype of Turner syndrome. The study of murine genes continues to provide a source of novel imprinted genes including that for neuronatin on chromosome 2; *Grb10*, a candidate for growth retardation on chromosome 7; the serotonin receptor 2a gene on chromosome 14 and *Impact* on chromosome 18.

In the lists that follow, we have attempted to include as many parent-of-origin effects as possible. The list is inclusive rather than critically selective, and reflects a wide variation in the quality and type of evidence for genomic imprinting. Several different types of evidence can suggest the presence of genomic imprinting. Firstly, the strongest evidence is provided by direct detection of parent-of-origin-specific transcription from a gene, for example as seen with *SNRPN* which is only transcribed from the paternally inherited allele. Detection of imprinted gene expression in some tissues does not necessarily indicate that the gene will be imprinted in all tissues. For example, *IGF2* which is imprinted in most tissues is expressed from both alleles in the liver and choroid plexus. Similarly, the absence of imprinting in some tissues obviously does not exclude imprinting in other tissues. For example, the Angelman syndrome gene, *UBE3A*, was thought not to be imprinted until allele-specific transcription was detected in the brain.

Secondly, several conditions show an imprinted pattern of inheritance, for example familial glomus tumours only occur by paternal inheritance. However, in this situation, linkage to the disease locus does not necessarily imply that the locus is directly responsible for the parent-of-origin effect.

Thirdly, the association of a specific phenotype with uniparental disomy (UPD) has implicated the presence of imprinted genes on many chromosomes. In humans, the presence of a phenotype in association with UPD does not necessarily indicate the involvement of imprinted genes since UPD is often associated with confined placental mosaicism which is itself associated with intrauterine growth retardation. In the presence of confined placental mosaicism, it is possible that the phenotype of a fetus or child with UPD may occur as a result of a population of ill-functioning trisomic cells in the placenta, rather than as a result of altered dose of an imprinted gene(s). For more detailed reviews of UPD, and for justification of conclusions regarding the likelihood of imprinting, see refs 8–11. In mice, UPD has been generated using animals heterozygous for various Robertsonian translocations (12,13). The presence of a developmental phenotype in association with UPD for a particular chromosomal region indicates the presence of imprinted genes within that segment. However, a normal phenotype cannot exclude the presence of an imprinted gene within the isodisomic segment, given that loss or gain of gene function might not necessarily give rise to a developmental phenotype.

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Table 1. Mapped parent-of-origin gene effects in humans

Chromosome	Location	Parent-of-origin effect	Reference
1	1p36	*p73* is maternally expressed and located in the region showing preferential maternal loss of heterozygosity in neuroblastoma.	22,23
	UPD	One case of maternal heterodisomy including partial isodisomy of 1q has been reported. No overt dysmorphic features or developmental anomalies were detected.	24
2	2p24	N-*Myc* is amplified preferentially from the paternal allele in neuroblastoma.	25
	UPD	Maternal UPD (five cases) is possibly associated with an abnormal phenotype.	26
4	4q21–q22	Anomalous imprinting has been hypothesized as the reason for the central nervous system overgrowth in the 4q21/4q23 syndrome (no direct evidence).	27
	UPD	Maternal UPD (one case) has been reported. Apart from infertility, the phenotype was normal and imprinting is unlikely.	10
5	5q22–q31	*U2AFBPL* the human homologue of *U2afbp-rs* (see mouse 11) is imprinted in mice but not in human placenta.	28
	UPD	Paternal UPD (one case) has been reported, but imprinting is unlikely.	10
6	6q25.3–q26	*MAS1* (a tyrosine kinase protooncogene) shows monoallelic expression in human breast, but was reported not to be imprinted in human fetuses.	29,30
	6q25.3	*IGF2R* (insulin-like growth factor II receptor; mannose 6-phosphate receptor, cation independent) is maternally expressed in mouse but there are conflicting data from humans. It may be imprinted polymorphically in humans. Allele-specific methylation (methylation of the active maternal allele) is maintained in humans.	2,31–36
	6q22–23	Neonatal diabetes mellitus. Two cases of neonatal diabetes had paternal UPD 6. Additionally, paternal UPD was associated with agenesis of pancreatic beta cells and neonatal diabetes although paternal UPD has also occurred in a normal child. The critical region may be 6q22–q23: two cases showed duplication 6q22–q23; one family showed linkage. The cases involving duplication suggest that gain of function of a paternally expressed gene is the mechanism of disease.	37–42
	UPD	UPD 6 has rarely been reported despite numerous studies of families at the HLA locus. Maternal UPD was detected in a developmentally normal patient. Paternal UPD is discussed above.	43
7	7p11.2–p12	*GRB10* (growth factor receptor-bound protein 10) is maternally expressed in mice but no human data have been reported (see mouse 7).	44
	7q11.23	Williams syndrome was associated with significantly more severe growth retardation and microcephaly if the associated deletion of 7q11.23 was maternally derived.	45
	7q32	*PEG1/MEST* (paternally expressed gene 1/mesoderm-specific transcript, member of the α/β-hydroxylase fold family) is paternally expressed in human fetal tissues, but biallelically expressed in adult blood. *Peg1* is imprinted in mice.	46–48
	UPD	Several cases of maternal iso- and heterodisomy in Russell–Silver syndrome indicate the presence of imprinted growth gene(s).	49,50
8	UPD	Paternal UPD is associated with normal development.	51
9	9q34	Loss of maternal ABO antigens has been reported in 4/4 acute myeloid leukaemia cases.	52
	UPD	Maternal UPD (four cases) has been reported, but parent-of-origin effects were considered unlikely.	8,10
10	UPD	Maternal UPD (two cases) has been reported, but parent-of-origin effects were considered unlikely.	8,10
11	11p15	The 11p15 region (involved in the Beckwith–Wiedemann syndrome) contains a number of imprinted genes, which are listed in order: *L23MRP* is at the telomeric end of this cluster and is not imprinted.	
		H19 is maternally expressed in mouse and humans. The gene product is an abundant untranslated RNA of unknown function.	2,53–56
		IGF2 (insulin-like growth factor 2, a fetal growth factor) is paternally expressed in humans and rodents. Expression is not imprinted in the choroid plexus, leptomeninges, brain, adult human liver and chondrocytes. It is probably imprinted secondarily under the control of the H19 locus.	4,55,57,58
		INS (insulin) is paternally expressed in mouse yolk sac, but not imprinted in human or mouse pancreas. Insulin is suspected to be imprinted in humans since the susceptibility to type 1 diabetes is significantly influenced by the parent-of-origin of insulin alleles, but the mechanism of this effect is unclear.	59–64
		ASCL2/HASH2 (achaete–scute complex like 2/human achaete–scute homologue 2, human homologue of murine *Mash2*, a helix–loop–helix transcription factor) is maternally expressed. It is expressed in human extravillous trophoblasts and in the spongiotrophoblast cells of mouse placenta.	65–67
		TAPA1: preliminary data suggest imprinting in the mouse (see mouse 7).	
		KCNA9 (KvLQT1, potassium channel involved in long QT syndrome) is maternally expressed. Its expression is imprinted in several tissues but not in the heart.	68

Table 1. *Continued*

Chromosome	Location	Parent-of-origin effect	Reference
		CDKN1C (*p57^{KIP2}*, a cyclin-dependent kinase inhibitor) was maternally expressed in humans and mouse. It is completely imprinted in mouse but only partially in humans.	69–72
		2G3–8 is under study, but may show allelic expression bias in some tissues.	73
		IMPT1/BWR1A.ORCTL2 (imprinted multi-membrane-spanning polyspecific transporter-like gene-1) is relatively repressed on the paternal allele.	73–75
		IPL/TSSC3/*BWR1C* (imprinted in placenta and liver, tumour-suppressing STF cDNA 3) shows maternal expression with relative repression of the paternal allele. It is expressed in placenta and most fetal tissues and is homologous to mouse apoptosis-promoting gene *TDAG51*.	75–77
		NAP2 is at the centromeric end of the cluster and is not imprinted.	
	11p13	*WT1* (Wilms tumour 1, a zinc finger protein): there are conflicting data. It was reported to be partially or completely imprinted and maternally expressed in some tissues (placenta and brain) but was paternally expressed in fibroblasts and lymphocytes from some individuals.	78,79
	11q13	*FCERIB* (β subunit of the high-affinity IgE receptor): in allergic asthmatics, the Leu181 allele was always maternally inherited (10/10 families).	80
	11q13.1, 11q22.3–q23.3	Familial glomus tumours (non-chromaffin paragangliomas): linkage studies suggest two distinct loci, but the tumour susceptibility is always inherited from carrier fathers.	81–84
13	13q14	*RB* locus: the retinoblastoma gene itself does not appear to be imprinted, but there may be parent-of-origin effects on the transmission of retinoblastoma susceptibility in humans and in mice (earlier onset of tumours when mutant *Rb* is paternally inherited). In an unexplained observation, the parental origin of a chromosomal rearrangement near *RB* affected the *Nru*I restriction enzyme digestion pattern.	85–87
	13q14	*HTR2a* [serotonin (hydroxytryptamine) receptor type 2a] was expressed biallelically in normal tissues, but in fibroblasts of retinoblastoma patients with germline deletions or translocations it was only expressed in those with a paternally derived deletion or translocation (5/5), but not in those with a maternal deletion (2/2). Promoter region methylation (partial) corresponded positively with expression. It is imprinted in mouse (see mouse 14).	88
	UPD	Maternal (three cases) and paternal UPD (one case) have been reported, but parent-of-origin effects are unlikely.	10
14	14q24.3–q31	A case report of dup(14q24.3–31), inherited from a phenotypically normal father, suggests that this region may be imprinted.	89
	UPD	Both paternal and maternal UPD suggest parent-of-origin effects on this chromosome. Maternal uniparental heterodisomy and isodisomy (eight cases in the literature) is associated with a characteristic phenotype [hypotonia, motor developmental delay, mild dysmorphic facial features, low birth weight, growth abnormalities (precocious puberty)]. Paternal UPD (four cases) is associated with a severe mental and musculoskeletal phenotype.	8,10,90–92
15	15q11–q13	The 15q11–q13 region contains a cluster of imprinted genes that may be involved in the pathogenesis of the Prader–Willi and Angelman syndromes; they are listed in order from the centromeric end:	93
		ZNF127 and *FNZ127* are two overlapping paternally expressed transcripts. ZNF127 putatively encodes a 505 amino acid polypeptide-containing zinc finger motif.	93–95
		NDN (necdin) is paternally expressed in brain (human and mouse) and fibroblasts. It is expressed in differentiated neurones.	96–98
		BD exons of *SNRPN*. This region may constitute the 15q imprinting centre and is comprised of alternate 5′ exons (the BD exons, BD1B, BD1B*, BD1A, BD2, BD3) of *SNRPN*. Mutations of these exons cause Angelman syndrome perhaps through failure to erase the imprint from the previous generation.	99–101
		SNRPN (small nuclear ribonucleoprotein-associated polypeptide N) is paternally expressed and may be involved in the pathogenesis of Prader–Willi syndrome. It may be imprinted secondarily, under the control of an imprinting centre.	102,103
		PAR-SN (an RNA transcript between *SNRPN* and *PAR5*) is paternally expressed in lymphoblasts.	100
		PAR5 (*D15S226E*) (Prader–Willi/Angelman region) is paternally expressed but contains no open reading frames.	103
		IPW (imprinted in Prader–Willi) is paternally expressed but probably untranslated.	104
		PAR1 (*D15S227E*) (Prader–Willi/Angelman region) is paternally expressed but probably contains no open reading frames.	103
		UBE3A/E6-AP (ubiquitin protein ligase 3A) is maternally expressed in human and mouse brain, but is biallelically expressed in other tissues. This gene is mutated in some cases of Angelman syndrome, deleted in others (60–70%), and affected by paternal UPD in others.	105,106
		GABAA receptor subunit genes (*GABRB3*, *GABRA5*, *GABRG3*) are paternally expressed. There is paternal methylation of the 5′ end of *GABRB3*.	107

Table 1. *Continued*

Chromosome	Location	Parent-of-origin effect	Reference
	15q11–q13	Autism in a family was associated with a 15q11–q13 duplication only when maternally transmitted.	108
16	UPD	Maternal UPD (nine cases) has been reported, but most had trisomy 16 mosaicism, to which growth retardation could be attributed. Imprinting was considered possible based on studies of 26 patients with placental mosaicism for trisomy 16 and based on developmental anomalies in a minority of patients (anal atresia and hypospadius). Paternal UPD (1 case) has been reported, but parent-of-origin effects were considered unlikely.	10,11
19	19q13.4	*PEG3*, the human homologue of imprinted mouse gene *Peg3* (see mouse 7) is located here, but its imprinting status has not been reported.	109
20	20q13.11	*GNAS* (Gs alpha, a G protein) is assumed to have specific paternal expression in some tissues based on *in situ* hybridization in mice with PatDp2 and MatDp2 and in humans because of the transmittance pattern of Albright hereditary osteodystrophy (33/36 transmitting parents were maternal). All 60 maternal offspring had full expression of the phenotype (pseudo-hypoparathyroidism type Ia) whereas all six paternal offspring had partial expression (pseudopseudo-hypoparathyroidism). However, transcription in human fetal tissues was not imprinted.	110–112
21	UPD	Maternal (three cases) and paternal UPD (two cases) have been reported, but parent-of-origin effects were considered unlikely.	10
22	UPD	Maternal (three cases) and paternal UPD (one case) have been reported, but parent-of-origin effects were considered unlikely.	10,113
X	Xq13.2	*XIST* shows preferential paternal expression with associated silencing of the paternal X chromosome in the extraembryonic tissues of mouse and in trophoblastic cells in humans. *XIST* is an untranslated RNA. Most genes on the X chromosome could be described as secondarily imprinted, in response to *XIST* expression.	114–117
	Xp11.23–Xqter	Turner syndrome patients with a maternally retained X (45,Xm) showed significantly poorer verbal and higher-order executive function skills than those with 45,Xp. A higher prevalence of cardiovascular abnormalities and neck webbing was noted when the retained X was maternal.	118,119
	UPD	Maternal UPD had no obvious clinical stigmata. Paternal UPD (one case) was associated with impaired gonadal function and shortness of stature.	120,121

Table 2. Other human conditions showing unmapped parental effects

Condition	Unmapped parental effects	Reference
Hirschsprung disease	Patients with familial Hirschsprung disease were more likely to inherit the mutant RET protooncogene (10q11.2) from their mothers.	122
Neurofibromatosis type 2	This shows earlier onset and more severe disease when maternally inherited. NF2 is caused by mutations of *SCH/Merlin* on 22q12.	123,124
Schizophrenia	Affected sibling pairs were more likely to be of the same sex when the history of schizophrenia was on the paternal side. Negative symptom scores and clinical course scores were significantly higher (worse) when paternally inherited, but there is also evidence for anticipation, suggesting the involvement of an unstable trinucleotide repeat. In contrast, some groups have found no evidence of true anticipation or of a parental effect on age of onset.	125–128
Bipolar affective disorder	Cases with paternal transmission showed earlier onset, and anticipation was found only with paternal inheritance. This effect may be attributable to trinucleotide repeat expansions. The presence of parental effects has been disputed by others.	127,129–135
Progressive diaphyseal dysplasia	Imprinting and/or paternal-specific repeat expansion has been proposed to explain phenotypic variability and possible anticipation in a three-generation family.	136
Brachmann–de Lange syndrome	In all convincing autosomal dominant cases, the transmitting parent was the mother. This syndrome shows a variable phenotype with growth retardation, facial dysmorphism including micrognathia, microbrachycephaly, small hands and feet, and mental retardation.	137
Familial hypertrophic cardiomyopathy	In a Mennonite kindred with dominant cardiomyopathy not linked to β-myosin heavy chain gene, a disproportionate number of transmitting parents were females, i.e. 2/32 (6%) offspring of males were affected versus 7/12 (58%) offspring of females.	138
Spina bifida	There were twice as many gene-carrying mothers as fathers.	139
Psoriasis vulgaris	Parental effect on birth weight has been reported, and paternal inheritance caused more severe disease.	140
Tourette syndrome	This syndrome showed parent-of-origin phenotype differences, and maternally transmitted offspring showed a significantly earlier age at onset. These differences have not been confirmed by others.	141–143
Polycystic kidney disease	Predominantly maternal transmission of PKD has been reported, along with an earlier onset of disease when maternally inherited, but this was not confirmed by others.	144,145
Crohn's disease	Among 33 non-Jewish parent–child pairs with Crohn's didease, 28 involved maternal transmission, whereas five involved paternal transmission.	146
Epilepsy	A higher risk of seizures has been reported in the offspring of mothers than of fathers with epilepsy.	147

Table 3. Mouse imprinted regions and genes

Chromosome	Region	Comments	Reference
2	Proximal	Maternal disomy causes early embryonic lethality.	13
	Distal	There may be two imprinted regions. Neuronatin (*Nnat, Peg5*) is paternally expressed, maternally methylated, and expressed in pituitary, central and peripheral nervous systems. In a more distal region which contains *Gnas* (see human 20q13), both maternal and paternal disomy cause neonatal lethality.	13,148,149
6	Proximal	Maternal disomy of this region, which includes *Peg1/Mest* (see human 7q), is associated with early embryonic lethality.	13,48
7	Proximal	*Peg3/Apoc2* is a paternally expressed, zinc finger protein. *Asp3* (audiogenic seizure prone gene 3) is an as yet unidentified gene linked to proximal chromosome 7. The susceptibility of epilepsy-prone mice to audiogenic seizures was dependent on parental origin. Maternal disomy shows late fetal lethality with fetal and placental growth retardation.	13,48,150,151
	Central	This region is syntenic with human 15q11–q13 and includes *Ndn, Snrpn, Ipw, Ube3a* and *Znf127*.	93,98,152–154
	Distal	This region is syntenic with human 11p15.5 and includes *H19, Igf2, Ins2, Mash2, Tapa1, Kvlqt1, p57^{Kip2}, Impt* and *Ipl*. Preliminary data indicate that *Tapa1* shows relative repression of the paternal allele in extra-embryonic tissues.	3,4,59,66,69,73, 77,155
		Evidence from marsupials suggests that the common location of the central 7 and distal 7 imprinted gene clusters has occurred by chance, and does not suggest an evolutionary relationship.	156
9		*Grf1 (Irlgs2/Cdc25Mm*, a guanine nucleotide exchange factor) is paternally expressed, but the maternal allele is expressed at low levels (<10% of paternal levels) in brain.	157
11	Proximal	*U2afbp-rs/U2af1-rs1/D11Ncvs75* (U2 small nuclear ribonucleoprotein auxiliary factor-binding protein-related sequence) is paternally expressed. The human homologue (*U2AFBPL*) is not imprinted in placenta.	28,158,159
		Grb10/Meg1 (growth factor receptor-bound protein 10/maternally expressed gene 1) is maternally expressed. The GRB10 protein binds to the insulin receptor and the IGF1 receptor, and is a candidate for the growth retardation of Russell–Silver syndrome in humans.	44
		Maternal disomy resulted in small size (0.7× normal) whereas paternal disomy resulted in large size (1.3× normal). The mice were otherwise normal and fertile.	13
12		*Gtl2lacZ*: a dwarfism phenotype resulting from an insertional mutation of a *LacZ*-containing transgene. Although expression from the transgene was not affected by its parent-of-origin, the mutant dwarfism phenotype was expressed most strongly when paternally inherited.	160
	Distal	Early embryonic lethality occurs when both alleles are inherited paternally.	13
14	Band D3	*Htr2* (serotonin receptor 2a) shows maternal expression in mouse cerebrum, ovary and embryonic eye.	161
		Rb1 (retinoblastoma gene): there is no direct evidence of imprinting, but melanotroph tumours have an earlier onset when mutant *Rb1* is paternally inherited.	86
17	Proximal	This includes the *Tme* locus (T-maternal effect) which is related to the Hairpin tail mutation locus. This phenotype is attributable to disruption of the imprinted gene *Igf2r* (insulin-like growth factor 2 receptor). *Igf2r* is maternally expressed in mouse but there are conflicting data in humans.	2,31–36
		Mas (65 kb from *Igf2r*; cell surface receptor and proto-oncogene) was reported to be paternally expressed but this has been disputed. The human data are also conflicting (see human 6q25.3–q26).	162,163
		Fu (fused): the penetrance of the autosomal fused gene was strongly dependent on its parental origin. For example, when maternally inherited, ~33% of heterozygotes had a fused skeletal phenotype compared with 81% when paternally inherited.	5
	Distal	Paternal disomy causes small body size (0.7× normal) evident from day 7 after birth.	13
18	Proximal	*Impact* (imprinted and ancient, belongs to the YCR59c/yigZ protein family with unknown function) is paternally expressed. It was identified by allelic message display.	164
		Maternal and paternal disomy are possibly associated with growth retardation.	165
19	Distal	*Ins1* (insulin 1) is paternally expressed. It was reported to be imprinted in yolk sac at day 16, but not in the pancreas. In contrast, others found no evidence of imprinting at days 12.5, 13.5 and 14.5. It has no human homologue.	59,166
X		*Xist*: there is preferential inactivation of the paternal X chromosome in extra-embryonic tissues, corresponding to preferential expression of the paternal Xist.	115,116,167
		Mdx (dystrophin) expression: parent-of-origin effects on the proportion of muscle cells expressing dystrophin in mice inheriting a heterozygous null mutation of dystrophin have been reported.	168
		Ovarian granulosa cell carcinoma: an X-linked imprinted gene modifies the predisposition to tumorigenesis in SWR and SWRXJ mice.	169

Where genes have shown to be imprinted in both mice in humans, we refer the reader to the appropriate human chromosome for additional details. For additional details and references see Cattanach and Beechey's mouse imprinting map (13).

Table 4. Other parent-of-origin effects in animals

Phenotype	Parent-of-origin effect	Reference
Mouse body size	In crosses between *Peromyscus polionotus* (the old field mouse, monogamous) and *P.maniculatus* (deer mouse, polygamous), the size of the offspring depended on the direction of the cross.	170
Mouse fat pad weight	Imprinting has been suggested as a possible explanation for matrilineal and patrilineal effects on the size of epididymal and retroperitoneal fat pads in SWR/J×AKR/J mice.	171
G6PD in mouse	A parental effect on allele-specific expression levels of G6PD has been reported.	172
Megakaryocyte production in mice	Platelet counts, total circulating platelet counts and platelet size were influenced by the parent of origin.	173
Egg susceptibility to hyaluronidase and pronase	In mice, this was influenced by the parent-of-origin.	174
MHC class I antigen expression in rats	Only paternal class I antigens were expressed in the placenta of crosses between WF(u) and DA(a) rat strains.	175–177
Transgene expression in mice	For many transgenes, the expression and methylation of the gene depends on the parental origin of the transgene. These models of imprinting also demonstrate the importance of strain-specific modifiers of the imprinting process.	178,179
Chorionic gonadotrophin beta in horses	This hormone is probably imprinted in the horse and donkey. The expression levels and its ovarian effects are dependent on the parental origin in horse–donkey crosses.	180–183
Horse size	Reciprocal crosses between the large Shire horse and the small Shetland pony showed marked and persistent differences in the size of the offspring, depending on the direction of the cross.	6
Appearance of horse–donkey cross	A horse mare–donkey cross gives rise to a mule, whereas a donkey–stallion cross produces a hinny.	184,185
Sheep buttock size	The callipyge gene phenotype (‘beautiful buttocks’) is only expressed when paternally inherited.	186
ADH expression in chicken–quail hybrids	Repression of the paternal alcohol dehydrogenase allele has been reported in unidirectional crosses.	187
Frog body size	In frog crosses, there was a parent-of-origin effect on the body and head size.	188
Enzyme expression in fish	There are several examples of repression of specific parental enzyme alleles, some of which may be attributable to inter-species effects. For example, the paternal allele of 6-phosphogluconate dehydrogenase was repressed at a specific developmental stage of Cyprinid fish (*Rutilus rutilus*). Transient repression of the maternal isozyme of α-glycerophosphate dehydrogenase was observed in offspring from a female brown trout and a male brook trout, but not for the reciprocal cross. Repression of the maternal allele of glucose 6-phosphate dehydrogenase, the maternal allele of a liver esterase, and repression of a paternal esterase has been observed in intertribal or interspecific sunfish hybrids (one directional crosses only).	189–192
Transgene expression in Zebra fish	Parental effects on transgene methylation have been reported, but androgenetic zebrafish develop normally, suggesting that genes essential for development are not imprinted.	193,194
Drosophila mutant phenotype	In 1959, Spofford reported that the greatest source of phenotypic variation in the expression of a mutant white locus gene was the parental source of the causative translocation. In a transgenic model of position effect variegation enhancement, using *Drosophila* with the *In(1)*w^{m4h} mutation, w^{m4h} gene repression in the offspring was strictly dependent on the previous paternal transmission of the transgene. This effect may correspond to the intergenerational Y chromosome-linked ‘genetic imprinting’ observed in an *E(var)3-93D* mutant. In another report, *In(l)*w^{m4} mutants were subject to ‘genomic imprinting’ in that the extent of variegation in eye colour was influenced by the genetic background that the variegating chromosome was subjected to during gametogenesis. However, the effect was not dependent on the parental origin.	195–198
Sex determination in *Nasonia vitripennis* (parasitic wasp)	Sex determination was directly correlated with the embryonic presence of correctly imprinted chromosomes of paternal origin, supporting a model of ‘genomic imprinting sex determination’.	199

Some of the putative imprinting parental effects may be attributable to a parental bias in the probability of a ‘mutational’ event occurring during the development of either the oocyte or of spermatozoa (14). For example, *de novo* mutations of several genes including *WT1* (15), *RB* (16,17), *NF1* (18) and *RET* (19) almost always occur during male gametogenesis, whereas deletions causing DiGeorge syndrome may occur more frequently during oogenesis (20). Similarly, the expansion of trinucleotide repeats associated with conditions such as fragile X syndrome, Huntington disease, myotonic dystrophy, spinal and bulbar muscular atrophy, spinocerebellar ataxia type 1, dentatorubral-pallidoluysian atrophy and Machado–Joseph disease almost all show expansion during male gametogenesis (21).

ACKNOWLEDGEMENTS

We thank the University of Otago Science Library staff and Sue Cleverley for assistance in collecting and collating reference material. This work has been supported by grants from the Cancer

Society of New Zealand, the New Zealand Lottery Grants Board and the Health Research Council of New Zealand.

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