Imprinted genes in mouse placental development and the regulation of fetal energy stores

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Abstract

Imprinted genes, which are preferentially expressed from one or other parental chromosome as a consequence of epigenetic events in the germline, are known to functionally converge on biological processes that enable *in utero* development in mammals. Over 100 imprinted genes have been identified in the mouse, the majority of which are both expressed and imprinted in the placenta. The purpose of this review is to provide a summary of the current knowledge regarding imprinted gene function in the mouse placenta. Few imprinted genes have been assessed with respect to their dosage-related action in the placenta. Nonetheless, current data indicate that imprinted genes converge on two key functions of the placenta, nutrient transport and placental signalling. Murine studies may provide a greater understanding of certain human pathologies, including low birth weight and the programming of metabolic diseases in the adult, and complications of pregnancy, such as pre-eclampsia and gestational diabetes, resulting from fetuses carrying abnormal imprints.

Reproduction (2013) **145** R117–R137

Introduction

The first evidence that both parental genomes are required for correct extraembryonic development in mammals came from studies on uniparental embryos generated by microsurgical manipulation of newly fertilised mouse embryos. Gynogenetic and parthenogenetic (two maternal genomes) embryos appear relatively normal but are growth restricted and die around embryonic day (E) 10 with abnormal development of the extraembryonic tissue. In contrast, androgenetic (two paternal genomes) embryos are both developmentally delayed and growth restricted, dying around E8.5, with an abundance of hyperplastic extraembryonic tissue (Kaufman *et al.* 1977, Surani & Barton 1983, Barton *et al.* 1984, McGrath & Solter 1984, Surani *et al.* 1986). Studies of uniparental disomic (UPD) embryos further highlighted the functional requirement for both parental genomes at certain chromosomal regions in placental development (Cattanach & Kirk 1985, Searle & Beechey 1990, McLaughlin *et al.* 1996, Cattanach *et al.* 2004). To date, over 100 imprinted genes have been identified in the mouse, the majority of which are both expressed and imprinted in the placenta (Table 1). Furthermore, X-linked genes that undergo inactivation can also be considered imprinted in the mouse placenta (Takagi & Sasaki 1975, West *et al.* 1977).

While imprinted genes have traditionally been described as genes that exhibit monoallelic expression in a parent-of-origin-dependent manner (Mochizuki

et al. 1996, Pfeifer 2000, Ferguson-Smith & Surani 2001, Reik & Walter 2001), such a definition belies the complex expression patterns exhibited by imprinted genes, with many displaying preferential, rather than strict monoallelic, expression of parental alleles (Khatib 2007). Some genes are imprinted in all cell types, while others are imprinted in only a subset (Deltour *et al.* 1995, Hu *et al.* 1998, Yu *et al.* 1998, Charalambous *et al.* 2003, Dockery *et al.* 2009). In particular, a number of genes imprinted in the placenta are not imprinted in the embryo (Hudson *et al.* 2010, Okae *et al.* 2012). Thus, genomic imprinting more accurately describes the complete or partial parental-allele-biased expression of a gene in one or more cell types.

Development and structure of the mouse placenta

The development of the mouse placenta and the characteristics and functions of the trophoblast cell types have been extensively reviewed (Rossant & Cross 2001, Watson & Cross 2005). Here, we briefly describe key features of placental development in the mouse relevant to this review.

The trophoblast is the first discernable lineage to arise during embryogenesis, which by E3 of development forms a monolayer of trophoblast cells encasing the inner cell mass (ICM; Fig. 1A). Following implantation at E4.5, the trophoblast cells overlying the ICM proliferate inwards to form the extraembryonic ectoderm and outwards to form the ectoplacental cone (Fig. 1B).

Table 1 Expression and imprinting of autosomal genes in the mouse placenta.

Gene	Active allele	Chr	Placental expression	Placental imprinting	Placenta functional data	Comments	References
<i>Cpr1</i>	P	1	Yes	Biallelic	No	Biallelic in E13.5 placenta Imprinted only in kidney	Hiura <i>et al.</i> (2010) and Okae <i>et al.</i> (2012)
<i>Zdbf2</i>	P	1	Yes	Conflicting data	No	Imprinted E13.5 and E17.5 placenta Imprinted in E9.5 embryo	Babak <i>et al.</i> (2008), Kobayashi <i>et al.</i> (2009), Hiura <i>et al.</i> (2010), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Sim1b2</i>	P	2	Yes	Imprinted	No	Biallelic in E15.5 placenta Imprinted in early embryo and placenta	Kuzmin <i>et al.</i> (2008), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Wt1</i>	M	2	Yes (decidua)	Conflicting data	No	Biallelic in embryo from ~E7.5 Previously reported placental allelic bias probably due to contamination with decidual cells	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Gatm</i>	M	2	Yes (decidua)	Conflicting data	No	Biallelic in E9.0 placenta Previously reported placental imprinting possibly due to contamination with decidual cells	Sandell <i>et al.</i> (2003) and Okae <i>et al.</i> (2012)
<i>H13</i>	M	2	Yes	Imprinted	No	Biallelic in E9.0 placenta	Wood <i>et al.</i> (2007b) and Wang <i>et al.</i> (2011)
<i>Mct52</i>	P	2	Not reported	Not reported	No	Imprinted in E13.5 placenta and embryo Imprinted in E13.5 embryo and newborn brain	Wood <i>et al.</i> (2007b)
<i>Nnat</i>	P	2	Yes	Imprinted	No	Biallelic in testes Imprinted in E17.5 placenta and brain	Kagitani <i>et al.</i> (1997), Kikyo <i>et al.</i> (1997) and Wang <i>et al.</i> (2011)
<i>Bicap</i>	M	2	Yes	Biallelic	No	Imprinted in brain Potentially a consequence of transcript interference from maternal <i>Nnat</i> expression	Schulz <i>et al.</i> (2009), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Zip64</i>	P	2	Yes	Imprinted	No	Imprinted in E17.5 placenta	Wang <i>et al.</i> (2011)
<i>Gnas</i>	M	2	Yes	Biallelic	No	Imprinted in adipose tissue Biallelic in kidney	Yu <i>et al.</i> (1998) and Okae <i>et al.</i> (2012)
<i>Nesp</i>	M	2	Yes	Imprinted	No	Imprinted in placenta and embryo	Peters <i>et al.</i> (1999) and Wang <i>et al.</i> (2011)
<i>Nespas</i>	P	2	Yes	Imprinted	No	Imprinted in E13.5 placenta and E15.5 embryo	Wroe <i>et al.</i> (2000) and Okae <i>et al.</i> (2012)
<i>Gnasxl</i>	P	2	Not reported	Not reported	No	Imprinted in E11.5 embryo	Peters <i>et al.</i> (1999)
<i>Ex1A</i>	P	2	Not reported	Not reported	No	Imprinted in brown adipose tissue (BAT)	Liu <i>et al.</i> (2000)
<i>Phf17</i>	P	3	Yes	Imprinted	No	Imprinted in E17.5 placenta	Wang <i>et al.</i> (2011)
<i>Magi2</i>	M	5	Yes	Imprinted	No	Imprinted in E14.5 and E17.5 placenta Imprinting reported in E17.5 placenta but expression restricted to decidua	Barboux <i>et al.</i> (2012) Nie <i>et al.</i> (2006) and Wang <i>et al.</i> (2011)
<i>Htra3</i>	M	5	Yes (decidua)	Imprinted	No		
<i>Calcr</i>	M	6	Not reported	Not reported	No	Imprinted in brain Biallelic in all other tissues examined	Hoshiya <i>et al.</i> (2003)
<i>Tipi2</i>	M	6	Yes (decidua)	Imprinted (TS cells)	No	Placental imprint masked by decidual contamination	Monk <i>et al.</i> (2008) and Okae <i>et al.</i> (2012)
<i>Casd1</i>	M	6	Yes	Conflicting data	No	Imprinted in TS cells Biallelic in embryo	Ono <i>et al.</i> (2003), Babak <i>et al.</i> (2008) and Okae <i>et al.</i> (2012)
<i>Sgce</i>	P	6	Yes	Imprinted	No	Imprinted in E13.5 placenta Biallelic in E10 and E13 placenta	Piras <i>et al.</i> (2000), Monk <i>et al.</i> (2008), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Peg10</i>	P	6	Yes	Imprinted	Yes	Imprinted in embryo Imprinted in placenta, embryo and adult	Ono <i>et al.</i> (2003), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Ppp1r9a</i>	M	6	Yes	Imprinted	No	Imprinted in placenta and embryo Biallelic in neonate	Ono <i>et al.</i> (2003), Nakabayashi <i>et al.</i> (2004), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Pon3</i>	M	6	Yes (decidua)	Conflicting data	No	Previously reported placental allelic bias probably due to contamination with decidual cells Biallelic in E9.0 placenta	Ono <i>et al.</i> (2003) and Okae <i>et al.</i> (2012)

<i>Pon2</i>	M	6	Yes (decidua)	Conflicting data	No	Imprinted in E10 placenta and E13 yolk sac Conflicting data from E13.5 placenta following embryo transfer to eliminate decidua contamination Biallelic in E17.5 placenta and neonate Biallelic in TS cells	Ono <i>et al.</i> (2003), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Asb4</i>	M	6	Yes	Imprinted	No	Imprinted in E9.5 and E15.5 placenta and embryo	Mizuno <i>et al.</i> (2002) and Wang <i>et al.</i> (2011)
<i>Peg1/Mest</i>	P	6	Fetal vasculature only	Imprinted	Yes	Imprinted in E13.5 placenta and E9.5 embryo	Kaneko-Ishino <i>et al.</i> (1995), Mayer <i>et al.</i> (2000), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Copg2as1</i>	P	6	Not reported	Not reported	No	Imprinted in embryos, neonates and adult	Lee <i>et al.</i> (2000)
<i>Copg2as2</i>	P	6	Yes	Imprinted	No	Imprinted in E13.5 placenta, from ~E13.5 in embryos and in neonate and adult	Lee <i>et al.</i> (2000) and Okae <i>et al.</i> (2012)
<i>Copg2</i>	M	6	Yes	Biallelic	No	Biallelic in E13.5 placenta	Lee <i>et al.</i> (2000) and Okae <i>et al.</i> (2012)
<i>Klf14</i>	M	6	Yes	Imprinted	No	Imprinted in embryo and brain	Parker-Katirae <i>et al.</i> (2007) and Wang <i>et al.</i> (2011)
<i>Nap1/5</i>	P	6	Yes (low)	Not reported	No	Imprinted in brain	Smith <i>et al.</i> (2003) and Davies <i>et al.</i> (2004)
<i>Cntn3</i>	M	6	E13.5: no E17.5: yes?	Unconfirmed	No	Imprinted in E17.5 placenta Biallelic in E17.5 brain	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Klrb1f</i>	M	6	E13.5: no E17.5: yes?	Unconfirmed	No	Not expressed in E13.5 placenta Biallelic in E17.5 brain	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Zim2</i>	M	7	Not reported	Not reported	No	Not expressed in E13.5 placenta	Kim <i>et al.</i> (2004)
<i>Zim1</i>	M	7	Yes	Imprinted	No	Imprinted in brain Biallelic in testes	Kim <i>et al.</i> (1999), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Peg3as</i>	P	7	Not reported	Not reported	No	Imprinted in E13.5 and E17.5 placenta, embryo and neonate	Choo <i>et al.</i> (2008)
<i>Peg3</i>	P	7	Yes	Imprinted	Yes	Biallelic in neonatal and adult brain Brain-specific expression and imprinting	Kaneko-Ishino <i>et al.</i> (1995), Kuroiwa <i>et al.</i> (1996), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Usp29</i>	P	7	Yes	Imprinted	No	Imprinted in placenta, embryo	Kim <i>et al.</i> (2000), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Zim3</i>	M	7	Not reported	Not reported	No	Imprinted in neonatal and adult brain	Kim <i>et al.</i> (2001)
<i>Zip264</i>	P	7	Not reported	Not reported	No	Imprinted in testes	Kim <i>et al.</i> (2001)
<i>Axl</i>	M	7	Yes	Imprinted	No	Imprinted in brain and testes Imprinted in extraembryonic tissue until mid gestation	Choutani <i>et al.</i> (2011)
<i>Atp10a</i>	M	7	Yes	Biallelic	No	Biallelic in embryo	Kashiwagi <i>et al.</i> (2003) and Okae <i>et al.</i> (2012)
<i>Ube3a</i>	M	7	Yes	Biallelic	No	Imprinted in some brain regions Biallelic in E13.5 placenta	Miura <i>et al.</i> (2002), Yamasaki <i>et al.</i> (2003) and Okae <i>et al.</i> (2012)
<i>Ube3a-as</i>	P	7	Not reported	Not reported	No	Imprinted in brain Biallelic in E13.5 placenta	Yamasaki <i>et al.</i> (2003)
<i>Ipw</i>	P	7	Not reported	Not reported	No	Imprinted in brain (overlapping expression with <i>Ube3a</i>)	Wevrick & Francke (1997)
<i>Snord115</i>	P	7	No	–	No	Imprinted in adult	Cavaille <i>et al.</i> (2000)
<i>Snord116</i>	P	7	No	–	No	Brain-specific expression and imprinting	Cavaille <i>et al.</i> (2000)
<i>Snord64</i>	P	7	No	–	No	Brain-specific expression and imprinting	Cavaille <i>et al.</i> (2000)
<i>Snrpn/Snrpf</i>	P	7	Yes	Imprinted (TS Cells)	No	Imprinted in all tissues examined from ~E7.5 Placental imprinting analysis complicated by maternal contamination	Leff <i>et al.</i> (1992), Barr <i>et al.</i> (1995), Gray <i>et al.</i> (1999), de los Santos <i>et al.</i> (2000) and Fortier <i>et al.</i> (2008)
<i>Pec2</i>	P	7	Not reported	Not reported	No	Imprinted in TS cells	Buettner <i>et al.</i> (2005) and Schulz <i>et al.</i> (2006)
<i>Pec3</i>	P	7	Not reported	Not reported	No	Imprinted in neonatal CNS Imprinted in neonatal CNS	Buettner <i>et al.</i> (2005) and Schulz <i>et al.</i> (2006)

(continued)

Table 1 Continued.

Gene	Active allele	Chr	Placental expression	Placental imprinting	Placenta functional data	Comments	References
<i>Ndn</i>	P	7	Yes	Conflicting data	No	Imprinted in brain Imprinted in E17.5 placenta	MacDonald & Wevrick (1997), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Mage2</i>	P	7	Yes	Imprinted	No	Biallelic in E13.5 placenta	Boccaccio <i>et al.</i> (1999) and Wang <i>et al.</i> (2011)
<i>Mkm3/Zip127</i>	P	7	Not reported	Not reported	No	Imprinted in E17.5 placenta and adult brain	Hershko <i>et al.</i> (1999) and Jong <i>et al.</i> (1999)
<i>Zfp127as</i>	P	7	Not reported	Not reported	No	Imprinted in brain, heart and kidney	
<i>Peg12</i>	P	7	Yes	Biallelic	No	Very low expression relative to <i>Mkm3</i> Imprinted in brain	Cattanach <i>et al.</i> (1997) and Jong <i>et al.</i> (1999)
<i>Art5</i>	M	7	E13.5: no E17.5: yes?	Unconfirmed	No	Biallelic in placenta	Chai <i>et al.</i> (2001) and Kobayashi <i>et al.</i> (2002)
<i>Ampd3</i>	M	7	Yes (decidua)	Conflicting data	No	Imprinted in E17.5 placenta Biallelic in E17.5 brain Not expressed in E13.5 placenta Previously reported placental imprinting possibly due to contamination with decidual cells	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Inpp5f_v2</i>	P	7	No	–	No	Brain-specific expression and imprinting	Schulz <i>et al.</i> (2006) and Okae <i>et al.</i> (2012)
<i>Inpp5f_v3</i>	P	7	No	–	No	Biallelic in E9.0 placenta	
<i>H19</i>	M	7	Yes	Imprinted	Yes	Brain-specific expression and imprinting Imprinted in placenta and embryo	Choi <i>et al.</i> (2005) Wood <i>et al.</i> (2007a) and Yan <i>et al.</i> (2011) Bartolomei <i>et al.</i> (1991), Svensson <i>et al.</i> (1998), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Igf2as</i>	P	7	Yes	Imprinted	No	Imprinted in E17.5 placenta	Moore <i>et al.</i> (1997) and Wang <i>et al.</i> (2011)
<i>Igf2</i>	P	7	Yes	Imprinted	Yes	Imprinted in placenta and embryo Restricted biallelic expression in adult	DeChiara <i>et al.</i> (1991), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Ins2</i>	P	7	Not reported	Not reported	No	Imprinted in yolk sac	Deltour <i>et al.</i> (1995)
<i>Th</i>	M	7	Yes	Imprinted	Homozygous lethal	Imprinted in placenta	Zhou <i>et al.</i> (1995) and Okae <i>et al.</i> (2012)
<i>Ascl2</i>	M	7	Yes	Imprinted	Yes	Imprinted in placenta from ~E8.5	Guillemot <i>et al.</i> (1995) and Okae <i>et al.</i> (2012)
<i>Tspan32</i>	M	7	Yes (TS cells)	Imprinted (TS cells)	No	Imprinted in TS cells	Okae <i>et al.</i> (2012)
<i>Cd81</i>	M	7	Yes	Imprinted	No	Imprinted in placenta and embryo until ~E8.5	Caspary <i>et al.</i> (1998)
<i>Tssc4</i>	M	7	Yes	Imprinted	No	Imprinted in E13.5 placenta	Okae <i>et al.</i> (2012)
<i>Kcnq1</i>	M	7	Yes	Imprinted	No	Imprinted in placenta Biallelic in yolk sac at E12.5	Gould & Pfeifer (1998), Umlauf <i>et al.</i> (2004) and Wang <i>et al.</i> (2011)
<i>Kcnq1ot1</i>	P	7	Yes	Imprinted	Yes	Imprinted in early embryo, progressively biallelic in placenta and embryo	Smilnich <i>et al.</i> (1999), Mancini-DiNardo <i>et al.</i> (2003, 2006) and Okae <i>et al.</i> (2012)
<i>Cdkn1c</i>	M	7	Yes	Imprinted	Yes	Imprinted in placenta, embryo and adult	Hatada & Mukai (1995), Takahashi <i>et al.</i> (2000) and Wang <i>et al.</i> (2011)
<i>Slc22a18</i>	M	7	Yes	Imprinted	No	Strong imprinting in placenta and embryo	Dao <i>et al.</i> (1998) and Wang <i>et al.</i> (2011)
<i>Phlda2</i>	M	7	Yes	Imprinted	Yes	Weak imprinting in adult tissues Imprinted in placenta and embryo Low-level expression and weak imprinting in adult	Qian <i>et al.</i> (1997)
<i>Nap1l4</i>	M	7	Yes	Conflicting data	No	Imprinted in E12.5 placenta Biallelic in E9.0, E13.5 and E17.5 placenta	Engemann <i>et al.</i> (2000), Umlauf <i>et al.</i> (2004) and Okae <i>et al.</i> (2012)
<i>Tnfrsf23</i>	M	7	Decidua only	Imprinted	No	Biallelic in embryo Placental imprinting reported but expression restricted to deciduas	Clark <i>et al.</i> (2002)
<i>Osblp5</i>	M	7	Yes (decidua)	Conflicting data	No	Previously reported placental imprinting possibly due to contamination with decidual cells Biallelic in E9.0 placenta	Engemann <i>et al.</i> (2000), Higashimoto <i>et al.</i> (2002) and Okae <i>et al.</i> (2012)

<i>Dhcr7</i>	M	7	Yes (decidua)	Conflicting data	No	Previously reported placental imprinting possibly due to contamination with decidual cells	Schulz <i>et al.</i> (2006) and Okae <i>et al.</i> (2012)
<i>Ano1</i>	M	7	Yes	Imprinted	No	Biallelic in E9.0 placenta	Okae <i>et al.</i> (2012)
<i>Gab1</i>	P	8	Yes	Imprinted	Homozygous null - only	Imprinted in E13.5 placenta and TS cells Biallelic in embryo, yolk sac and adult	Okae <i>et al.</i> (2012)
<i>mir184</i>	P	9	No (brain specific)	–	No	Brain-specific expression and imprinting	Nomura <i>et al.</i> (2008)
<i>A19</i>	P	9	No (brain specific)	–	No	Brain-specific expression and imprinting	de la Puente <i>et al.</i> (2002)
<i>AK029869</i>	P	9	No (brain specific)	–	No	Imprinted in embryonic, neonatal and adult brain	Brideau <i>et al.</i> (2010b)
<i>Rasgrf1</i>	P	9	Yes	Imprinted	No	Imprinted in placenta, neonatal brain, adult brain, heart and stomach	Plass <i>et al.</i> (1996) and Dockery <i>et al.</i> (2009)
<i>Mstr1</i>	M	9	Yes (decidua)	Conflicting data	No	Biallelic in thymus, testis and ovaries	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Plagl1/Zac1</i>	P	10	Yes	Imprinted	Yes	Biallelic in E9.0 placenta Imprinted in E13.5 and E17.5 placenta and embryo	Piras <i>et al.</i> (2000), Wang <i>et al.</i> (2011) and Iglesias-Platas <i>et al.</i> (2012)
<i>Phactr2</i>	M	10	Yes	Imprinted	No	Imprinted in adult, except liver	Wang <i>et al.</i> (2011)
<i>Dcn</i>	M	10	Yes (decidua)	Conflicting data	No	Previously reported placental imprinting probably due to contamination with decidual cells	Mizuno <i>et al.</i> (2002) and Okae <i>et al.</i> (2012)
<i>Ddc</i>	P	11	Yes (low)	Biallelic	No	Biallelic in E9.0 placenta	Menhennott <i>et al.</i> (2008) and Shiura <i>et al.</i> (2009)
<i>Grib10</i>	M	11	Yes	Imprinted	Yes	Imprinted in heart, neonatal brain and liver	Miyoshi <i>et al.</i> (1998), Charalambous <i>et al.</i> (2010), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Cobl</i>	M	11	Yes	Biallelic	No	Biallelic in placenta, embryo and neonate	Shiura <i>et al.</i> (2009)
<i>Zrsr1</i>	P	11	Yes	Imprinted	No	Imprinted in yolk sac	Hayashizaki <i>et al.</i> (1994), Hatada <i>et al.</i> (1995), Wang <i>et al.</i> (2004, 2011) and Okae <i>et al.</i> (2012)
<i>Commd1</i>	M	11	Yes	Biallelic	Homozygous lethal	Imprinted in E13.5 placenta	Wang <i>et al.</i> (2004, 2008) and Okae <i>et al.</i> (2012)
<i>Scin</i>	M	12	Yes (decidua)	Conflicting data	No	Imprinted in adult brain Previously reported placental imprinting probably due to contamination with decidual cells	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Begain</i>	P	12	Yes	Biallelic	No	Biallelic in E9.0 placenta	Tierling <i>et al.</i> (2009) and Okae <i>et al.</i> (2012)
<i>Dlk1</i>	P	12	Yes	Imprinted	Yes	Imprinted expression of one transcript in brain	Schmidt <i>et al.</i> (2000), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Mico1</i>	M	12	Not reported	Not reported	No	Imprinted E12.5, E17.5 and E18.5 placenta	Okae <i>et al.</i> (2012)
<i>Mico1-os</i>	M	12	Not reported	Not reported	No	Imprinted in brain, spleen and kidney	Labialle <i>et al.</i> (2008)
<i>Meg3/Clh2</i>	M	12	Yes	Imprinted	Yes	Imprinted in brain, spleen and kidney Imprinted in E13.5 and E17.5 placenta Imprinted in E8.5 and E12.5 embryos and adult brain	Labialle <i>et al.</i> (2008) Miyoshi <i>et al.</i> (1998) and Wang <i>et al.</i> (2011)
<i>Rtl1as</i>	M	12	Yes	Imprinted	No	Imprinted in E13.5 placenta	Okae <i>et al.</i> (2012)
<i>micro-RNAs</i>							
<i>Rtl1/Peg11</i>	P	12	Yes	Imprinted	Yes	Imprinted in placenta and embryonic brain	Seitz <i>et al.</i> (2003), Sekita <i>et al.</i> (2008) and Wang <i>et al.</i> (2011)
<i>Rian</i>	M	12	Yes	Imprinted	No	Imprinted in E13.5 and E17.5 placenta	Hatada <i>et al.</i> (2001), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>miR127</i>	M	12	Yes	Imprinted	No	Imprinted in embryo	Seitz <i>et al.</i> (2003)
<i>miR136</i>	M	12	Not reported	Not reported	No	Imprinted in embryo	Seitz <i>et al.</i> (2003)

(continued)

Table 1 Continued.

Gene	Active allele	Chr	Placental expression	Placental imprinting	Placenta functional data	Comments	References
<i>Mirg</i>	M	12	Yes	Imprinted	No	Imprinted in E13.5 and E17.5 placenta	Seitz <i>et al.</i> (2003), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>AK050713</i>	M	12	Yes	Imprinted	No	Imprinted in E13.5 placenta and parthenogenetic mouse embryonic fibroblasts	Hagan <i>et al.</i> (2009) and Okae <i>et al.</i> (2012)
<i>AK053394</i>	M	12	Not reported	Not reported	No	Imprinted in parthenogenetic mouse embryonic fibroblasts	Hagan <i>et al.</i> (2009)
<i>Dio3</i>	P	12	Yes	Conflicting data	No	Imprinted in placenta and embryo Biallelic in E13.5 placenta	Hernandez <i>et al.</i> (2002), Tsai <i>et al.</i> (2002), Yevtdiyenko <i>et al.</i> (2002) and Okae <i>et al.</i> (2012)
<i>Cmah</i>	M	13	E13.5: no E17.5: yes?	Unconfirmed	No	Imprinted in E17.5 placenta Biallelic in E17.5 brain	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Drd1a</i>	M	13	E13.5: no E17.5: yes?	Unconfirmed	No	Not expressed in E13.5 placenta Imprinted in E17.5 placenta Biallelic in E17.5 brain	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Pde4d</i>	P	13	Not reported	Not reported	No	Not expressed in E13.5 placenta	Babak <i>et al.</i> (2008)
<i>Htr2a</i>	M	14	Not reported	Not reported	No	Allelic bias in E9.5 embryo	Kato <i>et al.</i> (1998)
<i>Kcnk9</i>	M	15	Not reported	Not reported	No	Imprinted in brain, ovary and embryonic eye	Ruf <i>et al.</i> (2007)
<i>Peg13</i>	P	15	Yes (low)	Not reported	No	Imprinted in embryo and adult brain	Smith <i>et al.</i> (2003) and Davies <i>et al.</i> (2004)
<i>Trappc9</i>	M	15	Not reported	Not reported	No	Imprinted in brain	Wang <i>et al.</i> (2008)
<i>Slc38a4</i>	P	15	Yes	Imprinted	No	Imprinted in neonatal brain	Mizuno <i>et al.</i> (2002), Smith <i>et al.</i> (2003), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Fbx040</i>	M	16	E13.5: no E17.5: yes?	Unconfirmed	No	Imprinted in embryo and adult (except liver) Imprinted in E17.5 placenta Biallelic in E17.5 brain	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Pde10a</i>	M	17	Yes	Imprinted	No	Not expressed in E13.5 placenta	Wang <i>et al.</i> (2011)
<i>Slc22a3</i>	M	17	Yes	Imprinted	Yes	Imprinted in E17.5 placenta	Zwart <i>et al.</i> (2001a) and Okae <i>et al.</i> (2012)
<i>Slc22a2</i>	M	17	No	—	No	Imprinted in E11.5, E13.5 and E15.5 placenta Previously reported placental imprinting at E11.5, but biallelic at E15.5 Subsequently expression shown to be restricted to visceral yolk sac	Verhaagh <i>et al.</i> (1999), Zwart <i>et al.</i> (2001a), Hudson <i>et al.</i> (2011), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Aim</i>	P	17	Yes	Imprinted	Yes	Imprinted in E13.5 and E17.5 placenta	Wutz <i>et al.</i> (1997), Lyle <i>et al.</i> (2000), Wang <i>et al.</i> (2011) and Okae <i>et al.</i> (2012)
<i>Igf2r</i>	M	17	Yes	Imprinted	Yes	Imprinted in E13.5 and E17.5 placenta, and E15 embryos	Barlow <i>et al.</i> (1991), Lerchner & Barlow (1997) and Wang <i>et al.</i> (2011)
<i>Qpct</i>	M	17	Yes (decidua)	Conflicting data	No	Previously reported placental imprinting probably due to contamination with decidual cells	Brideau <i>et al.</i> (2010a) and Okae <i>et al.</i> (2012)
<i>Impact</i>	P	18	Yes	Imprinted	No	Biallelic in E9.0 placenta Imprinted in E17.5 placenta	Oakey <i>et al.</i> (1995), Hagiwara <i>et al.</i> (1997) and Wang <i>et al.</i> (2011)
<i>Tbc1d12</i>	P	19	Not reported	Not reported	No	Imprinted in brain	Babak <i>et al.</i> (2008)
<i>Ins1</i>	P	19	Conflicting data	Conflicting data	No	Allelic bias in E9.5 embryo Imprinted in yolk sac	Giddings <i>et al.</i> (1994) and Deltour <i>et al.</i> (2004)

Expansion and differentiation of the ectoplacental cone gives rise to the junctional zone, with cells at the maternal edge undergoing endoreduplication and forming a monolayer of parietal trophoblast giant cells (P-TGCs), although only half of this population of TGCs is derived from ectoplacental cone precursors (Simmons *et al.* 2007). Proliferation of the extraembryonic ectoderm generates the chorionic epithelium that initially forms a flat 'chorionic plate' at the base of the placenta and eventually gives rise to the labyrinth layer (Fig. 1C).

By midgestation (~E12.5), the mouse placenta comprises the labyrinth and junctional zones that together form the fetal-placenta, with proliferation and remodelling of the endometrial lining of the uterine wall at the implantation site forming the maternal decidua. At least eight trophoblast-derived cell types contribute to the fetal-placenta (John & Hemberger 2012), including four TGC subtypes with characteristic gene expression profiles and spatial localisation (Simmons *et al.* 2007). A monolayer of P-TGCs lines the implantation site forming a boundary between the fetal junctional zone and maternal decidua. Maternal spiral arteries penetrating the decidua are lined by spiral artery-associated trophoblast giant cells (SpA-TGCs), with canal-associated trophoblast giant cells (C-TGCs) surrounding maternal blood canals traversing the spongiotrophoblast and penetrating the labyrinth layer. A single layer of mononuclear sinusoidal trophoblast giant cells (S-TGCs) replaces the endothelial lining of maternal blood sinuses in the labyrinth through which maternal blood is drained from the placenta (Simmons & Cross 2005, Simmons *et al.* 2007).

In the labyrinth, a bilayer of multinucleated syncytiotrophoblast cells formed by cell fusion completes the characteristic trilaminar cellular structure along with the S-TGCs (Rossant & Cross 2001, Simmons & Cross 2005, Watson & Cross 2005, Simmons *et al.* 2008a). The junctional zone comprised spongiotrophoblast and glycogen cells, both of which express trophoblast-specific protein alpha (*Tpbpa*), which can be consequently used to identify these cells. Although formation of the junctional zone is essential for completion of embryogenesis (Guillemot *et al.* 1994), the precise functions of the two junctional zone cell types remain to be confirmed experimentally. Expression of protocadherin 12 (*Pcdh12*) specifically marks glycogen cells from ~E7.5 (Bouillot *et al.* 2005), with stores of glycogen primarily accumulating from E12.5, and migration of glycogen cells into the maternal decidua occurring from ~E14.5 (Adamson *et al.* 2002, Coan *et al.* 2006). These glycogen stores are thought to provide a source of energy for late-gestation embryonic growth and parturition (Coan *et al.* 2006). In contrast, the spongiotrophoblast cells, which form the bulk of the junctional zone, are thought to perform an endocrine role in synthesising and secreting a range of prolactin-related (Prl) proteins and

pregnancy-specific glycoproteins (Psgs) that act to modulate maternal physiology in response to pregnancy (Kromer *et al.* 1996, Wynne *et al.* 2006, Simmons *et al.* 2008b).

UPD and identification of imprinted regions

The purpose of this review is to provide a summary of the current knowledge regarding imprinted gene function in the placenta with respect to the various placental lineages. While the majority of imprinted genes reported are expressed in the placenta (Table 1), the precise spatial and temporal expression patterns have been described for a subset (Table 2).

The search for imprinted genes with placental functions was initially directed by the observation of placental defects associated with inheritance of mono-parental chromosomal regions (Fig. 2A). Such studies suggested the presence of imprinted genes with placental functions residing on proximal chromosomes 2, 7 and 11 and distal chromosome 7 (Cattanach & Kirk 1985, Searle & Beechey 1990, Cattanach *et al.* 1996, 2004, McLaughlin *et al.* 1996, 1997). Embryonic growth defects associated with UPD of proximal chromosomes 6 and 18 and distal chromosome 12, in addition to the embryonic lethality associated with UPD of proximal chromosome 17 (Johnson 1974, Winking & Silver 1984, Oakey *et al.* 1995, Beechey 2000, Georgiades *et al.* 2000, 2001, Tevendale *et al.* 2006), may also suggest placental defects.

Distal chromosome 7

The most extensively characterised of all imprinted regions in the mouse is distal chromosome 7. Maternal UPD of this region results in impaired fetal and placental growth, with death by E17.5. Paternal UPD of the same region results in a loss of the placental junctional zone and embryonic developmental delay and lethality by E10.5 (Searle & Beechey 1990, McLaughlin *et al.* 1996, 1997). Two mechanistically distinct imprinted domains, IC1 and IC2, are located on distal chromosome 7, with imprinting of each domain regulated through independent mechanisms.

The IC1 domain comprises the paternally expressed *Igf2*, *Igf2as* and *Ins2* genes and the maternally expressed non-coding *H19* RNA. The function of this domain in placental development has been reviewed recently and extensively (Lefebvre 2012, Sandovici *et al.* 2012); therefore, we will give a brief review here. *Igf2* is widely expressed in the placenta, with transcription of murine *Igf2* initiated from four promoters; P1, P2 and P3 driving expression in fetal endothelium, TGCs, spongiotrophoblast and, most highly, in glycogen cells, with a P0 transcript driving additional expression specifically in labyrinthine cell layers. Studies have been undertaken

Figure 1 Major stages of placental development in the mouse. (A) Before implantation, the blastocyst comprises a monolayer of trophoblast encasing the inner cell mass (ICM). (B) Proliferation of the trophoblast overlying the ICM forms the extraembryonic ectoderm and ectoplacental cone. (C) By mid gestation, expansion and differentiation of the ectoplacental cone forms the junctional zone with proliferation of the extraembryonic ectoderm generating the chorionic epithelium and eventually the labyrinth layer. The mature mouse placenta comprises at least eight trophoblast-derived cell types contributing to the fetal-derived labyrinth layers and junctional zone. Dec, maternal decidua; Jz, junctional zone; Lab, labyrinth; SpT, spongiotrophoblast; SpA-TGC, spiral artery-associated trophoblast giant cell; P-TGC, parietal trophoblast giant cell; C-TGC, canal trophoblast giant cell; S-TGC, trophoblast giant cell; SynT-I and SynT-II, syncytiotrophoblast layers I and II.

for both complete loss of function of *Igf2* and isolated loss of the P0 transcript. Loss of all paternal *Igf2* transcripts results in reduced placental weight, attributed to a disproportionate loss of the labyrinth layer and an 80% loss of the glycogen cell lineage, with reduced staining for placental glycogen. Loss of only the P0 transcript results in a proportionate reduction of both labyrinth and junctional zones, despite only 10% of total placental *Igf2* transcripts initiating at this promoter. Increased transport efficiency is observed in *Igf2*^{P0+/-} placentae but not in *Igf2*^{+/-} placentae, suggesting an adaptive response to the imbalance between demand for nutrients by the growing embryo and supply capacity of the placenta. To some extent, the consequence of elevated *Igf2* expression on placental development can be inferred from studies in which the imprinting centre for *Igf2* is disrupted. As this entails loss of expression of the mechanistically linked *H19* gene, either through direct targeting of *H19* or indirectly via loss of the imprint, placental phenotypes may reflect elevated *Igf2*, loss of *H19*, loss of the microRNA *miR675*, contained within *H19*, or a combination of these changes. Loss of imprinting (LOI) at the *H19* domain (*H19*^{Δ13}) results in fetal overgrowth and placentomegaly with a 2.5-fold expansion of the glycogen cell population. Placental glycogen stores are also significantly increased in mutant placentae at E15.5, but with no significant difference at E18.5, suggesting that these stores are either utilised by the overgrowing embryo or that the mutant placenta is unable to sustain them.

The adjacent IC2 domain contains a number of genes expressed and imprinted in the placenta with LOI of this domain, either through targeted deletion of the imprinting centre or termination of the long non-coding RNA

Kcnq1ot1 resulting in placental growth restriction with a compromised junctional zone (Fitzpatrick *et al.* 2002, Salas *et al.* 2004, Mancini-Dinardo *et al.* 2006). Within this domain, the three maternally expressed imprinted genes *Ascl2*, *Cdkn1c* and *Phlda2* have garnered the most interest with respect to placental development. *Ascl2* was the first imprinted gene to be shown to be absolutely required for embryonic viability (Guillemot *et al.* 1994). *Ascl2* switches from biallelic to monoallelic expression in the trophoblast cells at ~E8.5 (Tanaka *et al.* 1999). *Ascl2* is expressed abundantly in the ectoplacental cone and at lower levels in the chorionic epithelium at E8.5, becoming restricted to a subset of cells at E12.5 with expression undetectable by E18.5 (Rossant *et al.* 1998). Embryos inheriting a mutant *Ascl2* allele from their mother die at midgestation with a complete absence of junctional zone, expanded P-TGC layer and defective labyrinth development (Guillemot *et al.* 1994, 1995). *Ascl2* has since been confirmed to be essential for the differentiation of ectoplacental cone precursors into the established junctional zone cell types but is not essential for differentiation of the labyrinth from chorionic epithelium. The expanded P-TGC layer of *Ascl2* mutant placentae suggests a role for *Ascl2* in maintaining the junctional zone population by preventing their differentiation into P-TGCs. A reduced labyrinth layer has been proposed to reflect a loss of endocrine signalling emanating from the spongiotrophoblast (Tanaka *et al.* 1997). Deletion of the region between the IC1 and IC2 domains and encompassing the *Th* gene (*Del*^{7A1}) results in a twofold reduction in *Ascl2* alongside impaired placental and embryonic growth (Lefebvre *et al.* 2009, Oh-McGinnis *et al.* 2011). Mutant placentae are characterised by an expansion of P-TGCs, complete

Table 2 Placental expression patterns of imprinted genes.

Gene	Placental expression pattern	References
<i>Zdbf2</i>	Spongiotrophoblast	Hiura <i>et al.</i> (2010)
<i>Simbt2</i>	Extraembryonic ectoderm (precursor to labyrinth) at E6.5 and E7.5	Frankenberg <i>et al.</i> (2007)
<i>Peg10</i>	All trophoblast cell types	Ono <i>et al.</i> (2006)
<i>Peg1/Mest</i>	Fetal vasculature endothelium	Mayer <i>et al.</i> (2000)
<i>Peg3</i>	Junctional zone, P-TGCs and a subset of labyrinthine cells	Hiby <i>et al.</i> (2001)
<i>H19</i>	All trophoblast cell types	Sasaki <i>et al.</i> (1995) and Svensson <i>et al.</i> (1998)
<i>Igf2</i>	All trophoblast cell types (Labyrinth-specific transcripts from P0 promoter)	Redline <i>et al.</i> (1993), Moore <i>et al.</i> (1997) and Constância <i>et al.</i> (2002)
<i>Ascl2</i>	Labyrinth and junctional zone	Guillemot <i>et al.</i> (1994, 1995)
<i>Cdkn1c</i>	Highly expressed in labyrinth and glycogen cells Low expression in spongiotrophoblast cells	Takahashi <i>et al.</i> (2000)
<i>Slc22a3</i>	Subset of labyrinth cells	Verhaagh <i>et al.</i> (2001) and Zwart <i>et al.</i> (2001a)
<i>Slc22a18</i>	Labyrinth	Tunster <i>et al.</i> (2010)
<i>Phlda2</i>	Ectoplacental cone (E5.5), extraembryonic ectoderm and syncytiotrophoblast	Frank <i>et al.</i> (1999, 2002)
<i>Plagl1/Zac1</i>	Labyrinth	Arima <i>et al.</i> (2005)
<i>Grb10</i>	Fetal endothelium and trilaminar labyrinth	Charalambous <i>et al.</i> (2010)
<i>Dll1</i>	Fetal endothelium in labyrinth; some glycogen cells	da Rocha <i>et al.</i> (2007)
<i>Meg3/Gtl2</i>	Fetal endothelium and syncytiotrophoblast in labyrinth; P-TGCs and C-TGCs	da Rocha <i>et al.</i> (2007)
<i>Rtl1/Peg11</i>	Fetal endothelium of labyrinth layer	Sekita <i>et al.</i> (2008)

loss of glycogen cells, significant loss of spongiotrophoblast cells and disrupted labyrinth (Oh-McGinnis *et al.* 2011). This suggests that *Ascl2* is required for the development of both the spongiotrophoblast and the glycogen cell lineages, although *Phlda2* levels are also twofold elevated in this model and may contribute to the placental phenotype.

Cdkn1c encodes a cyclin-dependent kinase inhibitor that negatively regulates cell proliferation and is highly expressed in P-TGCs, glycogen cells, fetal endothelium, syncytiotrophoblast and some larger S-TGC nuclei dynamically during mid-to-late placental development (Georgiades *et al.* 2002). *Cdkn1c* mutant placentae are overgrown on the C57BL/6 strain background with an approximate doubling of spongiotrophoblast and labyrinthine cell number, although TGC and glycogen cell number was found to be unaffected at E17.5 in this early study (Takahashi *et al.* 2000). We studied *Cdkn1c*^{-/+} mutants on a 129S2/SvHsd strain background, and while we also observed profound placental overgrowth, the labyrinth of *Cdkn1c* mutant placentae was severely disrupted at E18.5 with substantial thrombotic lesions, collagen deposits, impaired vascularisation and a severe S-TGC deficit (Tunster *et al.* 2011). Similar thrombotic lesions were also reported in late-gestation PatUPD7 placentae rescued from lethality by restoration of *Ascl2* gene expression (Rentsendorj *et al.* 2010). We also observed a reduced junctional zone at E18.5, which we determined reflected a specific loss of the spongiotrophoblast lineage by marker analysis. While we found no alteration in expression of the glycogen cell marker *Pcdh12*, suggesting that expansion of the glycogen cell population was unaffected by loss of expression of *Cdkn1c*, expression of *Gjb3*, a marker of mature glycogen cells, was lower. This finding, coupled with a reduction in placental glycogen stores, might explain

why *Cdkn1c*^{-/+} mutant embryos have a growth advantage even during late gestation but fail to maintain this increased body weight to term.

The maternally expressed gene pleckstrin homology-like domain family a member 2 (*Phlda2*) encodes a small cytoplasmic protein (Qian *et al.* 1997, Frank *et al.* 2002). Although studies on a closely related gene, *Phlda3*, suggest a role for these PH domain-only proteins in inhibiting Akt-regulated processes (Kawase *et al.* 2009), this has not been formally demonstrated for *Phlda2*. Expression of *Phlda2* in the placenta is first detected in the ectoplacental cone following implantation, becoming restricted to the syncytiotrophoblast of the labyrinth layer by E10.5 (Frank *et al.* 1999). Significant maternal bias of *Phlda2* is observed in the placenta and embryonic tissues, with lower level expression and less-stringent imprinting in adult tissues (Qian *et al.* 1997). *Phlda2* null mice exhibit placentomegaly with a disproportionate expansion of the junctional zone and histologically exhibit an abundance of stored glycogen, although no direct quantitation of cell number or glycogen stores was undertaken in this study (Frank *et al.* 2002). We demonstrated that mice with entopic over-expression of *Phlda2* exhibit a disproportionate reduction of the junctional zone with limited glycogen stores and impaired fetal growth during late gestation (Salas *et al.* 2004, Tunster *et al.* 2010). Using placental marker analysis, we attributed the reduced size of the junctional zone to a specific loss of spongiotrophoblast cells, with no direct effect on glycogen cell abundance. This suggested the possibility that signals from the spongiotrophoblast modulate glycogen storage (Tunster *et al.* 2010), although this remains to be shown experimentally. Our unpublished studies on the *Phlda2* null placenta also suggest a spongiotrophoblast defect rather than an expansion of the glycogen cell lineage.

Figure 2 Chromosomal locations of genes expressed and imprinted in the mouse placenta. (A) Genes with confirmed imprinted expression in the mouse placenta that map to chromosomal regions associated with embryonic and/or placental phenotypes after monoparental chromosomal inheritance. (B) Genes with confirmed expression in the mouse placenta that map outside chromosomal regions associated with placental and/or embryonic phenotypes. P, placental phenotype; E, embryonic phenotype; L, embryonic lethality; PN, post-natal phenotype. Adapted from www.mousebook.org/catalog.php?catalog=imprinting.

Proximal chromosome 6

Two imprinted domains are located in close proximity in the proximal region of chromosome 6. Maternal duplication of the most proximal domain, which contains the paternally expressed *Peg10* and *Sgce* genes, results in embryonic lethality at ~E11.5. Maternal duplication of the more distal domain, which contains the paternally expressed *Mest* (*Peg1*) gene, results in embryonic growth retardation that persists into adulthood (Beechey 2000). Embryonic lethality associated with maternal uniparental inheritance of this region may be attributed to a placental defect as a consequence of loss of the retrotransposon-derived *Peg10* (Ono *et al.* 2006). *Peg10* is widely expressed in all trophoblast lineages of the placenta and also in several embryonic

tissues including brain and vertebral cartilage. Paternal inheritance of a targeted *Peg10* allele results in relatively normal placental development until ~E8.5. Embryonic death occurs between E9.5 and E10.5 as a consequence of the failure of spongiotrophoblast and labyrinth trophoblast lineages to differentiate from the ectoplacental cone and extraembryonic ectoderm precursors respectively. Formation of P-TGCs is apparently normal. This differs from the *Ascl2*^{-/+} phenotype in which this population has expanded. Although glycogen cells were not specifically examined in this study, the complete absence of *Tpbpa* staining in mutant placenta suggests that these cells also fail to develop. *Peg10* thus appears to be required for the differentiation of several trophoblast cell types. Functional analyses in the placenta have not

been undertaken for the paternally expressed *Sgce* and eight maternally expressed genes in the *Peg10* domain.

The second imprinted domain on mouse chromosome 6 contains the paternally expressed *Mest*. *Mest* is not expressed in trophoblast lineages, with expression restricted to fetal endothelial cells of the labyrinth (Mayer *et al.* 2000). Loss of function results in a placental weight deficit and late gestation embryonic growth restriction, although placental morphology appears otherwise normal (Lefebvre *et al.* 1998). Placental functions have not been ascertained for the other genes in this domain.

Distal chromosome 12

Maternal UPD of chromosome 12 results in a placental weight deficit with a proportionate reduction in all three layers, embryonic growth retardation and neonatal lethality. Paternal UPD of chromosome 12 results in placentomegaly affecting all three placental layers from E12.5, with embryos dying during late gestation (Georgiades *et al.* 2000, 2001). Defective vascularisation of the paternal UPD labyrinth occurs by E15.5, with an increased abundance of glycogen cells at E13.5 that fail to appropriately invade the decidua and do not decline in number towards term as normal (Georgiades *et al.* 2001). The placental defects can be traced to the most distal region of chromosome 12, with paternal UPD of this region associated with placentomegaly and maternal UPD associated with a placental weight deficit similar to those observed for UPD of the entire chromosome (Tevendale *et al.* 2006).

The imprinted domain on distal chromosome 12 comprises four paternally expressed protein-coding genes and at least seven maternally expressed non-coding RNAs that give rise to a number of microRNAs (reviewed in Hagan *et al.* (2009)). Imprinting of the domain is regulated by differential methylation of the intergenic differentially methylated region (IG-DMR), with deletion of this region resulting in biallelic expression of all genes in the domain (Lin *et al.* 2003).

The paternally expressed *Dlk1* marks fetal endothelial cells and a sub-population of glycogen cells (Yevtodiyeenko & Schmidt 2006, da Rocha *et al.* 2007). *Dlk1* mutant placentae have a smaller labyrinth area with reduced vascularisation, but no overall effect on placental weight. In the junctional zone, mutant placentae display an increased abundance of pre-glycogen, although no quantitation of glycogen stores was undertaken. A conditional deletion of *Dlk1* in labyrinth fetal endothelium does not produce any overt placental phenotype, although placental structure was not analysed in this model (Appelbe *et al.* 2012).

The paternally expressed *Rtl1* is specifically expressed in fetal endothelial cells of the labyrinth. *Rtl1* null mice are growth retarded with reduced viability associated with inheritance of the mutation on a pure C57BL/6 background. *Rtl1*-deficient placentae are characterised

by a severely disrupted labyrinth and impaired passive transport capacity (Sekita *et al.* 2008). Overlapping the paternal expression of *Rtl1* is maternal expression of an antisense *Rtl1* transcript (*Rtl1as*) that is processed into multiple microRNAs that target degradation of the paternal *Rtl1* transcript (Seitz *et al.* 2003, Davis *et al.* 2005). Maternal inheritance of the *Rtl1* null allele disrupts expression of *Rtl1as* from the maternal allele, thus preventing the targeted cleavage of *Rtl1* transcripts resulting in over-expression of *Rtl1*. Elevated *Rtl1* expression was associated with placentomegaly characterised by an expanded fetal capillary lumen and defective syncytiotrophoblast, although there was no effect on embryonic weight (Sekita *et al.* 2008).

Maternal deletion of the *Meg3* (*Gtl2*) promoter and exons 1–5 is associated with LOI of adjacent genes and results in neonatal death but with apparently normal placental development (Zhou *et al.* 2010). Paternal inheritance of the same *Meg3* deletion was associated with impaired fetal and placental growth and down-regulation of *Dlk1* and *Rtl1* in the placenta but not the embryo (Zhou *et al.* 2010). The paternally expressed *Dio3* encodes a type III iodothyronine deiodinase that inactivates thyroid hormones and is expressed on the trophoblast cell types of the labyrinth layer, although imprinted expression is not established until E15.5 (Hernandez *et al.* 1999, Tsai *et al.* 2002, Yevtodiyeenko *et al.* 2002, Okae *et al.* 2012). No phenotypic characterisation has been reported for specifically altered dosage of *Dio3*, nor the non-coding RNA designated RNA imprinted and accumulated in nucleus (*Rian*).

Proximal chromosome 11

Maternal UPD of chromosome 11 is associated with embryonic and placental growth retardation with paternal UPD leading to overgrowth of both embryo and placenta (Cattanach & Kirk 1985, Cattanach *et al.* 1996). Three of the genes located within this domain are expressed biallelically in the placenta (*Ddc*, *Cobl* and *Comm1*). *Zrsr1* (*U2af1-rs1*) resides within intron 1 of *Comm1*, is paternally expressed in the placenta, and although mice carrying a targeted deletion have been generated, a placental function has not been reported (Hatada *et al.* 1995, Sunahara *et al.* 2000).

The most extensively characterised imprinted gene on chromosome 11 is growth factor receptor-bound protein 10 (*Grb10*). *Grb10* expression is restricted to the fetal endothelium, where it is expressed only from the maternal allele, and a subset of trophoblast cells in the labyrinth layer where it is expressed biallelically (Charalambous *et al.* 2010). Maternal inheritance of a disrupted *Grb10* allele results in placental and embryonic overgrowth (Charalambous *et al.* 2003). The volume occupied by the labyrinth layer was increased by ~50%, although the potential effect on nutrient transport was not quantified (Charalambous *et al.* 2010). Paternal

transmission of a disrupted *Grb10* DMR results in biallelic expression of *Grb10* and largely recapitulates the phenotypes associated with maternal UPD of chromosome 11, with placental and embryonic growth retardation that persists into adulthood (Shiura *et al.* 2009).

Proximal chromosome 17

Maternal inheritance of a deletion of proximal chromosome 17 is associated with embryonic lethality (Johnson 1974, Winking & Silver 1984). This domain contains the maternally expressed IGF2 receptor (*Igf2r*), a multi-functional receptor that binds a range of ligands (Morgan *et al.* 1987), and two transporters, *Slc22a2* and *Slc22a3*. Loss of function of *Igf2r* results in placentomegaly (Wang *et al.* 1994, Wylie *et al.* 2003) whereas twofold expression of *Igf2r*, *Slc22a2* and *Slc22a3* has no gross effect on placental weights (Wutz *et al.* 2001). Placental weights were only examined at E17.5 in this study and no histology was reported. It remains possible that there might be an earlier or subtle placental phenotype resulting from elevated *Igf2r*.

Slc22a3 is expressed exclusively in a subset of cells of the labyrinth layer (Verhaagh *et al.* 2001, Zwart *et al.* 2001a), whereas *Slc22a2* expression is restricted to the visceral yolk sac (Hudson *et al.* 2011) and is not expressed in the placenta as previously reported (Zwart *et al.* 2001a). *Slc22a3* null mice are viable and fertile with no overt placental defect (Zwart *et al.* 2001b, Jonker *et al.* 2003).

Proximal chromosome 7

Maternal UPD of the proximal domain of chromosome 7 is associated with impaired fetal and placental growth (Searle & Beechey 1990). Functional data exist only for the paternally expressed *Peg3* within this domain, which encodes a zinc finger protein and is widely expressed in the junctional zone and P-TGCs, with weaker expression in a subset of labyrinthine cells (Kuroiwa *et al.* 1996, Relaix *et al.* 1996, Hiby *et al.* 2001). A significant placental weight deficit has been reported in response to *Peg3* deficiency (Li *et al.* 1999), but complete characterisation of the placental *Peg3* null phenotype has not been reported.

Proximal chromosome 2

Thirteen imprinted genes are located on mouse chromosome 2, although not all are imprinted in the placenta (Table 1). Maternal UPD of an extensive proximal region of chromosome 2 is associated with impaired placental and fetal growth, with paternal UPD of the same region associated with overgrowth of the placenta, but not the embryo (Cattanach *et al.* 2004). The only

imprinted protein-coding gene in this region is the paternally expressed *Sfmbt2* (Kuzmin *et al.* 2008), which suggests that this gene may have a role in promoting placental growth.

Proximal chromosome 18

Maternal and paternal UPD of proximal chromosome 18 is associated with perturbed fetal growth (Oakey *et al.* 1995), although to date the only imprinted gene reported in this region is the paternally expressed *Impact* (Hagiwara *et al.* 1997). No placental characterisation has been reported.

X-linked genes

The paternally inherited X-chromosome is preferentially inactivated in the extraembryonic tissue of mice, and thus, X-linked genes that undergo inactivation can also be considered imprinted in the mouse placenta (Takagi & Sasaki 1975, West *et al.* 1977). The existence of X-linked, imprinted genes with important placental functions was uncovered by studying mice with an XO karyotype. XO embryos with a paternal X (X^P O) display impaired ectoplacental cone expansion during early gestation whereas XO embryos carrying the maternal X (X^M O) do not (Ishikawa *et al.* 2003).

More recent gene targeting studies have identified five X-linked, imprinted genes with placental functions. *Esx1* is expressed in cells of the labyrinth layer (Li *et al.* 1997) with maternal inheritance of a targeted allele resulting in placentomegaly, defective labyrinthine vascularisation and an expansion of the glycogen cell population. The boundary between labyrinth and junctional zones was disrupted, with fluid-filled cysts appearing in the junctional zone in mutant placentae. Consistent with placental insufficiency, *Esx1* mutant mice display a late gestation growth restriction alongside post-natal catch-up growth (Li & Behringer 1998).

Cited1 is expressed in all trophoblast cell types of the placenta, with maternal deletion of *Cited1* associated with impaired placental growth and a disruption of the border between the junctional zone and labyrinth. The junctional zone of mutant placenta was enlarged with a concomitant decrease in labyrinthine area. Vascularisation of the labyrinth was defective, with increased sinusoidal spaces resulting in a reduced surface area for nutrient transport (Rodriguez *et al.* 2004). Consistent with placental insufficiency, mutant embryos were asymmetrically growth restricted during late gestation, with the majority of mutants dying in the neonatal period and survivors exhibiting catch-up growth within 8 weeks of birth (Rodriguez *et al.* 2004, Novitskaya *et al.* 2011).

The protein-kinase-encoding *Nrk* is expressed specifically in the junctional zone. Disruption of the maternal

copy of *Nrk* is associated with placentomegaly, with an expansion and disruption of the junctional zone and impaired fetal growth during late gestation. Delivery of litters entirely comprised of mutant conceptuses was significantly delayed, with some pregnant dams dying after failing to deliver by E22, suggesting a role for either the junctional zone or *Nrk* itself in the induction of labour (Denda *et al.* 2011).

Deletion of the maternal allele of the ubiquitously expressed *Chm* impairs placental growth, with reduction of both labyrinthine and junctional zones and an expansion of the P-TGC layer. Vascularisation of mutant placentae was severely disrupted, with thrombotic lesions observed in some mutants and embryonic lethality by E11.5 (Shi *et al.* 2004).

Plac1 is widely expressed in cells of both labyrinth and junctional zone. Despite escaping complete paternal X inactivation, maternal inheritance of a targeted *Plac1* allele results in placentomegaly with an expansion of the junctional zone and disruption of the boundary with the labyrinth layer. Increased TGCs were observed in the labyrinth of mutant placentae, although these cells were not confirmed as S-TGCs (Jackman *et al.* 2012).

Imprinted genes not associated with UPD placental phenotypes

Uniparental inheritance of some chromosomal regions is not associated with overt placental or embryonic growth defects. Additionally, a small number of imprinted genes have been identified that are not associated with established imprinted domains (Fig. 2B). However, this does not preclude a role for such genes in the formation of a functional placenta and awaits further experimental clarification.

Placental imprinting has been reported only for *Zdbf2* on chromosome 1. *Zdbf2* is highly expressed in the junctional zone, with conserved imprinting of *Zdbf2* in human placentae suggestive of an important function (Hiura *et al.* 2010). Maternal expression of *Magi2* and *Htra3* has been recently reported on chromosome 5 (Wang *et al.* 2011, Barbaux *et al.* 2012). A placental function for *Magi2* has not been investigated, whereas *Htra3* is expressed exclusively in decidual cells (Nie *et al.* 2006). *HTRA3* inhibits trophoblast invasion in humans (Singh *et al.* 2010, 2011), although its function in the murine placenta has not been investigated.

The imprinted domain located within the central region of chromosome 7 is referred to as the Prader–Willi/Angelman syndromes (PWS–AS) cluster in humans due to the involvement of genes in this region in the imprinted PWS/AS. Within this region, *Magel2* is expressed in the placenta (Kozlov *et al.* 2007), with some *Magel2* mutants lost relatively early in development, which may suggest a placental defect (Bischof

et al. 2007). Paternal expression of *Gab1* on chromosome 8 has recently been reported specifically in the placenta (Okoe *et al.* 2012). *Gab1* is expressed in cells of both the labyrinth and junctional zone. Homozygous *Gab1* deficiency results in a disproportionate loss of labyrinth layer, with embryonic lethality by E18.5, although heterozygous transmission of the deletion has not been examined (Itoh *et al.* 2000, Sachs *et al.* 2000, Schaeper *et al.* 2007). Five imprinted genes have been identified on distal chromosome 9. *Rasgrf1* is expressed in the placenta (Dockery *et al.* 2009), but maternal UPD of the region is associated only with a post-natal growth restriction phenotype (Itier *et al.* 1998, Clapcott *et al.* 2003, Cattanaach *et al.* 2004).

Imprinting of three genes on chromosome 10 has been reported, although a placental function has been reported for only the paternally expressed *Plagl1* (*Zac1*) gene, which encodes an anti-proliferative, pro-apoptotic zinc finger protein that interacts with an imprinted gene network including *Igf2*, *H19*, *Cdkn1c* and *Dlk1* (Spengler *et al.* 1997, Piras *et al.* 2000, Arima *et al.* 2005, Varrault *et al.* 2006). *Plagl1*-deficient placenta is lighter than wild type but otherwise morphologically similar to wild type with normal nutrient transport. Mutant embryos are asymmetrically growth restricted during late gestation, indicative of a placental defect (Varrault *et al.* 2006).

Imprinting of four distally located genes on chromosome 15 has been reported. Placental functions for three of these genes (*Kcnk9*, *Peg13* and *Trappc9*) have not been investigated. *Slc38a4* encodes a member of the system A amino acid transporters that is paternally expressed specifically in the placenta (Mizuno *et al.* 2002). Although generation of an *Slc38a4* null mouse model has been alluded to in recent publications (Coan *et al.* 2010, Fowden *et al.* 2011), a complete characterisation of the phenotype has yet to be published.

Discussion

Our knowledge of the function of imprinted genes in the placenta has advanced considerably since the identification of the first imprinted gene over two decades ago. However, despite the demonstrable importance of imprinted genes in placental development, it is perhaps surprising that placental functions have been characterised in detail for only a minority of these genes (Table 3). Of perhaps greater concern is the assumption that loss-of-function models can be used to formulate hypotheses regarding the function of imprinting in placental development with little acknowledgement that these models fail to address dosage-related function. While loss-of-function models provide invaluable data regarding gene function, they do not address imprint function. ‘LOI’ models have been generated for some imprinted domains but the interpretation of the resulting phenotypes is confounded by the combined effects of

Table 3 Phenotypes associated with targeted deletion of imprinted genes.

Gene	Active allele	Phenotype	References
<i>Ascl2</i>	M	Loss of junctional zone, disrupted labyrinth and embryonic lethality	Guillemot <i>et al.</i> (1994, 1995)
<i>Cdkn1c</i>	M	Placentomegaly Expansion of labyrinth and spongiotrophoblast on C57BL/6 background Thrombotic lesions, loss of S-TGCs and failure of glycogen cell maturation on 129/Sv background	Takahashi <i>et al.</i> (2000) and Tunster <i>et al.</i> (2011)
<i>Dlk1</i>	P	Reduced size and vascularisation of labyrinth; impaired glycogen cell differentiation	Appelbe <i>et al.</i> (2012)
<i>Grb10</i>	M	Placentomegaly; expansion of labyrinth; embryonic overgrowth	Charalambous <i>et al.</i> (2003, 2010)
<i>H19^{d13}</i> (LOI <i>Igf2</i>)	M	Placentomegaly and expansion of glycogen cell population	Leighton <i>et al.</i> (1995) and Esquiliano <i>et al.</i> (2009)
<i>H19^{d3}</i>	M	Placentomegaly	Keniry <i>et al.</i> (2012)
<i>Igf2</i>	P	Placental weight deficit; disproportionate loss of labyrinth, reduced glycogen storage; intrinsic embryonic growth retardation	DeChiara <i>et al.</i> (1990, 1991) and Lopez <i>et al.</i> (1996)
<i>Igf2 P0</i>	P	Placental weight deficit; proportionate loss of labyrinth and junctional zone; late gestation embryonic growth restriction	Constância <i>et al.</i> (2002)
<i>Igf2r</i>	M	Placentomegaly, fetal overgrowth	Lau <i>et al.</i> (1994) and Ludwig <i>et al.</i> (1996)
<i>Kcnq1ot1</i>	P	Placental and embryonic growth deficit Decreased junctional zone (due to LOI of IC2 domain genes)	Fitzpatrick <i>et al.</i> (2002), Salas <i>et al.</i> (2004) and Mancini-Dinardo <i>et al.</i> (2006)
<i>Peg1/Mest</i>	P	Placental weight deficit, but normal morphology Embryonic growth restriction	Lefebvre <i>et al.</i> (1998)
<i>Peg3</i>	P	Placental and embryonic growth deficit	Li <i>et al.</i> (1999) and Hiby <i>et al.</i> (2001)
<i>Peg10</i>	P	Failure of junctional zone and labyrinth layer to form Embryonic lethal by E10.5	Ono <i>et al.</i> (2006)
<i>Phlda2</i>	M	Placentomegaly and disproportionate expansion of junctional zone	Frank <i>et al.</i> (2002)
<i>Plagl1/Zac1</i>	P	Placental weight deficit, but normal morphology Embryonic growth restriction	Varraut <i>et al.</i> (2006)
<i>Rtl1</i>	P	Disruption of labyrinth structure, impaired passive transport	Sekita <i>et al.</i> (2008)

both loss of expression and gain-in-expression of multiple imprinted genes. Modelling LOI at the individual gene level is considerably more difficult to achieve, although arguably provides the best evidence to elucidate the advantage of imprinting specific genes while maintaining biallelic expression of others.

As it stands, loss-of-function studies have identified seven imprinted genes that are required for the proper formation of the labyrinthine tissue and thus likely to be directly important for nutrient transport (Table 3). Imprinted genes also functionally converge on the spongiotrophoblast and giant cell lineages, which perform key endocrine functions in maternal physiology, both locally and systemically. The glycogen cell lineage also appears to be a target for several imprinted genes, most notably *Igf2*. While loss-of-function models may not provide definitive clues as to the evolution of imprinting, further investigation of these models will provide information on the function of various placental lineages, potentially clarifying the function of these cell types in driving the adaptations in maternal physiology that are required for a successful and healthy pregnancy.

One aspect of placental biology that stands out is the relationship between the spongiotrophoblast and glycogen storage. In several models, glycogen stores in a late-gestation placenta correlate more strongly with the amount of spongiotrophoblast present than with the glycogen cell population. For example, elevated *Phlda2* results in a failure of the spongiotrophoblast lineage to

expand and a subsequent depletion of glycogen stores, despite no apparent effect on expansion of the glycogen cell population. Similarly, loss of function of *Cdkn1c* results in a reduction of the spongiotrophoblast lineage alongside a depletion of glycogen stores, but with no overt effect on the glycogen cells. Even with *Igf2*, where elevated expression is associated with both an increase in glycogen cell number and increased glycogen stores, these stores are not maintained late in gestation, which may reflect the lack of a positive effect of *Igf2* on the spongiotrophoblast. We have observed a similar relationship between the spongiotrophoblast lineage and glycogen stores in different strains of inbred mice with C57BL/6 placenta expressing higher levels of spongiotrophoblast-specific markers and carrying considerably higher amounts of glycogen than 129S2/SvHsd placenta (Tunster *et al.* 2012). Taken together, these data suggest the possibility that signals emanating from the junctional zone promote the uptake and storage of glycogen by the glycogen cell population.

In conclusion, while a great deal of further work is required to assess both the function of imprinted genes in the placenta and the significance of their regulated dosage, current evidence highlights the role of imprinted genes in regulating birth weight both directly and indirectly via placental function. Moreover, the influence of these imprinted genes probably extends beyond early life into adulthood, either as a consequence of the intrinsic activity of the gene or through adaptations that

have occurred in the fetus in response to poor *in utero* growth. Finally, aberrant imprinting in the placenta may have a profound effect on the well-being of the mother during pregnancy. Alterations in the expression of members of this relatively obscure family of genes may therefore have profound and wide reaching consequences for human health.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

S J Tunster was supported by the Biotechnology and Biological Sciences Research Council (grant numbers BB/G015465/1 and BB/J015156/1). A B Jensen was supported by a Biotechnology and Biological Sciences Research Council Doctoral Training Grant to Cardiff University.

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Received 20 December 2012

First decision 25 January 2013

Accepted 25 February 2013