S3 | Human diseases associated with aberrant DNA methylation[+].

Disease type	Chromosomal location	Phenotype	Affected genes or regions*	Involvement of DNA methylation[#]
Cancer (General)	Many	Uncontrolled cell growth; metastasis	Many	Hypermethylation and silencing of CpG-island associated genes involved in many cellular processes, including transcription, cell cycle, DNA repair, and apoptosis. Hypomethylation of repetitive DNA and single copy genes, leading to increased expression of oncogenes, metastasis-associated genes, and genomic instability.
Imprinting disorders				
Cancer (LOI)	11p15.5 Many	Overexpression of growth promoter Overexpression of growth promoters, reduced expression of growth inhibitors	*IGF2* Others	*De novo* methylation of ICR1 on maternal allele; loss of methylation from *IGF2* DMRs upstream of *IGF2*; loss of CTCF binding and insulator function. Loss of allele-specific DNA methylation or *de novo* methylation of unmethylated allele, resulting in improper gene dosage.
Beckwith-Wiedemann syndrome (BWS)	11p15.5	Fetal and postnatal overgrowth, enlarged organs, increased risk of tumors, facial abnormalities	*IGF2*, *CDKN1C*, *H19*, *ASCL2*, *KCNQ1 KCNQ1OT1*	LOI at *KCNQ1OT1* ICR2 (loss of maternal methylation); LOI at *IGF2*/*H19* ICR1 (*de novo* methylation of maternal allele); translocations that disrupt ICR2, and therefore DNA methylation patterns; increased *IGF2* expression; decreased *H19* and *CDKN1C* expression.
Prader-Willi syndrome (PWS)	15q11.2	Mental retardation, obesity short stature, behavioral problems	*MKRN3*, *MAGEL2 NDN*, *SNURF*/ *SNRPN*, *IPW*	LOI at PWS ICR (*de novo* methylation of paternal allele); deletion of ICR; loss of expression of paternally expressed genes.
Angelman syndrome (AS)	15q12	Severe mental retardation, lack of speech, behavioral problems, facial abnormalities	*UBE3A*, *ATPC10C*	LOI at AS ICR (loss of maternal DNA methylation); deletion of ICR; loss of expression of maternally expressed genes (in the brain).
Albright hereditary osteodystrophy (AHO)	20q13	Developmental delay, mental retardation, obesity, short stature	GNAS locus: *NESP55*, *XLαs*, $G_s\alpha$	No DNA methylation defect, but is related to the imprinted state of the locus. Paternal transmission of mutations in the gene that encodes $G_s\alpha$.
Pseudohypopara-thyroidism type 1A (PHP-IA)	20q13	As for AHO, plus resistance to several hormones, including parathyroid hormone	GNAS locus: *NESP55*, *XLαs*, $G_s\alpha$	No DNA methylation defect, but is related to imprinted state of locus. Mat. transmission of $G_s\alpha$ mutations.
Pseudohypopara-thyroidism type 1B (PHP-IB)	20q13	Renal parathyroid hormone resistance	GNAS locus: *NESP55*, *XLαs*, $G_s\alpha$	LOI at exon 1A DMR (loss of methylation from maternal allele) in familial form; LOI at DMRs of exon 1A, *NESP55* (*de novo* methylation of maternal allele), and *NESP55-AS*/*XLαs* (loss of maternal methylation) in sporadic form.

Transient neonatal diabetes mellitus (TNDM)	6q24	Growth retardation, low insulin levels during fetal life and infancy, remission, type 2 diabetes as young adults	*PLAGL1*, *PLAGL1-AS*, HYMAI	LOI at ICR in *HYMAI* (loss of maternal DNA methylation), resulting in increased *PLAGL1* expression.
Repeat instability diseases				
Fragile X syndrome (FRAXA)	Xq27.3	Mental retardation, macro-orchidism, autistic behavior	*FMR1*	Expansion of CGG repeat in *FMR1* 5' UTR to >200 copies via transmitting female, accompanied by *de novo* methylation of the repeat and the *FMR1* promoter region, and silencing of the gene.
Myotonic dystrophy (DM1)	19q13.2-q13.3	Weakness/wasting of limb and facial muscles, myotonia, cataracts	*DMPK*, *SIX5*, others	Expansion of CTG repeat in *DMPK* UTR to > 80 copies more frequently upon maternal transmission. In its most severe form, *de novo* methylation of CpG island adjacent to CTG repeat occurs, disrupting a putative enhancer region and CTCF binding sites that may regulate adjacent SIX5 gene. Also sequestration of RNA binding proteins & transcription factors by mutant mRNA.
Facioscapulohumeral muscular dystrophy (FSHD)	4q35	Weakness/wasting of facial, shoulder girdle and upper arm muscles	*FRG2*, *FRG1*, *SLC25A4* (*ANT1*)	Contraction (to <10 copies) and hypomethylation of D4Z4 repeat; misregulation of genes near D4Z4 repeat or homologous repeat on 10q or other unknown genes.
Diseases involving the DNA methylation and chromatin remodeling machinery				
Systemic lupus erythematosis (SLE)	Many	Skin rash, joint pain, glomerulonephritis, anti-DNA antibodies, auto-antibodies, defective T cells	Many, including *CD11a*, *CD70*	Global hypomethylation in T cells and reduced DNMT activity. Demethylation of promoter regions of CD11a and CD70 and increased expression. Demethylation and re-expression of HERV transcripts. Induced by DNMT inhibitor procainamide.
ICF syndrome (ICF)	20q11.2	Immunodeficiency, chromosomal instability, developmental delay	*DNMT3B*	Mutations in *DNMT3B* that partially inactivate its function; hypomethylation of satellite 2 and satellite 3 repeats on chromosomes 1, 9, and 16, genes on the inactive X chromosome and other repeats in the genome, leading to disruption of gene expression patterns.
ATRX syndrome (ATRX)	Xq13	Mental retardation, genital abnormalities, alpha-thalassemia	*ATRX*	Mutations in *ATRX* (which encodes an ATP-dependent chromatin remodeling enzyme) which disrupt its enzymatic activity and/or nuclear localization; hypomethylation and hyper-methylation of certain repetitive DNAs (rDNA and DYZ2, respectively).
Other				
Disorders associated with ARTs	Probably many, including 11p15.5 and 15q12	Low birth weight, possibly others BWS or AS phenotypes	Potentially any imprinted gene BWS, AS locus genes	For ART BWS cases, LOI at *KCNQ1OT1*/*LIT1*; for AS cases, LOI at the AS ICR. The defect is loss of maternal DNA methylation in most cases, and may arise from *in vitro* embryo culture procedures.

[+]This represents only a partial list of such disorders, primarily those for which the underlying defect has been well characterized. For a more complete list, the reader should refer to articles cited in the main text. *Genes that are known or suspected to be involved in the disease. [#]Other genetic mechanisms are

also involved in several cases; see main text for details. *ASCL2*, achaete-scute complex-like 2; ARTs, assisted reproductive technologies; *ATPC10C,* ATPase, Class V, type 10A (also known as *ATPC10C*); *ATRX*, alpha thalassemia/mental retardation syndrome X-linked; *CDKN1C*, cyclin-dependent kinase inhibitor 1C; CTCF, CCCTC-binding factor; DMR, differentially methylated region; DNMT, DNA methyltransferases; *FRG1*, FSHD region gene 1; *FRG2*, FSHD region gene 2; *FMR1*, fragile X mental retardation 1; $G_s\alpha$, the α subunit of the heterotrimeric GTP-binding protein $_G$; *HYMAI*, hydatidiform mole associated and imprinted; ICR, imprinting control region; *IGF2*, insulin-like growth factor 2; *INS*, insulin; *IPW*, imprinted in Prader-Willi syndrome; *KCNQ1*, potassium voltage-gated channel, KQT-like subfamily, member 1; *KCNQ1OT1*, KCNQ1 overlapping transcript 1; LOI, loss of imprinting; *MAGEL2*, MAGE-like 2; *MKRN3*, makorin, ring finger protein, 3; *NDN*, necdin homologue; *NESP55*, neuroendocrine secretory protein 55; *PLAGL1*, pleiomorphic adenoma gene-like 1; *SLC25A4*, solute carrier family 25, member 4 ; *SNRPN*, small nuclear ribonucleoprotein polypeptide N; *SNURF*, *SNRPN* upstream reading frame; *TSSC3*, tumor-suppressing STF cDNA 3 (also known as *PHLDA2*); *UBE3A*, ubiquitin protein ligase E3A; *XLαs*, G-protein *XLαs*.