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SUPPLEMENTARY INFORMATION

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Genomic imprinting disorders: lessons on how genome, epigenome and environment interact

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Supplementary Table 1. Imprinting disorders and their main molecular defects and clinical features.

Imprinting disorder [OMIM]	Prevalence	Chromosome	Molecular defect (frequency)	Main clinical features
Transient neonatal diabetes mellitus (TNDM)[1,2-4] [601410]	1/300.000	6q24	- Upd(6)pat (41%) - Paternal duplications (29%) - *PLAGL1:alt-TSS-DMR* LOM (30%) (MLID: 30% caused by pathogenic *ZFP57* variants[5])	IUGR, TNDM, hyperglycaemia without ketoacidosis, macroglossia, abdominal wall defects
Silver-Russell syndrome (SRS)[6] [180860]	1/75.000–1/100.000	7 11p15 12q14 8q12	- Upd(7)mat (5–10% (MLID: rare[7])) - Upd(11p15)mat (rare) - 11p15 CNVs (<1%) - *H19*–IGF2:IG-DMR LOM (30–60% (MLID: 7–10% [8-10])) - *CDKN1C, IGF2, HMGA2, PLAG1* point mutations (rare)	IUGR, PNGR, relative macrocephaly at birth, body asymmetry, prominent forehead, feeding difficulties
Birk–Barel syndrome[11] [612292]	Unknown	8q24.3	- *KCNK9* point mutations (100%)	Intellectual disability, hypotonia, dysmorphism
Beckwith–Wiedemann syndrome (BWS)[12] [130650]	1/15.000	11p15	- Upd(11p15)pat (20%) - 11p15 CNVs (2–4%) - *H19*–IGF2:IG:DMR GOM[a] (5%) - *KCNQ1OT1*:TSS-DMR LOM (50% (MLID: 25%[8,9])) - *CDKN1C* point mutations (5% sporadic; 40–50% in families)	Macroglossia, exomphalos, lateralized overgrowth, Wilms tumour or nephroblastomatosis, hyperinsulinism, adrenal cortex cytomegaly, placental mesenchymal dysplasia, pancreatic adenomatosis
Kagami–Ogata syndrome (KOS14) [13,14] [608149]	Unknown	14q32	- Upd(14)pat (65%) - 14q32 mat deletion (20%) - *MEG3–DLK1*:IG-DMR GOM (15%)	IUGR, polyhydramnion, abdominal wall defects, bell-shaped thorax, coat-hanger ribs
Temple syndrome (TS14)[15-17] [616222]	Unknown	14q32	- Upd(14)mat (29%) - 14q32 pat deletion (10%) - *MEG3–DLK1*:IG-DMR LOM (61%)	IUGR, PNGR, neonatal hypotonia, feeding difficulties in infancy, truncal obesity, scoliosis, precocious puberty, small feet and hands

Prader–Willi syndrome (PWS)[18-20] [176270]	1/25.000 –1/10.000	15q11–q13	- 15q11–q13 pat deletion (75-80%) - Upd(15)mat (20-25%) - *SNURF*:TSS-DMR GOM[a] (~1% (MLID: rare[21]))	PNGR, Intellectual disability, neonatal hypotonia, hypogenitalism, hypopigmentation, obesity, hyperphagia
Angelman syndrome (AS)[22,23] [105830]	1/20.000 –1/12.000	15q11–q13	- Mat deletion (70-75%) - Upd(15)pat (3-7%) - *SNURF*:TSS-DMR LOM[a] (2-3% (MLID: rare[21])) - *UBE3A* point mutations (10%)	Severe intellectual disability, microcephaly, no speech, unmotivated laughing, ataxia, seizures, scoliosis
Central precocious puberty 2 (CPPB2) [24] [615356]	Unknown	15q11.2	*MKRN3* point mutations (100%)	Early activation of the hypothalamic–pituitary–-gonadal axis resulting in gonadotropin-dependent precocious puberty
Schaaf–Yang syndrome (SYS)[25] [615547]	Unknown	15q11.2	*MAGEL2* point mutations (100%)	Delayed psychomotor development, intellectual disability, hypotonia
Pseudohypo-parathyroidism 1A (PHP1A) including PHP1C[26] [103580] [612462]	Unknown	20q13	*GNAS*-inactivating variants of the mat allele (100%)	Resistance to PTH and other hormones, Albright hereditary osteodystrophy, moderately reduced birth weight, obesity, cognitive impairment (70% of patients)
Pseudohypo-parathyroidism 1B (PHP1B)[26] [603233]	Unknown	20q13	- 20q13 mat deletion (8.5%) - *GNAS* DMRs LOM (42.5%; MLID: 12.5%[27,28]) - Upd(20)pat (2.5%) - 20q13 point mutations (46.5%)	Resistance to PTH and other hormones Albright hereditary osteodystrophy, subcutaneous ossifications, feeding behaviour anomalies, abnormal growth patterns
Pseudopseudohypo-parathyroidism (PPHP)[26]	Unknown	20q13	*GNAS*-inactivating variants of the pat allele (100%)	Mild resistance to PTH and other hormones, subcutaneous

[612463]				ossifications, birth weight and length restrictions
Progressive osseous heteroplasia (POH)[26] [166350]	Unknown	20q13	*GNAS*-inactivating variants of the pat allele (100%)	Ectopic ossifications
Mulchandani–Bhoj–Conlin syndrome (MBCS)[29,30] [617352]	Unknown	20	Upd(20)mat (100%)	IUGR, PNGR, feeding difficulties

[a] Imprinting defects can be due either to primary imprinting epimutations without DNA sequence alterations or to deletions in the imprinting center (IC) critical regions. GOM, gain of methylation; IG-DMR, intergenic DMR; IUGR, intrauterine growth restriction; LOM, loss of methylation; mat, maternal; pat, paternal; PNGR, postnatal growth restriction; PTH, parathyroid hormone; UPD, uniparental disomy.

Supplementary Table 2. Human germline and somatic DMRs with regulated imprinted genes.

HGVS approved DMR name[31]	**Previous names**	**Location (hg19/GRCh37)**	**Methylated allele**	**Germline or somatic**	**TF binding sites[c]**	**Cis-regulated genes**
PPIEL:Ex1-DMR		1:40024626-40025540	Mat	Oocyte gDMR		*PPIEL*
DIRAS3:TSS-DMR	*NOEY2, ARH1*	1:68513430-68517450	Mat	Oocyte gDMR		*DIRAS3, GNG12-AS1*
DIRAS3:Ex2-DMR		1:68512505-68513486	Mat	Oocyte gDMR	ZFP57	
GPR1-AS:TSS-DMR		2:207066967-207069445	Mat	Oocyte gDMR		*GPR1-AS, ZDBF2, ADAM23*
ZDBF2/GPR1-AS:IG-DMR		2:207114583-207136544	Pat	Sperm gDMR-secondary DMR	CTCF, RAD21	
*JAKMIP1:*Int2-DMR		4:6106594-6108185	Mat	Oocyte gDMR		
NAP1L5:TSS-DMR		4:89618184-89619237	Mat	Oocyte gDMR	ZFP57	*NAP1L5*
[a]*VTRNA2-1*:DMR	*Nc886*	5:135414802-135416645	Mat	Oocyte gDMR	CTCF, RAD21	
[a]*FAM50B*:TSS-DMR		6:3849082-3850359	Mat	Oocyte gDMR	CTCF, RAD21	*FAM50B, PXDC1*
PLAGL1:alt-TSS-DMR	*LOT1, ZAC1*	6:144328078-144329888	Mat	Oocyte gDMR	ZFP57	Multiple *PLAGL1*

						transcripts, *HYMAI*
IGF2R:Int2-DMR		6:160426558-160427561	Mat	Oocyte gDMR		
[a]*WDR27*:Int13-DMR		6:170054504-170055618	Mat	Oocyte gDMR	CTCF	*WDR27*
*RPS2P32:*TSS-DMR		7:23530017-23530976	Mat	unclear		*RPS2P32*
GRB10:alt-TSS-DMR		7:50848726-50851312	Mat	Oocyte gDMR	CTCF, RAD21, ZFP57	*GRB10, DDC*
*PEG10:*TSS-DMR		7:94285537-94287960	Mat	Oocyte gDMR		*PEG10, SGCE, PPP1R9A, TFPI2, CALCR, DLX5*
MEST:alt-TSS-DMR	*PEG1*	7:130130122-130134388	Mat	Oocyte gDMR	CTCF, RAD21, ZFP57	*MEST, MESTIT1, COPG2IT1, CPA4, KLF14*
[a]*SVOPL*:alt-TSS-DMR		7:138348118-138349069	Mat	Oocyte gDMR		*SVOPL*
HTR5A:TSS-DMR		7:154862719-154863382	Mat	Oocyte gDMR		*HTR5A*
[a]*ERLIN2*:Int6-DMR		8:37604992-37606088	Mat	Oocyte gDMR		*ERLIN2*
PEG13:TSS-DMR	*TRAPPC9* intronic DMR	8:141108147-141111081	Mat	Oocyte gDMR	CTCF, RAD21, ZFP57	*PEG13, TRAPPC9, KCNK9*
[a]*FANCC*:In61-DMR		9:98075400-98075744	Mat	Oocyte gDMR		
*PTCHD3:*TSS-DMR		chr10:27702514-27703363	Mat	Oocyte gDMR		*PTCHD3*
INPP5F:Int2-DMR	*INPP5FV2*	10:121578046-121578727	Mat	Oocyte gDMR		*INPP5FV2*
H19/IGF2:IG-DMR	IC1, ICR1, *H19* DMD	11:2018812-2024740	Pat	Sperm gDMR	CTCF, RAD21, ZFP57, POU5F1	Multiple *IGF2 transcripts, IGF2-AS, INS-IGF2,* miR483, *H19, HOTS, 91H,* miR675
IGF2:Ex9-DMR	*IGF2*-DMR2	11:2153991-	Pat	Secondary		

		2155112		DMR		
IGF2:alt-TSS-DMR	*IGF2*-DMR0	11:2168333-2169768	Pat	Sperm gDMR		
KCNQ1OT1:TSS-DMR	*IC2, ICR2, KvDMR1, KvLQT1, LIT1*	11:2719948-2722529	Mat	Oocyte gDMR	ZFP57	*KCNQ1OT1, CDKN1C, PHLDA2, SLC22A18, KCNQ1*
RB1:Int-DMR		13:48892341-48895763	Mat	Oocyte gDMR	ZFP57	*LPAR6*
LPAR6:TSS-DMR		13:48984639-48987689	Mat	Secondary DMR		
DLK1:Int2-DMR		14:101193446-101195447	Mat	Secondary DMR		
MEG3/ DLK1:IG-DMR	IG-DMR, *GLT2-DLK1*	14:101275427-101278058	Pat	Sperm gDMR		*MEG3, DLK1, MEG8, DIO3, RTL1, RTL-AS, MEG9, SNORD113, SNORD114* and microRNA cluster
MEG3:TSS-DMR	*GTL2*	14:101290524-101293978	Pat	Secondary DMR	CTCF, ZFP57	
MEG8:Int2-DMR		14:101370410-101371410	Mat	Secondary DMR	CTCF, RAD21	
MKRN3:TSS-DMR		15:23807086-23812495	Mat	Oocyte gDMR-secondary DMR		
MAGEL2:TSS-DMR		15:23892425-23894029	Mat	Secondary DMR		
NDN:TSS-DMR		15:23931451-23932759	Mat	Secondary DMR		
[b]*SNRPN*:alt-TSS-DMR		15:25068564-25069481	Mat	Secondary DMR		
[b]*SNRPN*:Int1-DMR1		15:25093008-25193829	Mat	Secondary DMR	POU5F1	
[b]*SNRPN*:Int1-DMR2		15:25123027-25123905	Mat	Secondary DMR		
SNURF:TSS-DMR		15:25200004-25201976	Mat	Oocyte gDMR	YY1	*MKRN3, MAGEL2, NDN,*

						PWRN1, SNRPN, IPW, SNHG14, SNORD116, SNORD115, UBE3A
SNORD116:DMR	*SNHG14, UBE3A-AS*	15:25156289-25405834	Pat	Secondary DMR		
IGF1R:Int2-DMR	*IRIAN*	15:99408496-99409650	Mat	Oocyte gDMR		*IRIAN*
ZNF597: 3'-DMR		16:3481801-3482388	Mat	Oocyte gDMR		*ZNF597, NAA60*
ZNF597:TSS-DMR	*NAT15*	16:3492828-3494463	Pat	Secondary DMR		
ZNF331:alt-TSS-DMR1		19:54040510-54042212	Mat	Oocyte gDMR	CTCF	
ZNF331:alt-TSS-DMR2		19:54057086-54058425	Mat	Oocyte gDMR		
PEG3:TSS-DMR	*ZIM2, ZNF904*	19:57348493-57353271	Mat	Oocyte gDMR	ZFP57	*PEG3, ZIM2, MIMT1*
MCTS2P:TSS-DMR	*psMCT1, MCST2*	20:30134663-30135933	Mat	Oocyte gDMR	YY1	*MCST2, HM13*
NNAT:TSS-DMR	*PEG5*	20:36148604-36150528	Mat	Oocyte gDMR	ZFP57	*NNAT, BLACP*
L3MBTL1:alt-TSS-DMR	*ZC2HC3, KIAA0681*	20:42142365-42144040	Mat	Oocyte gDMR	CTCF, RAD21	*L3MBTL1, SGK2*
GNAS-NESP:TSS-DMR	*NESP55*	20:57414039-57418612	Pat	Secondary DMR	CTCF, RAD21	Multiple *GNAS* transcripts, miR296, miR298
GNAS-AS1:TSS-DMR	*NESP-AS*	20:57425649-57428033	Mat	Oocyte gDMR	CTCF, RAD21,	
GNAS-XL:TSS-DMR	Secretogramin VI	20:57428905-57431463	Mat	Oocyte gDMR	ZFP57	
GNAS A/B:TSS-DMR	Secretogramin VI	20:57463265-57465201	Mat	Oocyte gDMR		
WRB:alt-TSS-DMR		21:40757510-40758276	Mat	Oocyte gDMR		
[a]*SNU13*:alt-TSS-DMR	*NHP2L1*	22:42077774-42078873	Mat	Oocyte gDMR		

[a]These imprinted DMRs show evidence for mosaicism in the general population with low-frequency hypomethylation reported. [b]The entire ~1 MB interval between the *NDN* and *SNURF* DMRs (chr15:24112253-25108042) is preferentially methylated on the maternal allele. [c]TF binding sites taken from: YY1 ChIP–seq

ENCODE data sets (March 2012); CTCF ChIP–seq ENCODE data sets (March 2012); ZFP57 ChIP-seq data set[32]; POU5F1 ChIP-seq ENCODE data sets (March 2012). gDMR, germline differentially methylated region; HGVS, Human Genome Variation Society; IG-DMR, intergenic DMR; Mat, maternal; Pat, paternal; TF, transcription factor.

Supplementary Table 3. Factors with potential roles in imprinting control.

Factor	Function	Mouse KO phenotype	Associated imprinting disorders
AID, APOBEC1	Possible role in active demethylation in PGCs	Modest global hypermethylation in deficient PGCs[33]	NR
TET1, TET2	Implicated in demethylation as they have specific activity for converting 5mC to 5hmC	DKO mice have reduced 5hmC and increased 5mC levels at some imprinted loci (*Mest, Peg3, Igf2r, H19*)[34]	NR
DNMT3A/B	De novo DNMT	No methylation at gDMRs[35]	NR
DNMT3L	Associate factor for DNMT3	No methylation at gDMRs[36]	No pathogenic variants identified in SRS[37]
KDM1B	Oocyte-specific H3K4 demethylase	LOM at multiple gDMRs (*Mest*, *Grb10, Zac1, Impact, U2af1-rs1, Peg10, Nnat, KvDMR1, Igf2r, Gnas*)[38,39]	NR
KDM1A	H3K4 demethylase	LOM at transient *Cdh15* gDMRs [39]	NR
NLRP7	Potentially a SCMC-interacting protein	No mouse orthologue	Biparental hydatidiform moles with complete lack of maternal imprints[40,41] MLID in rare hypomorphs[42-44]
DNMT1 (both oocyte and somatic isoforms)	Maintenance DNMT	Widespread LOM during embryonic cleavage stages[45,46]	BWS with IC2 LOM[47]
DNMT3A/B	De novo DNMT	No methylation at gDMRs[35,48]	NR
ZFP57	KAP1 recruiting zinc-finger protein	Widespread LOM during embryonic cleavage stages[49]	TNDM patients with MLID[1]
TRIM28 (also known as KAP1)	KRAB1-associated protein repressor complex	Partial LOM during embryonic cleavage stages (*H19, Snrpn*)[50]	No pathogenic variants identified in MLID[51]
UHRF1	Guides DNMT1 to hemi-methylated DNA during replication	Partial LOM during embryonic cleavage stages (*H19*, KvDMR1, *Meg3/Dlk1*:IG-DMR)[52]	Single case of MLID[9]
Histone H1	Linker histone	Triple KOs result in Partial LOM (*H19*, *Meg3/Dlk1*:IG-DMR)	NR
MBD3	Methyl-CpG binding protein	Partial LOM at *H19*[53]	No pathogenic variants

			identified in SRS[37]
MTA2	- Metastasis tumour antigen 2 - Member of NuRD complex	Partial LOM at *H19* and *Peg3*[54]	NR
RBBP1 (also known as Arid4a), RBBP1L1 (also known as Arid4b)	Retinoblastoma-binding proteins	LOM at *Snrpn* in DKOs[55]	NR
DPPA3 (also known as STELLA)	Binds to methylated and H3K9 decorated gDMRs	Partial LOM at several gDMRs (*Snrpn, Mest, Peg3, Nnat, Peg10, H19, Rasgrf1*)[56]	No pathogenic variants identified in MLID[10]
NLRP2	Potentially a SCMC member	Aberrant gDMRs (GOM and LOM) in embryos that survive to mid-gestation[57]	MLID[58]
KHDC3L (also known as C6orf221 or FILIA)	KH domain-containing 3 like, Member of SCMC	Imprinting not assessed[59]	Biparental hydatidiform moles LOM at several DMRs (KvDMR1, SNRPN, MEST, PEG3, GNAS XL, GNAS A/B)[60,61] No pathogenic variants identified in MLID[44,51]
NLRP5 (also known as MATER)	Member of SCMC	Imprinting not assessed[62]	MLID[8]
OOEP	Member of SCMC	Imprinting not assessed[63]	Single case of MLID[9]
PADI6	Member of SCMC	Imprinting not assessed[64]	MLID[9]
ZAR1	Oocyte-specific zinc finger protein	Imprinting not assessed[65]	Single case of MLID[9]
VEZF1	Zinc finger TF DB1	Partial LOM at *H19* and *Igf2r* gDMRs[66]	No pathogenic variants identified in MLID[10]
SMCHD1	Structural maintenance of chromosome flexible hinger domain-containing protein	LOM of secondary DMRs in mouse 7qB5 domain[67]	NR
YY1	Transcriptional repressor protein	Aberrant gDMRs (GOM and LOM)[68]	NR
ZBTB33	Zinc finger and BTB-domain-containing TF	Imprinting not assessed[69]	shRNA-targeting resulting in partial LOM at H19[70]
CTCF	Zinc finger protein involved in chromatin organization	GOM at *H19*[71]	Microdeletions of CTCF binding sites result in IC1 GOM in BWS[72-74]

ZFP42 (also known as REX1)	Zinc finger protein	GOM at *Peg3* and *GNAS*[75]	NR
POU5F1	Pioneer pluripotency TF	Imprinting not assessed[76]	Binding site pathogenic variants lead to IC1 GOM in BWS[77-79]
SOX2	Pioneer pluripotency TF	Imprinting not assessed[80]	Binding site pathogenic variants lead to IC1 GOM in BWS[77-79,81]

BWS, Beckwith–Wiedemann syndrome; DKO, double KO; DNMT, DNA methyltransferase; gDMR, germline differentially methylated region; GOM, gain of methylation; IC, imprinting centre; IG-DMR, intergenic DMR; KO, knockout; LOM, loss of methylation; MLID, multi-locus imprinting defects; NLRP, NACHT, LRR and PYD domains-containing protein; NR, not reported; PGCs, primordial germ cells; shRNA, small hairpin RNA; SRS, Silver–Russell syndrome; TF, transcription factor, TNDM, transient neonatal diabetes mellitus.

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