Genomic Imprinting Syndromes and Cancer

Ken Higashimoto, Keiichiro Joh, and Hidenobu Soejima

Abstract Genomic imprinting is an epigenetic phenomenon that leads to parent-specific differential expression of a subset of mammalian genes. Some imprinted genes are expressed from the maternal allele and repressed on the paternal allele, whereas others are expressed from the paternal and not the maternal allele. Because most imprinted genes play important roles in growth and development, and metabolism, the aberrant expression of imprinted genes due to epigenetic or genetic alterations often causes human disorders. These include genomic imprinting syndromes and tumors. Since loss of imprinting (LOI) of *IGF2* (which means biallelic expression of *IGF2*) was first reported in Wilms tumor in 1993, aberrant methylation of differentially methylated regions (DMRs), which regulate expression of imprinted genes and/or aberrant expression of imprinted genes, have been reported in various tumors. In this section, general imprinting mechanisms, representative clinical features and causative molecular alterations of eight imprinting syndromes are described. In addition, representative molecular alterations of imprinted DMRs or imprinted genes associated with tumors are also described.

Keywords Genomic imprinting • Imprinting syndromes • Imprinted genes • Differentially methylated regions (DMRs) • Imprinting control regions (ICRs)

1 Genomic Imprinting

1.1 Genomic Imprinting and Human Disorders

Genomic imprinting is an epigenetic phenomenon that leads to parent-specific differential expression of a subset of mammalian genes. Some imprinted genes are expressed from the maternal allele and repressed on the paternal allele, whereas others are expressed from the paternal not maternal allele. Because most imprinted

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genes play important roles in the growth and development of embryos, placental formation, and metabolism, the aberrant expression of imprinted genes due to epigenetic or genetic alterations often cause human disorders, such as genomic imprinting syndromes and tumors [2, 220]. In addition, recent studies show that imprinted genes are involved in wide biological phenomena, such as feeding, maintenance of body temperature, neurological and behavioral processes, sleep, and stem cell maintenance and renewal. These indicate that altered expression of imprinted genes may influence the development of a wide-range of human disorders [181].

Genomic imprinting in mammals was identified by pronuclear transplantation experiments in the early 1980s [150, 214]. Such experiments indicated that maternal and paternal contributions to the mouse embryonic genome are not equivalent. It is noteworthy that ovarian teratoma developed by parthenogenesis and complete hydatidiform mole developed by androgenesis both also indicate separate contributions of the two parental genomes in humans. In 1991, three imprinted genes were firstly identified in mice. These include: insulin-like growth factor 2 (*Igf2*), insulin-like growth factor 2 receptor (*Igf2r*), and *H19*, a non-coding RNA. In humans, uniparental disomy was described as a new genetic concept in 1980 [50]. This was defined as the inheritance of two copies of a chromosome or part of a chromosome from one parent and no copies from the other parent. In addition, Prader-Willi syndrome (PWS) was identified as the first imprinting disorder in 1989 [170]. Thus far, eight genomic imprinting syndromes are known. These are: Beckwith-Wiedemann syndrome (BWS), Silver-Russell syndrome (SRS), Prader-Willi syndrome (PWS), Angelman syndromes (AS), Kagami-Ogata syndrome (KOS), Temple syndrome (TS), pseudohypoparathyroidism (PHP), and transient neonatal diabetes mellitus type 1 (TNDM1).

1.2 The Control of DNA Methylation Imprints

To date, approximately 150 imprinted genes have been identified in the mouse with approximately 70% conserved in humans. Many imprinted genes form clusters, or imprinting domains. The expression of imprinted genes within these domains is regulated by imprinting control regions (ICRs) [181, 209]. ICRs show differential methylation between the two parental alleles, forming so-called differentially methylated regions (DMRs). DMRs are classified into maternally and paternally methylated DMRs, as well as into gametic and somatic DMRs. Maternally methylated DMRs are methylated maternal alleles only, and not paternal alleles, and vice versa for paternally methylated DMRs. Gametic DMRs acquire DNA methylation in the maternal and paternal germ cells and most gametic DMRs are identical to ICRs. In contrast, methylations of somatic DMRs are established after fertilization in response to nearby gametic DMRs (ICRs) [55, 209].

To date, there are 28 known gametic DMRs (ICRs) in the mouse and 38 in humans [153]. DNA methylation of the genome, including DMRs, is erased in primordial germ cells (PGCs). After this, sex-specific methylation marks at DMRs

(ICRs) are acquired and established in developing germ cells. The establishment of methylation marks requires *de novo* DNA methyltransferase Dnmt3a and its regulatory factor Dnmt3l [18, 96]. In mouse developing oocytes, the Dnmt3a-Dnmt3l complex shows low affinity to H3K4me3, but interacts with unmethylated H3K4. This suggests that demethylation of H3K4 is a prerequisite for *de novo* DNA methylation at some ICRs [30, 176]. Transcription through the ICR regions would thus be critical for methylation acquisition in developing oocytes because transcription may make the chromatin more accessible via the Dnmt3a-Dnmt3l complex [29, 55].

After fertilization, zygotes undergo global demethylation until implantation. The paternal genome is rapidly demethylated, indicating an active mechanism associated with Tet3-mediated oxidation of 5 mC converting to 5 hmC [66]. The maternal genome is gradually demethylated due to a passive replication-dependent dilution mechanism. During the global demethylation, methylation of ICRs must be maintained. Dppa3 (also known as Pgc7 or Stella) is a factor protecting methylation of the maternal genome, including ICRs. Dppa3 recognizes and binds to H3K9me2 on the methylated ICRs and prevents them from Tet3-mediated demethylation [166, 236]. Dppa3 also protects paternally methylated ICRs, such as *H19*-DMR and *Rasgrf1*, in the mouse [166].

Zfp57 is another factor, which protects imprinted methylation. This KRAB zinc-finger protein binds to a methylated sequence, such as TGCCGC, and interacts with Trim28 (also known as Kap1) to recruit Dnmt1 and H3K9 methyltransferase Setdb1. This results in protection of methylated ICRs [125, 186]. In humans, homozygous recessive mutations of *ZFP57* have been found in TNDM1 patients. Such patients show loss of DNA methylation (LOM) at several ICRs other than *ZAC*-DMR, which is an ICR responsible for TNDM1 [138].

After implantation, the global DNA methylation level increases. Dnmt3b is a responsible *de novo* methyltransferase for this increase [153]. At this stage, it is important to protect unmethylated DMRs against *de novo* methylation. CTCF binds to unmethylated maternal *H19*-DMR and protects it from *de novo* methylation [51, 205]. Rex1/Zfp42 also protects *Peg3* and *Gnas* DMRs [131]. In addition, most unmethylated ICRs overlap promoter CpG islands with active transcription enriched with H3K4me3. Since H3K4me3 prevents binding of DNMT3L, which leads to impairment in *de novo* methylation, those ICRs may be protected [176]. Furthermore, formation of R-loops (double-stranded RNA-DNA structures forming on the transcribed DNA strand) on the unmethylated transcriptional active ICRs protects the unmethylated status against *de novo* DNA methylation by Dnmt3b in the early embryo [63].

1.3 Regulation of Imprinted Gene Expression by ICRs

Imprinting domains contain both maternally and paternally expressed genes, as well as genes that encode proteins and those that encode non-coding RNAs. Gene expression within the domains is also regulated by ICRs, as previously mentioned [181].

Maternally methylated ICRs are found at promoters of protein-coding genes or non-coding RNA genes, whereas paternally methylated ICRs are found in intergenic regions [55]. ICRs act in *cis* to express genes within the domains monoallelically. Although the precise mechanisms differ among loci, there are two principal models—the long non-coding RNA (lncRNA) model and the insulator model [181].

The lncRNA model is thought to implicate four imprinting domains: *Igf2r*, *Kcnq1ot1*, *Snrpn*, and *Gnas* [55, 181]. Maternally methylated ICRs at promoters repress lncRNAs, but unmethylated ICRs on the paternal alleles are active in transcription and repression of neighboring protein-coding genes in *cis*. The best characterized locus for the insulator model is *H19*-DMR. When CTCF binds to unmethylated *H19*-DMR on the maternal allele, it insulates the *Igf2* promoter from downstream enhancers, resulting in silencing of *Igf2* [14, 71].

2 Genomic Imprinting Syndromes

2.1 Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS; OMIM 130650) is a model of imprinting disorder, which shows prenatal and postnatal macrosomia, macroglossia, abdominal wall defects, a predisposition to tumorigenesis, and other variable features. Incidence is approximately one in 13,700 live births [208]. The chromosomal locus for BWS is 11p15.5, which consists of two imprinting domains: *IGF2*/*H19* and *CDKN1C*/*KCNQ1OT1*. *H19*-DMR and *Kv*DMR1 are the ICRs for the *IGF2*/ *H19* and *CDKN1C*/*KCNQ1OT1* domains, respectively (Fig. 1a). The important genes in the *IGF2*/*H19* domain are insulin-like growth factor 2 (*IGF2*) and lncRNA, *H19*. *IGF2* is expressed from the paternal allele and *H19* is expressed from the maternal allele. For the *CDKN1C*/*KCNQ1OT1* domain, the important genes are *CDKN1C* and *KCNQ1OT1*. *CDKN1C* encodes cyclin-dependent kinase (CDK) inhibitor and shows preferential maternal expression. *KCNQ1OT1* is a paternally expressed gene encoding lncRNA.

So far, several causative alterations have been identified. These are gain of methylation (GOM) at *H19*-DMR (~5% of patients), loss of methylation (LOM) at *Kv*DMR1 (~50% of patients), paternal uniparental disomy (pUPD) encompassing 11p15.5 (~20% of patients), loss of function mutation of *CDKN1C* (~5% of patients), and chromosomal rearrangement involving 11p15.5 (<1% of patients). However, no alteration of 11p15.5 can be found for ~20% of BWS patients [209]. *H19*-DMR-GOM leads to biallelic expression, or *IGF2* LOI and reduced expression of *H19*. *Kv*DMR1-LOM leads to expression of *KCNQ1OT1* RNA, which in turn results in repression of *CDKN1C* expression on the maternal chromosome. In Sects. 3.1 and 3.2 the detailed molecular mechanisms of the domains are described. The minimal region of pUPD is 2.7 Mb from the 11p telomere, which includes both *H19*-DMR and *Kv*DMR1-LOM, leading to both *IGF2* LOI and silencing of *CDKN1C* [175].

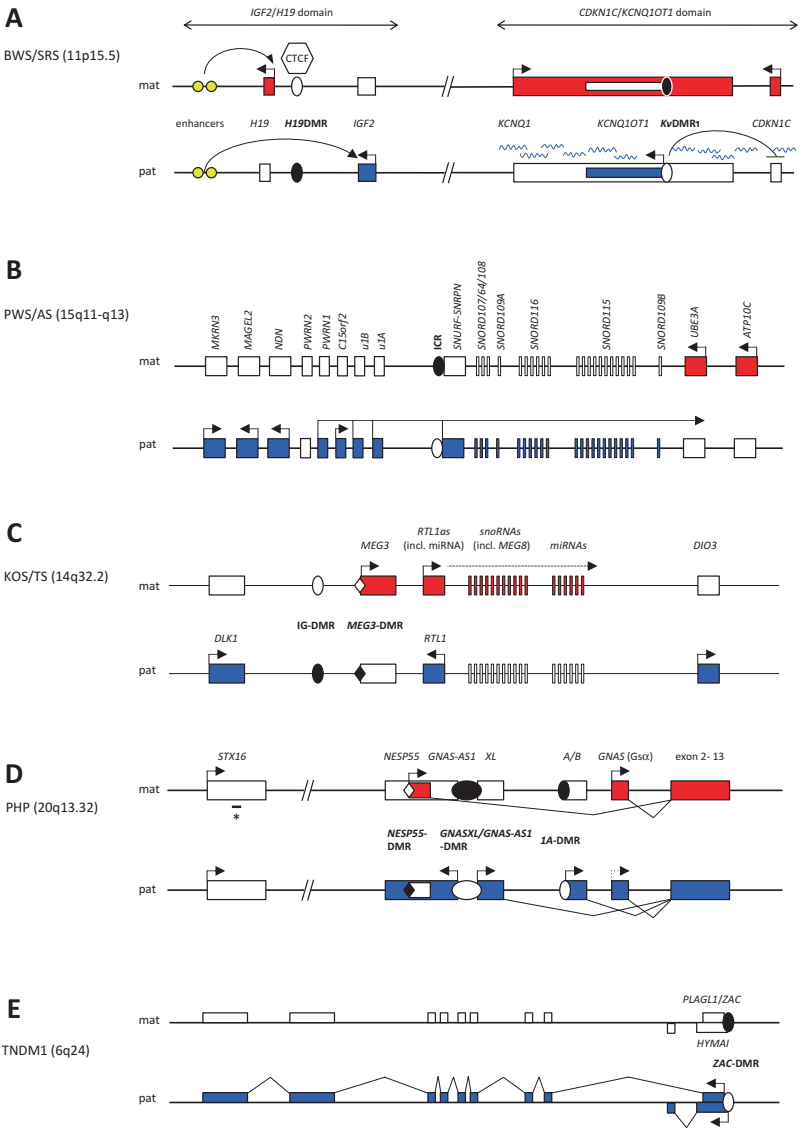

Fig. 1 Human imprinting domains and representative imprinted genes associated with imprinting syndromes. (**a**) Beckwith-Wiedemann syndrome (*BWS*)/Silver-Russell syndrome (*SRS*) locus at 11p15.5. The *IGF2*/*H19* domain is the best characterized domain for the insulator model. The *CDKN1C*/*KCNQ1OT1* domain is one of the representatives of the lncRNA model. Yellow circles: enhancers; wavy line: non-coding RNA transcribed from the paternal *KCNQ1OT1* gene. Blue: paternally expressed genes; red: maternally expressed genes; filled ovals: methylated gametic DMRs; open ovals: unmethylated gametic DMRs; filled diamonds: methylated somatic DMRs; open diamonds: unmethylated somatic DMRs. (**b**) Prader-Willi syndrome (*PWS*)/Angelman syndrome (*AS*) locus at 15q11-q13. (**c**) Kagami-Ogata syndrome (*KOS*)/Temple syndrome (*TS*) locus at 14q32.2. (**d**) Pseudohypoparathyroidism (*PHP*) locus at 20q13.32. *: a deleted region in familial PHP1b, suggesting the existence of a *cis* regulatory element for *A/B*-DMR methylation status. (**e**) Transient neonatal diabetes mellitus type 1 (TNDM1) locus at 6q24

The development of embryonal tumors is an important feature of BWS, where the overall tumor risk has been estimated at 7.4% [163]. Tumor risk is different depending on molecular alterations. It is 22.8% in *H19*-DMR-GOM, 13.8% in pUPD, 8.6% in *CDKN1C* mutation, and 2.5% in *Kv*DMR1-LOM. A specific type of pUPD, denoted as genome-wide pUPD (GWpUPD) mosaic, has been recognized among patients of pUPD. Patients with mosaic GWpUPD showed a high incidence (81%) of tumor development, significantly higher than in segmental pUPD patients [175]. Tumor type also differs depending on molecular alteration, e.g. Wilms tumor is associated with *H19*-DMR-GOM and pUPD, hepatoblastoma and adrenal carcinoma associated with pUPD, and neuroblastic tumors associated with *CDKN1C* mutation [163]. In addition, there are reports of altered gene expressions and methylation status of DMRs in many tumors (Table 1). These alterations are described in detail in Sects. 3.1 and 3.2.

2.2 Silver-Russell Syndrome

Silver-Russell syndrome (SRS; OMIM 180860) is characterized by clinical phenotypes opposite to BWS, such as intrauterine growth restriction, poor postnatal growth, relative macrocephaly, triangular face, asymmetry, and feeding difficulties [46]. Incidence is one in 100,000. SRS patients do not appear to have a significantly increased incidence of neoplasia [197]. *H19*-DMR becomes hypomethylated (*H19*-DMR-LOM) in more than 45% of SRS patients, leading to increased *H19* expression and decreased *IGF2* expression [46] (Fig. 1a). Maternal uniparental disomy of chromosome 7, or upd(7)mat, is found in 4.5% of SRS patients. The disturbed expression of imprinted genes on chromosome 7 has been estimated and several imprinted genes were found at 7p11.2-p13 and 7q31-qter. However, the molecular link between upd(7)mat and SRS is currently unknown [46].

2.3 Prader-Willi Syndrome and Angelman Syndrome

Incidence of Prader-Willi syndrome (PWS; OMIM 176270) and Angelman syndrome (AS; OMIM 105830) is 1:15,000–1:25,000 live births. PWS is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity [23]. The evaluation of the cancer risk using the PWS registry in the US showed an increased risk of myeloid leukemia, but not other cancers [39]. AS is characterized by microcephaly, gait ataxia, severe mental retardation, and absent or severely limited speech [23]. Tumor development in AS has been rarely reported.

These two distinct disorders develop as a result of imprinting disruption of 15q11-q13 (Fig. 1b). ICR is maternally methylated and regulates expression of the genes within this region [23]. Approximately 70% of patients with PWS show

Table 1 Aberrantly methylated DMRs in tumors

Chromosomal location	Imprinted locus	DMR	Normally methylated allele	Aberrant methylation	Tumor	Refs
1p31.3	*DIRAS3 (ARHI)*	*DIRAS3*-DMRs	Mat	Hyper	Breast cancer	[12, 53, 248]
					Follicular thyroid carcinoma	[233]
					Hepatocellular carcinoma	[80]
					Oligodendroglioma	[190]
					Ovarian cancer	[54]
				Hypo	Breast cancer	[12, 248]
					Hepatoblastoma	[196]
2q33.3	*ZDBF2*	*ZDBF2*-DMR	Pat	Hypo	Hepatoblastoma	[196]
4q22.1	*NAP1L5*	*NAP1L5*-DMR	Mat	Hyper	Hepatoblastoma	[196]
5q31	*nc886*	*nc886*	Mat	Hyper	Bladder cancer	[195]
					Breast cancer	[195]
					Colon cancer	[195]
					Lung cancer	[195]
				Hypo	Bladder cancer	[195]
					Breast cancer	[195]
					Colon cancer	[195]
					Lung cancer	[195]
6q24	*ZAC/PLAGL1*	*ZAC*-DMR	Mat	Hyper	Ovarian cancer	[91]
					Diffuse large B-cell lymphoma	[224]
				Hypo	Diffuse large B-cell lymphoma	[224]
6p25.2	*FAM50B*	*FSM50B*-DMR	Mat	Hypo	Testicular germ cell tumor	[249]
6q25.3	*IGF2R*	*IGF2R*-DMR (Region2)	Mat	Hypo	Osteosarcoma	[202]

(continued)

Table 1 (continued)

Chromosomal location	Imprinted locus	DMR	Normally methylated allele	Aberrant methylation	Tumor	Refs
				Hypo	Ovarian cancer	[83]
7p12.1	*GRB10*	*GRB10*-DMR	Mat	Hyper	Breast cancer	[12]
				Hypo	Breast cancer	[12]
7q32.2	*MEST*	*MEST*-DMR	Mat	Hyper	Breast cancer	[12]
					Dermoid cyst	[191]
					Glioblastoma multiforme	[146]
				Hypo	Breast cancer	[12]
					Testicular type I teratoma	[191]
					Seminoma	[191]
7q21.3	*PEG10*	*PEG10*-DMR	Mat	Hypo	Hepatoblastoma	[196]
10q26.1	*INPP5F*	*INPP5Fv2*-DMR	Mat	Hyper	Hepatoblastoma	[196]
11p13	*WT1*	*WT1-AS*-DMR		Hyper	Hepatoblastoma	[196]
11p15.5	*CDKN1C/KCNQ1OT1*	*Kv*DMR1	Mat	Hyper	Breast cancer	[194]
					Colorectal cancer	[167]
					Ovalian teratoma	[4]
					Yolk sac tumor	[4]
				Hypo	Breast cancer	[12, 194, 204]
					Cervical carcinoma	[204]
					Colorectal cancer	[167]
					Esophageal cancer	[210]
					Extragonadal teratoma	[4]
					Gastric carcinoma	[204]
					Germ cell tumor	[4]

					Hepatoblastoma	[196]
					Hepatocarcinoma	[204]
					Teratoma	[4]
					Vulva carcinoma	[204]
					Wilms tumor	[201, 204]
		CDKN1C promoter		Hyper	Acute lymphocytic leukemia	[207]
					Acute myeloid leukemia	[103]
					Breast cancer	[107]
					Diffuse large B-cell lymphoma (DLBCL)	[69, 118, 130]
					Follicular lymphoma	[130]
					Gastric cancer	[103]
					Hepatocellular canecr	[103]
					Leukemia	[111]
					Lung cancer	[107]
					Malignant mesothelioma	[107]
					Pancreatic cancer	[103]
				Hypo	B cell lymphoma	[184]
		PHLDA2 promoter		Hypo	Osteosarcoma	[128]
				Hyper	Osteosarcoma	[127]
11p15.5	*IGF2/H19*	*H19*-DMR	Pat	Hyper	Adrenal tumor	[171]
					Breast cancer	[12]
					Choriocarcinoma	[9]
					Colorectal cancer	[165]
					Germ cell tumor	[84, 60, 191]
					Head-and-neck squamouse cell carcinoma	[40]

(continued)

Table 1 (continued)

Chromosomal location	Imprinted locus	DMR	Normally methylated allele	Aberrant methylation	Tumor	Refs
					Hepatoblastoma	(Li 1998; Honda 2008; Rumbajan 2013)
					Hepatocellular carcinoma	[237]
					Osteosarcoma	[223]
					Ovarian carcinoma	[38]
					Prostate hyperplasia	[179]
					Wilms tumor	[16, 25, 34, 61, 162, 164, 201, 247]
				Hypo	Bladder cancer	[12, 160, 215]
					Cervical carcinoma	[44]
					Colorectal cancer	[28, 35]
					Dermoid cyst	[191]
					Germ cell tumor	[4, 60, 84, 100]
					Hepatocellular carcinoma	[237]
					Lung cancer	[109]
					Malignant mixed Müllerian tumor	[72]
					Osteosarcoma	[128, 223]
					Rhabdmyosarcoma	[137]
					Synovial sarcoma	[213]

					Teratoma	[4, 191]
		H19 promoter	Pat	Hyper	Hepatoblastoma	[196]
				Hypo	Hepatocellular carcinoma	[114]
					Lung cancer	[109]
		IGF2-DMR0	Pat	Hyper	Adrenal tumor	[171]
					Breast cancer	[86, 87]
					Leukemia	[86]
					Lung cancer	[86]
					Esophageal cancer	[239]
				Hypo	Bladder cancer	[24]
					Breast cancer	[12, 86, 87]
					Colorectal cancer	[11, 28, 35, 86, 87]
					Esophageal squamous cell carcinoma	[157]
					Gastrinoma	[42]
					Hepatoblastoma	[52, 126, 185, 196]
					Non-functioning pancreatic endocrine tumor (PET)	[42]
					Osteosarcoma	[129]
					Ovarian cancer	[38, 158]
					Wilms tumor	[162, 212]
		IGF2-DMR2	Pat	Hyper	Breast cancer	[86]
					Colorectal cancer	[86]
					Hepatoblastoma	[196]

(continued)

Table 1 (continued)

Chromosomal location	Imprinted locus	DMR	Normally methylated allele	Aberrant methylation	Tumor	Refs
					Leukemia	[86]
					Lung cancer	[86]
					Insulinoma	[42]
				Hypo	Adrenal tumor	[171]
					Breast cancer	[12]
					Hepatoblastoma	[196]
		IGF2-DMR[a]	Pat	Hypo	Teratoma	[4]
				Hypo	Germ cell tumor	[4]
13q14.2	*RB1*	CpG85	Mat	Hyper	Hepatoblastoma	[196]
					Hepatocellular carcinoma	[7]
					Retinoblastoma	[49]
				Hypo	Hepatocellular carcinoma	[7]
14q32.2	*DLK1/DIO3*	IG-DMR	Pat	Hyper	Cholangiocarcinoma	[5]
					Giant Cell Tumor of bone	[119]
					Hepatoblastoma	[196]
					Hepatocellular carcinoma	[6, 81]
					Meningioma	[250]
					Neuroblastoma	[10]
					Phaeochromocytoma	[10]
					Pituitary tumor	[62]
					Renal cell carcinoma	[99]
					Wilms tumor	[10]
				Hypo	Hepatocellular carcinoma	[6]

		MEG3-DMR	Pat	Hyper	Colorectal adenoma	[151]
					Hepatoblastoma	[196]
					Hepatocellular carcinoma	[6]
					Meningioma	[250]
					Neuroblastoma	[10]
					Pheochromocytoma	[10]
					Pituitary tumor	[252]
					Wilms tumor	[10]
				Hypo	Hepatocellular carcinoma	[6]
15q11.2	*SNRPN/SNURF*	*SNRPN*-DMR	Mat	Hyper	Acute myeloid leukemia	[15]
					Germ cell tumor	[84, 60]
					Ovarian teratoma	[4]
				Hypo	Biparental complete hydatidifrom mole	[48]
					Breast cancer	[12]
					Extragonadal teratoma	[4]
					Germ cell tumor	[4, 60, 84, 117, 191]
					Hepatocellular carcinoma	[114]
					Ovarian teratoma	[4]
15q26.3	*IRAIN*	*IRAIN* promoter	Unknown	Hypo	Breast cancer	[97]
17q13.1	*(pri-miR)-497/195*	*(pri-miR)-497/195* promoter	Unknown	Hyper	Hepatocellular carcinoma	[114]

(continued)

Table 1 (continued)

Chromosomal location	Imprinted locus	DMR	Normally methylated allele	Aberrant methylation	Tumor	Refs
19q13.4	*PEG3*	*PEG3*-DMR	Mat	Hyper	Breast cancer	[12]
					Glioma	[140, 177]
					Ovarian cancer	[45, 54, 64]
					Ovarian teratoma	[4]
					Yolk sac tumor	[4]
				Hypo	Biparental complete hydatidifrom mole	[48]
					Breast cancer	[12]
					Extragonadal teratoma	[4]
					Germinoma	[4]
20q11.21	*MCTS2P*	*MCTS2*P-DMR	Mat	Hypo	Hepatoblastoma	[196]
20q11.23	*NNAT*	*NNAT*-DMR	Mat	Hyper	Acute myeloid leukaemia	[112]
					Pituitary adenoma	[189]
20q13.12	*L3MBTL*	*L3MBTL*-DMR	Mat	Hyper	Myeloid malignancy	[121]
				Hypo	Myeloid malignancy	[121]
20q13.32	*GNAS*	*NESP55*-DMR	Pat	Hyper	Biparental complete hydatidifrom mole	[48]
				Hypo	Hepatoblastoma	[196]
		GNAS-AS1-DMR	Mat	Hyper	Colorectal adenoma	[151]
				Hypo	Colorectal adenoma	[151]
		XLαs-DMR	Mat	Hyper	Hepatoblastoma	[196]
		A/B-DMR	Mat	Hypo	Hepatoblastoma	[196]

[a]The precise location of this DMR is not described in the reference

5–7 Mb *de novo* interstitial deletion of paternal 15q11-q13. In addition, PWS develops as a result of maternal uniparental disomy 15 (upd(15)mat) (20–30%) and GOM at the ICR (1–3%). These alterations lose or reduce the expression of paternal genes, including *SNORD116*, which is a probable major gene contributing to the PWS phenotype [41, 198]. As for AS, maternal deletion of 15q11-q13 (70%), paternal uniparental disomy (15upd(15)pat) (3–7%), LOM at the ICR (2–4%), and mutation in the *UBE3A* (10%) are found. A causative gene, *UBE3A*, which is expressed from the maternal allele in the brain, is inactivated by the alterations [23, 106].

2.4 Kagami-Ogata Syndrome and Temple Syndrome

Since chromosome 14q32.2 harbors an imprinting domain, paternal uniparental disomy 14 (upd(14)pat) results in Kagami–Ogata syndrome (KOS, OMIM 608149) and maternal uniparental disomy 14 (upd(14)mat) results in Temple syndrome (TS, OMIM 616222). This domain contains three paternally expressed protein-coding genes and numerous maternally expressed genes that encode noncoding RNAs (Fig. 1c). The IG-DMR and the *MEG3*-DMR are paternally methylated and function as ICRs for the domain [173].

The two disorders are very rare with approximately 50 reported patients for each syndrome [85, 173].

KOS shows unique phenotypic features, which include increased coat-hanger angle to the ribs and decreased ratio of the mid to widest thorax diameter, abdominal wall defects, prenatal overgrowth/overweight, and developmental delay. The ribs and thorax abnormalities are detectable by chest roentgenogram. KOS is developed as a result of upd(14)pat (65%), deletion of maternal 14q32.2 (19%), and GOM at the IG-DMR and the *MEG3*-DMR (19%). These alterations induce the excessive *RTL1* expression and reduced expression of maternally expressed genes, which are the primary underlying factors for phenotypic development [173]. Hepatoblastoma has been identified in three infantile patients with KOS, which invariably occurred before 4 years of age [173]. Aberrant methylations of DMRs within this imprinted region were reported in several tumors (Table 1), which are described in Sect. 3.3.

The cardinal features of TS are low birth weight, hypotonia and motor delay, feeding problems early in life, early puberty onset, and significantly reduced final height. Many of the clinical features are nonspecific, making diagnosis difficult [85]. Tumor development has been rarely reported in TS. TS is developed by upd(14)mat (70–80%), microdeletion of paternal 14q32.2 (~12%), and LOM at the IG-DMR and the *MEG3*-DMR (~12%). Such alterations decrease *DLK1* and *RTL1* expression, which both play a major role in the development of TS phenotypes [85, 90].

2.5 Pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) is an endocrine disorder characterized by resistance to the parathyroid hormone. The GNAS locus at 20q13.32, a disease locus for PHP, is imprinted and contains three protein coding transcripts. These are: the *GNAS* gene encoding α–subunit of heterotrimeric guanine nucleotide-binding protein (Gsα), extra-large Gsα (XLαs), neuroendocrine secretory protein 55 (NESP55). And two noncoding RNAs, including the *A/B* transcript and an antisense *GNAS* transcript (*GNAS-AS1*) are also contained in this locus (Fig. 1d). The imprinted expressions are regulated by multiple DMRs (see Sect. 3.4). *GNAS* is a tissue-specific imprinted gene showing maternal expression in renal proximal tubules, thyroid, gonads, hypothalamus, and pituitary. There are several disorders associated with *GNAS* mutations or defective imprinting. These are pseudohypoparathyroidism type 1A (PHP1a, OMIM 103580), PHP1b (OMIM 603233), pseudo-PHP (PPHP, OMIM 612463), progressive osseous heteroplasia (POH; OMIM 166350), and McCune-Albright syndrome (MAS; OMIM 174800) [101, 144]. Of these, PHP1a and PHP1b are related to genomic imprinting. PHP1a is caused by maternally transmitted inactivating mutations of *GNAS*, resulting in loss of function in imprinted tissues. Sporadic PHP1b is caused by LOM at *A/B*-DMR, which is normally methylated on the maternal allele. The LOM induces expression of *A/B* transcript, resulting in suppression of *GNAS*. Familial PHP1b shows a microdeletion within the maternal *STX16* gene, which is located approximately 220 Kb upstream of *A/B*-DMR (Fig. 1d). The deletion induces LOM at *A/B*-DMR, which also results in suppression of *GNAS*. PPHP and POH are caused by paternally transmitted inactivating mutations of *GNAS*, and results in haploinsufficiency in non-imprinted tissues. MAS is caused by activating mutations of *GNAS*. Several cancers including bone, thyroid, testicular, and breast have been reported in MAS [19]. Aberrant methylations of DMRs within the *GNAS* locus were reported in several tumors (Table 1), which are described in Sect. 3.4.

2.6 Transient Neonatal Diabetes Mellitus Type 1

Transient neonatal diabetes mellitus type 1 (TNDM1; OMIM #601410) is a subtype of neonatal diabetes. It presents as hyperglycemia that begins in the neonatal period and resolves by age 18 months, as well as dehydration, absence of ketoacidosis, and intrauterine growth retardation [139]. Approximately 50% of TNDM1 patients relapse diabetes in adolescence or early adulthood. Its incidence was estimated at 1:215,000 to 1:400,000 births [216]. TNDM1 is caused by overexpression of the imprinted genes *PLAGL1/ZAC*, which encode a transcription factor and *HYMAI*, a non-coding RNA, on chromosome 6q24. It is due to paternal uniparental disomy of chromosome 6 (40%), duplication of the imprinted region at 6q24 (32%), and maternal hypomethylation of the *ZAC*-DMR (28%), which is normally methylated

on the maternal allele (Fig. 1e). Tumor development in TNDM1 has not been reported, however, *PLAGL1* is downregulated in cancers, including breast, ovarian and cervical cancer, hepatocellular carcinoma (HCC), and squamous cell carcinoma of the head and neck [1].

3 Imprinted Genes and Cancer

As previously mentioned, imprinted genes play an important role in growth and development. Disruption of imprinting due to aberrant methylation of DMRs and/or aberrant expression of imprinted genes is associated with tumor growth. Indeed, global loss of imprinting is associated with increased tumorigenesis in mice [77]. In humans, loss of imprinting (LOI) of *IGF2*, which is the same as biallelic expression of *IGF2*, was first reported in Wilms tumor in 1993 [174, 187]. *IGF2* LOI in Wilms tumor has been associated with hypermethylation of *H19*-DMR [155, 211]. *IGF2* LOI is also reported in many adult tumors [31]. To date, aberrant methylation of DMRs and/or aberrant expression of imprinted genes occurs in various tumors from individuals lacking imprinting disorders [181]. Aberrant methylation of DMRs involved in tumors is summarized in Table 1. In this section, representative imprinted domains or DMRs associated with tumors are described.

3.1 IGF2/H19

3.1.1 The Regulation of the Imprinted *IGF2*/ *H19* Domain

The *IGF2*/*H19* domain is one of the firstly identified imprinted domains. The ICR of this domain is *H19*-DMR, located upstream of *H19*, and is DNA methylated on paternal but not maternal allele. For unmethylated maternal *H19*-DMR, the CTCF insulator protein can successfully bind as a result of methylation sensitive binding to *H19*-DMR. In maternal allele, the existence of CTCF at *H19*-DMR blocks access of enhancers downstream of *H19* to the *IGF2* promoters. This instead activates the *H19* promoter, resulting in maternal *H19* expression. Conversely, in paternal allele, *IGF2* is activated by allowing the promoters to access the enhancers due to the unbound of CTCF on methylated *H19*-DMR, resulting in paternal *IGF2* expression [74] (Fig. 1a).

The CTCF also involves the formation of chromatin looping in addition to insulator function. Studies of chromosome conformation capture (3C) show that, depending on the methylation status of *H19*-DMR, *H19*-DMR alters interaction regions, such as *Igf2*-DMR1, DMR2, or *Igf2* promoters, and *Igf2*/*H19* domain forms allele specific chromatin-looping that regulates the expression of *Igf2* and *H19* [113, 161, 243]. Furthermore, interaction between CTCF bound maternal *H19*-DMR and *Igf2* promoters forms chromatin-loop and polycomb repressive complex 2 (PRC2)

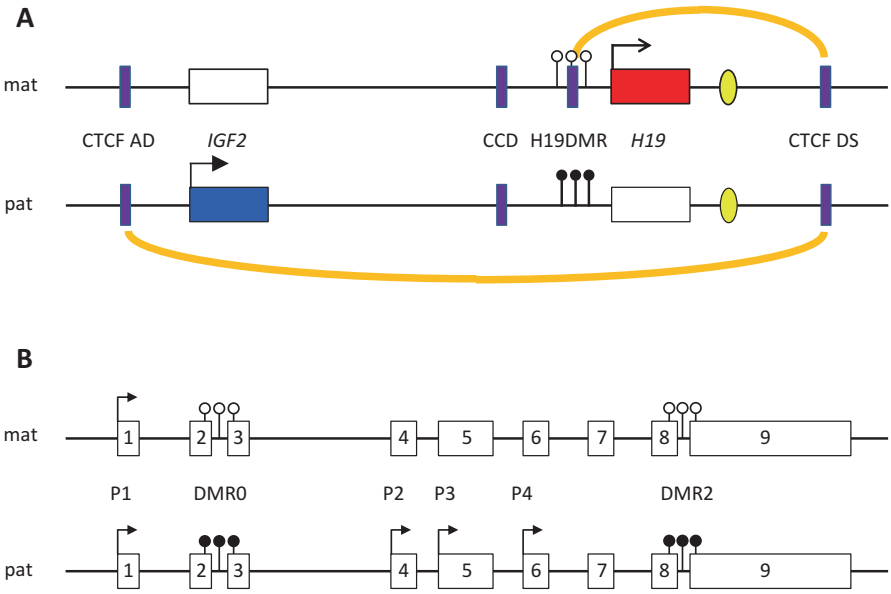

Fig. 2 (**a**) Simplified model of CTCF/cohesin complex mediated interactions in the human *IGF2*/*H19* domain. The CTCF/cohesin binding region and enhancer are indicated by purple rectangles and yellow ovals, respectively. Methylated and unmethylated CpG dinucleotides regions are shown by black and open lollipops, respectively. On the maternal allele, unmethylated *H19*-DMR interacts with CTCF DS, resulting in maternal *H19* expression. Conversely, on the paternal allele, CTCF DS interacts with CTCF AD because methylated *H19*-DMR prevents CTCF binding, resulting in paternal *IGF2* expression. The allele specific chromatin-loops, formed by these interactions, regulate imprinted expression in this domain by bringing enhancers into the proximity of the promoters. The interaction between CTCF AD and CCD on both alleles is omitted. (**b**) Structure characteristics of the human *IGF2* gene. The nine exons of the *IGF2* gene are indicated by the numbered boxes and the promoters (P1–P4) are indicated by *arrows*. The transcripts from P2, P3, and P4 promoters are expressed from the paternal allele, whereas transcripts from P1 are expressed from both parental alleles. *IGF2*-DMR0 and DMR2 are methylated on the paternal allele

is recruited through the CTCF. This results in maternal specific histone H3 lysine 27 methylation (H3K27me) and represses maternal *Igf2* promoters [123]. Subsequently, genome-wide analyses of CTCF and cohesin, a ring-like protein complex, reveal that both proteins were largely co-localized [235]. Cohesin is required to stabilize CTCF-mediated chromatin-loop in the *IGF2*/*H19* domain [169].

Most of the above studies have been performed using mice. In human cells, novel CTCF/cohesin-binding sites, were identified at the upstream site of the *IGF2* gene (CTCF AD), upstream site of *H19*-DMR (CCD), and at the downstream site of the enhancer (CTCF DS) (Fig. 2a). CTCF/cohesin bound to all these sites on both alleles because they were unmethylated. 3C studies show that unmethylated *H19*-DMR interacted with CTCF DS on the maternal allele, while CTCF DS interacts with CTCF AD on the paternal allele. The allele specific chromatin-loop formed by

these interactions regulates imprinted expression in this domain by bringing enhancers into the proximity of the promoters [168].

3.1.2 The Role of IGF2 in Cancer

IGF2 is a potent mitogenic growth factor, which is particularly important for embryonic and placental growth during embryogenesis [21]. IGF2 signals occur via the IGF1 receptor (IGF1R), insulin receptor isoform A (IR-A), and the IGF1R/ IR-A hybrid receptor. The binding of IGF2 to IGF1R activates the tyrosine kinase receptor. Tyrosine kinase phosphorylates two main substrates: the insulin receptor substrates (IRSs) and Src homologous and collagen (Shc). Phosphorylated IRSs recruit the phosphatidylinositol 3-kinase (PI3K) and activates the PI3K/AKT pathway. The PI3K/AKT pathway exerts a variety of functions, such as releasing the anti-apoptotic protein Bcl-2 from BAD, activating protein synthesis via mTOR and promoting glucose metabolism by inhibiting GSK-3β, which is implicated in preventing cell death [43]. Conversely, activating Shc by IGF1R stimulates the Ras/mitogen-activated protein (MAP) kinase pathway, resulting in increased cellular proliferation [43].

The upregulation of *IGF2*, observed in various tumors, is associated with promoting tumor development, tumor angiogenesis, drug resistance, and prognosis [21]. One cause of this upregulation is *IGF2* LOI, which occurs in childhood tumors (*e.g.*, Wilms tumor, rhabdomyosarcoma, and hepatoblastoma) and a majority of adult tumors (*e.g.*, prostate, breast, lung, colon, and liver cancer) [31]. Theoretically, the *IGF2* LOI leads to a 2-fold increase in *IGF2* expression. In fact, Wilms tumors with *IGF2* LOI showed a 2.2-fold increase in *IGF2* expression compared with normal imprinting of *IGF2* [188]. The relationship between LOI and intestinal tumorigenesis was investigated using a mouse model of *Igf2* LOI in the APC^{min} background. Compared with LOI negative APC^{min} mice, LOI positive APC^{min} mice develop about twice the adenomas in both the small intestine and colon. LOI positive APC^{min} also show a shift toward a less differentiated normal intestinal epithelium. The same phenomenon is seen in the normal colonic mucosa with LOI in humans [199]. In addition, *Igf2* LOI *per se* led to increased expression of proliferation-related genes in intestinal crypts and enhancement of sensitivity to IGF2 signaling in *Igf2* LOI mice [95].

Endothelial progenitor cells (EPCs) contribute to tumor angiogenesis, which plays a critical role in tumor growth and progression. Both recruiting and incorporating EPCs to ischemic sites are involved in IGF2-IGF2R-PLCβ2 axis [141]. IGF2 also promotes embryonic stem cell differentiation into endothelial cells through IGF1R [183]. Thus, IGF2 may contribute to tumor angiogenesis.

The development of drug-resistant tumors is an obstacle to effective treatment. The ovarian cancer cell lines resistant to Taxol and other microtubule-stabilizing drugs increase *IGF2* expression compared with their drug sensitive cell lines of origin. Inhibition of IGF2 signaling in the Taxol-resistant ovarian tumor cell lines by IGF1R/IR inhibitor NVP-AEW541 or *IGF2* RNAi restores Taxol sensitivity

[79]. High *IGF2* mRNA expression is also significantly associated with clinically evident drug resistance and poor prognosis in ovarian tumor patients [22, 79].

Increased *IGF2* expression is associated with a poor prognosis in various tumors, including: ovarian, breast, esophageal tumor, and chronic myeloid leukemia [132]. Meanwhile, *IGF2* LOI can occur in normal colonic mucosa and peripheral blood of patients with LOI in cancer tissues and, less frequently, in normal individuals [33]. These results suggest the possibility that LOI may be an effective marker of colorectal cancer risk. In a pilot study, the adjusted odds ratio for LOI in lymphocytes was 5.15 for patients with a positive family history, 3.46 for those with adenomas, and 21.7 for those with colorectal cancer. This supports that LOI in lymphocytes may be able to predict colorectal cancer risk [32].

3.1.3 The Mechanisms of *IGF2* LOI

The mechanisms of *IGF2* LOI can be caused by alteration in *IGF2* promoter usage, *H19*-DMR hypermethylation, and the aberrant methylation of *IGF2*-DMRs. There are, however, many unsolved and controversial issues (Table 1).

3.1.3.1 Alterations in *IGF2* Promoter Usage

IGF2 mRNA is transcribed from separate promoters (P1-P4), which are activated in a developmental stage, in a tissue-specific manner. The transcripts from P2, P3, and P4 promoters are imprinted and activated during fetal development. Conversely, the transcripts from P1 are expressed from both parental alleles in the liver and chondrocytes (Fig. 2b). P1 promoter activity is very weak in the fetal, but increases in the adult liver [47, 124, 229]. This suggests that *IGF2* LOI may occur by promoter switching from imprinted promoters P2–P4 to non-imprinted promoter P1. This assumption has been tested in several types of tumor. However, it was recognized only in cervical carcinoma [105]. Many other tumors, such as laryngeal squamous cell carcinoma and Wilms tumor, did not show the promoter switch [65, 228].

3.1.3.2 *H19*-DMR Hypermethylation

Given regulation of the imprinted *IGF2*/*H19* domain, gain of methylation of unmethylated maternal *H19*-DMR (*H19*-DMR hypermethylation) leads to *IGF2* LOI and *H19* repression because the maternal *H19*-DMR changes to paternal mode. *IGF2* LOI and *H19* repression by *H19*-DMR hypermethylation has been identified in Wilms tumor and hepatoblastoma [16, 78, 201]. Conversely, some Wilms tumors with *H19*-DMR hypermethylation show normal *IGF2* imprinting. This indicates that hypermethylation is necessary, but not sufficient for *IGF2* LOI in Wilms tumor [34]. Of note, *IGF2* LOI and *H19* LOI (biallelic expression of *H19*) are accompanied by *H19*-DMR hypermethylation and hypomethylation, respectively, in osteosarcoma [223].

3.1.3.3 Aberrant Methylation of *IGF2*-DMRs

The human *IGF2* gene contains two DMRs, DMR0 and DMR2. The aberrant methylation of these DMRs is reported in various tumors. *IGF2*-DMR0, which is paternally methylated, is located between exons 2 and 3 of *IGF2* (Fig. 2b). *IGF2* LOI is tightly connected with *IGF2*-DMR0 hypomethylation, but not *H19*-DMR methylation status, in colorectal tumors and matched normal mucosae [35]. This suggests that *IGF2*-DMR0 hypomethylation is a different mechanism for LOI from *H19*-DMR aberrant methylation [35]. However, *IGF2*-DMR0 hypomethylation was not always associated with LOI because some tumors with *IGF2*-DMR0 hypomethylation showed normal *IGF2* monoallelic expression in colorectal tumors [87]. Further, there was no association between DMR0 hypomethylation and LOI in osteosarcoma, bladder, and ovarian tumors [24, 158, 223]. These results suggest that *IGF2*-DMR0 hypomethylation does not directly induce LOI. Furthermore, since it appears unlikely that paternally methylated *IGF2*-DMR0 contributes to *IGF2* repression from maternal allele in *trans*, no association is plausible. Determining the function of *IGF2*-DMR0 could resolve the above controversy. Meanwhile, *IGF2*-DMR0 hypomethylation is associated with poor prognosis in colorectal tumor and esophageal squamous cell carcinoma, suggesting its potential role as a prognostic marker [11, 157].

IGF2-DMR2, which is paternally methylated, is located between exons 8 and 9 of *IGF2* (Fig. 2b). The function of *IGF2*-DMR2 is unknown. In pancreatic endocrine tumors (PETs), *IGF2*-DMR2 hypermethylation occurs specifically in insulinomas, but not in any of other tumor types, namely gastrinomas or non-functioning PETs. DMR2 hypermethylation in insulinomas is also correlated with *IGF2* LOI and overexpression. Gastrinomas and non-functioning PETs also show significant DMR0 hypomethylation and some degree of DMR2 hypomethylation while exhibiting less *IGF2* expression than normal pancreatic tissue. In addition, decreased levels of methylation in DMRs is associated well with worse malignancy according to the World Health Organization (WHO) classification of PETs, except insulinomas, which suggests it has a potential role as a methylation-based biomarker for classification and staging [42].

3.1.4 The Role of *H19* in Cancer

H19 is the first imprinted ncRNA identified. It is highly expressed during embryonic development, but decreases significantly in most tissues after birth [93]. *H19* has been identified as a tumor suppressor candidate due to its inactivation in Wilms tumors [155, 211]. The growth inhibition by exogenous expression in embryonal tumor cell lines and the tumorigenesis in murine models lacking *H19* indicate the tumor suppressor activity [70, 244].

Conversely, exogenous expression of *H19* in choriocarcinoma cell lines and its expression pattern in the testicular germ cell tumors of adolescents and adults suggests *H19* shows oncogenic activity [135, 225]. Indeed, overexpression of *H19* is

observed in several tumors [147] and the molecular evidence for oncogenic *H19* functions has been demonstrated recently. For example, tumor suppressor p53 was partially inactivated via the association between p53 and *H19* in a gastric cancer cell line [241]. *H19* is also associated with EZH2, which is known to methylate H3K27. This association results in inhibition of E-cadherin, associated with invasion and metastasis of tumor cells through Wnt/β-catenin activation in bladder cancer [133]. Furthermore, *H19* acts as a molecular sponge for *let-7* tumor suppressor miRNA. *H19* trapping of *let-7* promotes tumor metastasis [240]. *H19* is also a primary miRNA precursor of *miR-675*. Although *miR-675* is expressed exclusively in the placenta under normal physiological conditions, aberrant expression of *miR-675* can directly suppress the tumor suppressor *RB1* in colorectal cancer [102, 221]. The above results underline the oncogenic functions of *H19*. Thus, this gene may play contrary roles in tumorigenesis and may differ between embryonal and adult tumors in the human and mouse.

3.1.5 *H19* LOI and its Mechanism

H19 LOI (biallelic expression of *H19)* is observed in several tumor types and can result in its overexpression [147]. Indeed, previous work shows *H19* LOI is associated with its overexpression in lung and esophageal cancers [75, 109]. Hypomethylation of *H19*-DMR and *H19* promoter has also been correlated with *H19* LOI in osteosarcoma and lung cancer, respectively [109, 223] (Table 1). However, due to a lack of comprehensive research into the association between LOI, DNA methylation, and/or histone modifications in *H19*-DMR and *H19* promoter in various tumors, the mechanism behind LOI has not been fully elucidated.

3.2 KCNQ1OT1/CDKN1C

3.2.1 The Regulation of the Imprinted *KCNQ1OT1/CDKN1C* Domain

The ICR of this domain is *Kv*DMR1, located in intron 10 of *KCNQ1*, and is methylated on the maternal but not paternal allele. It also contains the promoter of *KCNQ1OT1*, a long non-coding RNA. The paternal *KCNQ1OT1* is expressed from unmethylated paternal *Kv*DMR1 in the antisense direction to *KCNQ1*, resulting in *cis*-repression of neighboring genes [143]. On the maternal allele, neighboring genes, such as *CDKN1C*, *KCNQ1*, *SLC22A18*, and *PHLDA2* are expressed due to lack of *KCNQ1OT1* expression (Fig. 1a). The regulatory mechanisms have been studied in genetically engineered mice and *in vitro* systems, *e.g.* episomal vector system in detail. In mice, when deletion of *Kv*DMR1 or the *Kcnq1ot1* promoter within *Kv*DMR1 is paternally transmitted, the paternal *Kcnq1ot1* transcript is eliminated and leads to LOI in maternal expressed genes within the domain [57, 143].

However, in the above results, it is difficult to distinguish which is important for imprinting regulation: the act of *Kcnq1ot1* transcription or *Kcnq1ot1* RNA itself. It was documented conclusively that *Kcnq1ot1* RNA was necessary for imprinting by truncating *Kcnq1ot1* in an episomal vector system and in mice, in which transcription was preserved, and by flanking the destabilizing sequences from the c-*fos* 3′UTR to the *Kcnq1ot1* in an episomal vector system [143, 178, 219]. Furthermore, *Kcnq1ot1* RNA interacts with H3K9 methyltransferase G9a and the H3K27 methyltransferase complex PRC2. It does so by recruiting these proteins in *cis* to neighboring gene promoters to deposit repressive chromatin marks, such as H3K9me3 and H3K27me3 in mouse placenta, but not in the liver [178, 217, 230]. In the mouse liver, *Kcnq1ot1* RNA interacts with Dnmt1 and contribute to maintaining somatic DMRs of *Cdkn1c* and *Slc22a18* [152]. In normal human fibroblast cell lines, accumulation of *KCNQ1OT1* RNA has been recognized at *CDKN1C* and *SLC22A18* [156]. Together, these findings indicate that paternal *KCNQ1OT1* RNA is pivotal in imprinting, although the imprinting regulation of this domain shows lineage-specific differences.

Conversely, *Kv*DMR1 itself can function as a regulatory element, such as a silencer or an insulator in enhancer-blocking assays [94, 142, 218]. The insulator protein CTCF binding sites conserved between mouse and human have also been identified, whereby CTCF binds to *Kv*DMR1 *in vivo* in a methylation-sensitive manner [56]. Currently, it is unclear whether *Kv*DMR1 represses paternal *Cdkn1c* expression by a *Kcnq1ot1* RNA-independent mechanism. However, given that imprinting regulation differs between extra-embryonic tissues and the embryo proper [120, 152], this suggests that the mechanistic differences of imprinting regulation may exist among various embryonic lineages.

3.2.2 The Role of CDKN1C in Cancer

CDKN1C is a type of cyclin-dependent kinase inhibitor (CKI) belonging to the Cip/Kip family and the first imprinted cell-cycle regulator. CDKN1C binds to cyclin-CDK complexes and inhibits cell cycle progression [116, 148]. In addition, CDKN1C regulates tumor differentiation, apoptosis, cell invasion and metastasis, and angiogenesis [98]. For example, *CDKN1C*-overexpressed LNCaP prostate cancer cells reduce invasive ability *in vitro* and, when transplanted to a nude mouse, can form well-differentiated squamous lesions [89]. Induction of *CDKN1C* expression in HeLa cells enhances sensitivity to apoptotic agents through the mitochondrial apoptotic cell death pathway [227]. The interaction between CDKN1C and the actin cytoskeleton modifying enzyme, LIM-kinase 1 (LIMK-1), can enhance the kinase activity of LIMK-1 and thereby stabilize actin filaments. This results in inhibited cell migration [226]. In placenta of mice lacking *Cdkn1c*, the expression of vascular endothelial growth factor (VEGF), a potent angiogenic factor, increased compared with wild type mice [149]. The aforementioned studies combined with reports of decreased *CDKN1C* expression in various tumors [17] suggest that *CDKN1C* is a multifunctional tumor suppressor gene [98].

3.2.3 The Mechanism of CDKN1C Inactivation

CDKN1C inactivation occurs in various tumors but mutation is infrequent. Abnormal expression of CDKN1C is caused by multiple mechanisms at transcriptional and posttranscriptional levels, as well as by posttranslational modification. Here, we focus on the mechanisms of epigenetic transcriptional silencing in *CDKN1C*.

3.2.3.1 *CDKN1C* Promoter Silencing by DNA Methylation

Aberrant DNA methylation in the promoter region is often invoked as a mechanism, which causes transcriptional inactivation of tumor suppressor genes. Aberrant DNA methylation at *CDKN1C* promoter is also a strong mechanism, which attenuates CDKN1C expression in many tumors. These include gastric, hepatocellular, pancreatic, and breast cancers, and acute myeloid leukemia [17, 103, 107] (Table 1). The clinical significance of the *CDKN1C* methylation status was reported in hematological malignancies. In acute lymphocytic leukemia (ALL), the methylation status in *p73*, *p15*, and *CDKN1C* composing a cell-cycle regulatory pathway was investigated. Philadelphia chromosome-negative patients with two or three methylated genes of this pathway showed significantly worse overall survival compared with those with zero or one methylated genes. Although, *CDKN1C* methylation status alone had no relevance to any clinical parameters [207]. In diffuse large B-cell lymphoma (DLBCL), *CDKN1C* promoter methylation occurs frequently [130]. Thus is may be applied as a biomarker for detecting minimal residual disease in DLBCL [69]. However, *CDKN1C* methylation was proposed as a favorable prognostic marker for a low-risk DLBCL group based on the International Prognostic Index. This is because patients with rather than without methylation show longer overall survival despite the unknown mechanism behind this favorable prognosis [118].

3.2.3.2 *CDKN1C* Promoter Silencing by Histone Modifications

The chromatin structure is regulated by histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, as well as DNA methylation [110]. The chromatin structure in gene regulatory elements such as promoter and enhancer could influence the accessibility of transcriptional factors. In rhabdoid tumor cell lines lacking SMARCB1, a subunit of the SWI/SNF ATP-dependent chromatin-remodeling complex, induction of SMARCB1 upregulates *CDKN1C* expression by increasing permissive modifications, H3 and H4 acetylation at the *CDKN1C* promoter. In addition, the histone deacetylase (HDAC) inhibitor can restore *CDKN1C* expression in these cell lines [3]. In breast cancer cell lines, *CDKN1C* is repressed by repressive modification, H3K27me3 by histone methyltransferase EZH2 [242]. These results highlight the important role of histone modifications in *CDKN1C* repression.

3.2.3.3 *CDKN1C* Repression by DNA Hypomethylation at *Kv*DMR1

DNA hypomethylation of maternal *Kv*DMR1, leading to aberrant maternal *KCNQ1OT1* expression, is consequently associated with *CDKN1C* repression. Such methylation abnormalities have previously been described in various tumors, such as liver, breast, cervical, gastric, vulva, Wilms tumors, and colorectal cancer cell lines [167, 201, 204] (Table 1). However, *CDKN1C* expression is not associated with *Kv*DMR1 methylation status in colorectal cancer cell lines and Wilms tumors [167, 201]. Conversely, in esophageal cancer cell lines, diminished *CDKN1C* expression is statistically correlated with *Kv*DMR1 hypomethylation, but not methylation of the *CDKN1C* promoter itself [210]. Thus, the *CDKN1C* silencing mechanism associated with *Kv*DMR1 may depend on cancer type. In addition, it is difficult to explain the mechanisms of *CDKN1C* repression in only the epigenetic status of *CDKN1C* promoter and *Kv*DMR1, as the expression is also regulated by microRNAs and signaling pathways [67].

3.2.4 PHLDA2 in Cancer

PHLDA2, a homologue of mouse *TDAG51*, is the first apoptosis-related imprinted gene. *PHLDA2* is related to growth inhibition and apoptosis induction via the mitochondrial apoptosis pathway, and enhanced chemosensitivity, as well as stemness decrease in osteosarcoma [37, 82]. Furthermore, it is regulated by EGFR/ErbB2 signaling and inhibits cell proliferation through repressing AKT activation in lung cancers in a negative feedback loop [232]. Thus, PHLDA2 plays a potent role in tumor suppression.

The loss of *PHLDA2* expression has been reported in Wilms tumors, complete hydatidiform moles, and osteosarcomas [37, 203, 206]. Previous work has shown that DNA methylation or EZH2-associated H3K27me3 of the promoter in osteosarcoma cell lines mediates transcriptional repression of *PHLDA2* (Table 1), although its molecular mechanisms in primary tumors have not been well investigated [127, 136].

3.3 DLK1/MEG3

The human *DLK1-MEG3* locus spans about 840 kb at 14q32.2. This imprinted domain contains three paternally expressed protein-coding genes and numerous maternally expressed genes that encode noncoding RNAs, such as lncRNAs, miRNAs, and small nucleolar RNAs (snoRNAs) (Fig. 1c) [36, 173]. Parental allele-specific expression of the imprinted genes is controlled by two paternally methylated DMRs: IG-DMR and *MEG3*-DMR. The methylation of IG-DMR is established in germ cells and *MEG3*-DMR methylation is established after fertilization. The *MEG3* gene (referred to as *Gtl2* in mice) encodes an lncRNA and is expressed in

many normal human tissues, but repressed in various types of human cancers and cancer cell lines. Ectopic gene expression shows various tumor suppressor functions, such as inhibited cellular proliferation, induced apoptosis, and induced p53 activity in many types of cancer and normal cell lines [20, 231, 250, 251]. *RTL1* is a paternally expressed protein-coding gene in this locus. In mice, hepatic expression of this gene can promote cell growth *in vitro* and drive carcinogenesis of HCC *in vivo*. 30% (10/33) of human HCC also shows *RTL1* expression, while normal livers show no significant expression of this gene [192].

Silencing or reduced *MEG3* expression is observed in many types of tumors, such as pituitary tumors [252], neuroblastoma [10], meningioma and meningioma cell lines [250], HCC and HCC cell lines [20], and glioma [231]. In addition to reduced expression, hypermethylation at the *MEG3*-DMR occurs in these tumors and cell lines. *MEG3*-DMR hypermethylation also occurs in a small fraction of pheochromocytomas and Wilms' tumors [10]. Further, treatment with 5-aza-dC can reactivate *MEG3* in neuroblastoma, meningioma, and HCC cell lines [10, 20, 250]. In addition to reactivation by 5-aza-dC, overexpression of *miR-29*, which modulates the expression of DNMT1 and DNMT3B, can also reactivate *MEG3* expression in HCC cell lines [20]. Furthermore, HCC tissues show frequently reduced *miR-29* expression [238]. These results indicate that *MEG3* is inactivated by hypermethylation of maternal *MEG3*-DMR in many types of cancers.

miR-370, maternally expressed from the genomic region between *RTL1* and *MEG8* in the locus, is downregulated in cholangiocarcinoma [5]. Cancers with reduced *miR-370* expression harbor hypermethylation at IG-DMR. Further, *miR-370* expression levels show negative correlations with methylation levels of the DMR. Among the possible targets of *miR-370* is *WNT10B*, whose role is not clear, but enhances cellular proliferation. *miR-127-3p, miR-154*, and *miR-495*, are expressed from the *anti-RTL1* region, the proximal miRNA cluster, and the snoRNA region in *DLK1-MEG3* locus, respectively. Hypermethylation at *MEG3*-DMR is found in majority of colorectal adenomas [151]. Two of the three miRNAs: *miR-127-3p* and *miR-154*, show lower expression in adenomas with hypermethylation than in adenomas with normal methylation. Conversely, *miR-495* is expressed in similar or slightly higher levels in adenomas with hypermethylation. These four miRNAs inhibit cellular proliferation when overexpressed in cancer cell lines [26, 27, 58]. In contrast to the downregulation in adenomas, expression of *miR-379* from the snoRNA region and *miR-154* is elevated in prostate cancer cell lines and primary cancer tissues [68]. Expression levels are correlated with cancer malignancy and overexpression of these miRNAs induces epithelial to mesenchymal transition in prostate cancer cells. DNA methylation was not analyzed in these cancer tissues and cell lines. Some miRNAs expressed from this imprinting locus, may have oncogenic or tumor suppressing functions. Further investigation is needed to elucidate how such miRNAs are involved in carcinogenesis of various types of cancer.

3.4 GNAS *Locus*

The *GNAS* complex locus occurs on the long arm of human chromosome 20 (20q13.32) and is a complex imprinted domain, which contains multiple imprinted genes and DMRs [13, 222] (Fig. 1d). As mentioned in Sect. 2.5, this locus expresses multiple transcripts that encode Gsα (*GNAS* gene), XLαs, and NESP55. The transcripts initiate from unique first exons: *GNAS*, *XL*, and *NESP55*, and are spliced onto a common set of exons 2-13.

Gsα is involved in a signaling pathway that mediates the actions of various hormones by elevating intracellular cyclic AMP levels. The roles of the proteins, XLαs and NESP55, are not yet well understood. Two noncoding RNAs: *A/B* and *GNAS-AS1*, are expressed from the locus in addition to the protein-coding transcripts. Transcript *A/B* is transcribed from exon A/B and is spliced onto the common exons 2-13 (Fig. 1d). *GNAS-AS1* initiates from exon AS1 and is transcribed in an antisense orientation to other transcripts.

The transcripts, *XLαs, GNAS-AS1*, and *A/B* are expressed only from the paternal allele, while *NESP55* is expressed only from the maternal allele. *GNAS* is expressed biallelically in most human tissues, but shows maternal expression in some tissues, such as renal proximal tubules, thyroid, gonads, hypothalamus, and pituitary. The imprinted expressions are regulated by multiple DMRs. The *GNAS-AS1*, *XL*, and *A/B* promoters are DMRs that are methylated on the maternal allele, while the *NESP55* promoter is a DMR methylated on the paternal allele. The promoter of *GNAS* is not methylated on both alleles. The *A/B* transcript and/or *A/B*-DMR is involved in the tissue-specific imprinting of *GNAS*.

Constitutively activating *GNAS* mutations have been reported in endocrine tumors. Further, elevated activity of the Gsα signaling pathway may contribute to the pathogenesis of endocrine tumors. The mutations are always of maternal origin in growth hormone-secreting pituitary adenoma, consistent with the imprinted maternal expression of *GNAS* in the pituitary [115, 145]. De-repression of the *GNAS* paternal allele was found in somatotroph pituitary adenomas [73, 182]. However, the loss of imprinting did not result in the increase of total *GNAS* mRNA levels because decrease of the maternal expression was concomitant with increased paternal expression [182]. This result suggests that imprinting relaxation is not involved in tumorigenesis, but is a secondary phenomenon that is part of the tumorigenic process.

Recently, human miRNAs: *miR-296* and *miR-298*, were found to lie within the *GNAS-AS1* transcription unit and show paternal allele-specific expression as members of the *GNAS* imprinting locus [193]. Prostate cancer cell lines and cancer tissues express *miR-296* at low levels and *HMGA1*, a high-mobility group AT-hook gene, at high levels. The expression of *miR-296* inversely correlates with the expression of *HMGA1* mRNA and the HMGA1 protein. *HMGA1* is an oncogene involved in carcinogenesis of prostate cancer and one of the target genes of *miR-296* [234]. Reduced expression of the miRNA was also observed in pancreatic intraepithelial tumors and pancreatic ductal adenocarcinomas [245]. The more progressed pancreatic

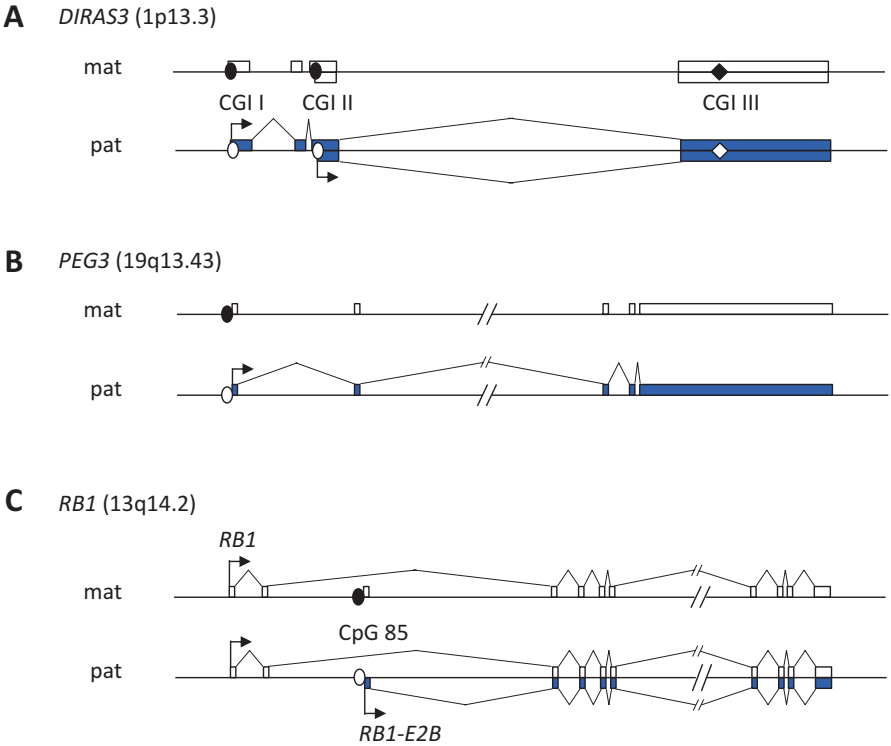

Fig. 3 Representative human imprinting loci associated with tumors. (**a**) *DIRAS3* locus at 1p13.3. (**b**) *PEG3* locus at 19q13.43. (**c**) *RB1* locus at 13q14.2. Blue: paternally expressed genes; filled ovals: methylated gametic DMRs; open ovals: unmethylated gametic DMRs; filled diamond: methylated somatic DMR; open diamond: unmethylated somatic DMR

tumors expressed the lower *miR-296*. Methylation analysis at *GNAS-AS1*-DMR was not performed in these tumors, but colorectal adenoma showed reduced expression of *miR-296* along with aberrant methylation at *GNAS-AS1*-DMR [151]. Frequent hypermethylation (ca. 50%) and some hypomethylation were found in 50 colorectal adenomas. Expression of *miR-296* in adenomas with hypermethylation is lower than those in adenomas with normal methylation [151].

3.5 DIRAS3/ARHI

The *DIRAS3* gene at 1p13.3, also known as *ARHI*, encodes small 26 kDa GTP binding GTPase belonging to the Ras/Rap superfamily. This is a maternally imprinted tumor suppressor gene that is expressed exclusively from the paternal allele in many adult human tissues. The gene contains two start exons and three CpG islands designated as CGI I, CGI II, and CGI III (Fig. 3a). The CGI I and the CGI II identify

the first and second start exons, respectively, and are gametic DMRs with maternal methylation. The CGI III lies within the last exon and its methylation level varies from hypermethylation to intermediate levels among different tissues, so is presumably a tissue-specific somatic DMR [134, 172, 248] (UCSC browser, chr1:68,045,962-68,051,631, hg38, http://genome.ucsc.edu/).

DIRAS3 is silenced in most ovarian and breast cancer cell lines [246] and can inhibit growth of breast and ovarian cancer cell lines when the expression constructs are introduced in the cancer cells. This growth inhibition is accomplished by down-regulation of cyclin D1 and up-regulation of $p21^{WAF1/CIP1}$. In a study of ovarian cancer, cancer cell lines showed *DIRAS3* silencing and CGI I hypermethylation with frequencies of 80% (8/10) and 60% (6/10), respectively [54]. Analysis of cancer tissues showed 88% (35/40) of the cancers expressed lower levels of *DIRAS3* than normal ovarian tissues. CGI I and CGI II were hypermethylated in 31% (13/42) and 12% (5/42) of cancers, respectively. All cancers with hypermethylation showed reduced expression of the gene. Frequent LOH (41%, 9/22) occurred in these cancers, which led to loss of the active paternal allele. In spite of the frequent LOH, there were many cancers that retained heterozygosity and thus the gene was also silenced by aberrant hypermethylation at the CGIs.

CGI methylation status of the *DIRAS3* gene has also been reported in breast cancer cell lines, in which *DIRAS3* was silenced. CGIs I and III were frequently hypermethylated and CGI II showed either hypermethylation or hypomethylation in the cell lines [248]. Aberrant methylation at the *DIRAS3*-CGIs was also observed in breast cancer tissues [53, 248]. However, no characteristic feature was seen in the aberrant methylation, such as hypermethylation or hypomethylation, and frequencies at each of the CGIs. Because *DIRAS3* expression and chromosomal abnormality were not analyzed in either of these studies on breast cancer tissues, it is not clear whether the observed aberrant methylation alters *DIRAS3* expression and whether aberrant methylation is due to changes in DNA methylation or loss of methylated or unmethylated alleles. On the other hand, some studies suggest that histone modifications are also involved in inactivation of the *DIRAS3* gene. A histone deacetylase inhibitor, trichostatin A, could reactivate gene expression in breast cancer cells, in which *DIRAS3* is repressed without hypermethylation at CGI II [59]. Breast cancer tissues highly express JMJD2A, a histone demethylase, which acts on tri- and di-methylated H3K9 and H3K36. Expression of this enzyme is positively correlated with progression of cancers and negatively correlated with *DIRAS3* expression. JMJD2A binds the *DIRAS3* promoter together with HDAC1 and HDAC3 and represses gene expression [122].

Many other types of cancer, such as follicular thyroid carcinoma, oligodendroglioma, and HCC, have downregulated *DIRAS3* and shown aberrant methylation of *DIRAS3* CGIs. LOH of the *DIRAS3* locus was found in 64% (9/14) of follicular thyroid carcinoma [233] and 53% (20/38) of oligodendrogliomas [190]. A LOH case of follicular thyroid carcinoma showed hypermethylation at all *DIRAS3* CGIs and most LOH cases of oligodendroglioma showed hypermethylation of at least one of three CGIs. These indicate deletion of the paternal allele. Furthermore, among oligodendroglioma cases with ROH, several cases showed hypermethylation of the CGIs,

resulting in reduced expression of the gene. In contrast to the above two types of tumors, LOH of the *DIRAS3* locus was a very rare event in HCC, which showed frequent reduction of *DIRAS3* expression [80]. Downregulation of the gene was observed in 79% (33/42) of HCCs; however, only one HCC showed LOH of the locus. Methylation analysis of the CGIs detected hypermethylation only at CGI II with a 47% (8/17) frequency. No aberrant methylation was observed at CGIs I and III. These results strongly suggest that hypermethylation at the promoter of *DIRAS3* occurred in HCCs and such hypermethylation caused downregulation of the gene.

3.6 PEG3

The *PEG3* gene on chromosome 19q13.43 encodes a Krüppel-C2H2 type zinc finger protein and is expressed in a wide variety of human tissues. The gene is imprinted and is expressed from the paternal allele the same as its mouse homologue, *Peg3* [76, 140, 159]. Exon 1 of the gene lies within a CpG island, which is a maternally methylated gametic DMR (*PEG3*-DMR) (Fig. 3b) [140, 159]. *PEG3* shows tumor suppressor activity in human glioma cell lines upon its overexpression [108].

This gene is silenced or downregulated with hypermethylation of *PEG3*-DMR in glioma cell lines [108, 140]. Treatment with 5-aza-dC can reactivate the silenced *PEG3* [140]. Primary glioma tissues also show aberrant hypo- or hypermethylation at *PEG3*-DMR together with changes in *PEG3* expression [177]. Hypermethylation at *PEG3*-DMR and downregulation of the gene are more frequent in grade IV glioblastoma than lower-grade gliomas, such as astrocytoma, oligodendroglioma, and ependymoma. Further, hypomethylation is observed only in lower-grade gliomas. In contrast to glioma cell lines, methylation levels at *PEG3*-DMR correlate weakly with *PEG3* expression in glioma tissues and some tumors with normal methylation also show reduced *PEG3* expression [177]. These results suggest that *PEG3* is downregulated by various mechanisms, including hypermethylation at *PEG3*-DMR in glioma.

Further work shows *PEG3* is downregulated and *PEG3*-DMR is hypermethylated in ovarian cancer cell lines and cancer tissues. Gene expression is also shown to be negatively correlated with DMR methylation level [45, 54, 64]. Treatment with 5-aza-dC and/or a histone deacetylase inhibitor, trichostatin A, can reactivate the gene in silenced cell lines [45, 54]. Overexpression of *PEG3* also inhibits proliferation of ovarian cancer cells [54]. *PEG3* silencing and *PEG3*-DMR hypermethylation are also found in two other gynecologic cancer cell lines, endometrial cancer and cervical cancer [45].

Pediatric germ cell tumors show aberrant methylation at *PEG3*-DMR with patterns characteristic of histologic tumor subtypes. Hypermethylation has been observed in ovarian teratoma and yolk sac tumors, and hypomethylation in female germinoma [4]. Aberrant methylation, mainly hypermethylation, at *PEG3*-DMR also occurs in invasive breast cancers [12].

3.7 RB1

RB1 was the first identified tumor suppressor gene and is frequently inactivated in several cancers. This gene is expressed biallelically; however, a variant transcript, *RB1-E2B*, was found to be imprinted and expressed only from the paternal allele in lower levels than the main *RB1* transcript (Fig. 3c) [92]. The variant transcript initiates from a novel first exon, called *E2B*, which lies in intron 2, and is spliced onto exon 3 of the *RB1* gene. The *RB1-E2B* transcript harbors a coding sequence in the same reading frame as one of the *RB1* mRNAs, which encodes a shortened version of pRb.

The function, if any, of the presumptive protein is not well understood yet. The exon *E2B* lies in a CpG island called CpG85 that is a maternally methylated DMR. The *RB1-E2B* transcription interferes with expression of the main *RB1* mRNA. This results in an allelic imbalance of the *RB1* expression in favor of the maternal allele. Frequent aberrant methylation, hyper- or hypomethylation, at CpG85 has been found in HCC [7]. Some HCCs with hyper- or hypomethylation retains both alleles, suggesting that aberrant methylation occurs on the methylated or unmethylated allele. Further work suggests hypermethylation at CpG85 causes reduced *RB1-E2B* expression, which results in increased primary *RB1* expression [7, 92]. Hypermethylation at CpG85 is also associated with reduced overall survival of HCC patients. These results are contradictory to the tumor suppressor activity of pRB1 [7]. Eloy *et al*. also reported frequent hypermethylation (93%, 42/45) at CpG85 in retinoblastoma, although no expression analysis was performed [49].

3.8 Multilocus Methylation Defects at Imprinted DMRs in Cancers

Complete hydatidiform mole (CHM) is an abnormal form of pregnancy carrying diploid genomes with the risk of developing into choriocarcinoma. Most CHMs are sporadic and carry only paternal genomes (androgenetic CHM). A fraction of CHMs can be recurrent and familial. These CHMs have biparental genomes (biparental CHM). Biallelic mutations of *NLRP7* and *KHDC3L* genes occur in patients with familial biparental CHM [154, 180]. Multilocus methylation defects at imprinted loci have been reported in androgenetic CHM and familial biparental CHM from mothers with *NLRP7* mutations [200]. Hypomethylation occurs in the majority of more than 30 maternal gametic DMR analyzed in androgenetic and biparental CHM. *H19*-DMR is the only analyzed DMR of paternal gametic imprinting and is hypermethylated in androgenetic CHM, but normally (ca. 50%) methylated in biparental CHM. Multilocus methylation analysis has not yet been reported in biparental CHM with *KHDC3L* mutation. It is highly possible that *NLRP7* and *KHDC3L* involves establishment and/or maintenance of maternal imprints and that mutations in these genes may cause methylation defects at maternally methylated imprinted

loci. Multilocus aberrant methylation at imprinted loci could result in abnormal proliferation of trophoblastic tissue to form CHM, and may result in tumors, such as choriocarcinoma.

These days, DNA methylation analysis of cancer genomes is performed in a more comprehensive or genome-wide manner. Recent work has analyzed 33 imprinted DMRs for aberrant methylation in hepatoblastoma tissues by quantitative methylation analysis with MALDI-TOF MS [196]. Such research has found frequent hypermethylation at *INPP5Fv2*-DMR, CpG85 (*RB1*-DMR), and *GNASXL*-DMR. *IGF2*-DMR0 and *Kv*DMR1 showed frequent hypomethylation. Bisulfite-pyrosequencing at *IGF2*-DMR2, *IGF2*-DMR0, *DIRAS3*-DMR, *GRB10*-DMR, *PEG3*-DMR, *MEST*-DMR, *H19*-DMR, *Kv*DMR1, and *SNRPN*-DMR has also revealed aberrant DNA methylation in breast cancer tissues [12].

DNA methylation microarray analyses can identify aberrant methylation of genes, including imprinted genes in cancers. DNA methylome analyses were performed in three subtypes of pediatric germ cell tumors, including germinoma, teratoma, and yolk sac tumor. Hyper- or hypomethylation were found at several imprinted genes, such as *H19*-DMR, *IGF2*, *Kv*DMR1, *SNRPN*, and *PEG3* [4]. Similarly, 22 out of 56 imprinted genes analyzed were aberrantly methylated in prostate tumors. This work also found that hypermethylation was more frequent than hypomethylation [88]. In contrast, in HCC, hypomethylation was observed more frequently than hypermethylation [8, 114]. Aberrant methylation, mainly hypomethylation, was observed in 27 genes out of 59 imprinted genes [114]. These results suggest that paternally expressed imprinted genes are more susceptible to epigenetic disruption. Hypomethylation at imprinted loci correlates with global loss of DNA methylation, mutation in *CTNNB1* gene encoding β-catenin, and shortened overall survival of HCC patients [8].

Kim *et al*. analyzed data sets from TCGA (The Cancer Genome Atlas) to identify aberrant expression and epigenetic change at promoters and/or ICRs of imprinted genes in multiple human cancers [104]. They found some abnormal characteristics of imprinted genes in cancer. The number of cancers showing aberrant expression of imprinted genes is greater than those showing aberrant methylation at imprinted loci. DNA methylation instability among the imprinted genes is relatively higher than those among total genes. The number of imprinted genes with hypermethylation is much greater than those with hypomethylation. Some imprinted genes, such as *PEG3*, *DLK1*, *MEST*, and *GNAS*, are more susceptible to epigenetic change than others.

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