TABLE 1 (EXPANDED)

Transgenerational epigenetic inheritance in prokaryotes and eukaryotes

Taxon	Trait	Locus/Cellular System	Conditions of Heredity: Stability and Inducibility	EI Mechanism	Reference
Bacteria and their viruses					
λ phage of *Escherichia coli*	Lysogenic/lytic cycle of λ phage	*Cl* and *Cro*	Nutritional state of the host, phage density Stable	Self-sustaining loops	Ptashne (2005)
Bacillus subtilis	Inactivation of chromosome	Whole chromosome	Polyethylenglycol (PEG) induced fusion Stable	Structural inheritance	Landman (1991)
Bacillus subtilis	Lack of cell wall	Balance between peptidoglycan synthesis and destruction	Experimental removal of cell wall Stable on agar	Chromatin-marking	Grandjean et al. (1998)
Bacillus subtilis	Sporulation capacity	Spo0A phosphorelay	Nutritional deprivation Stable	Self-sustaining loops	Veening et al. (2005)
Bacillus subtilis	Natural competence (K state)	*ComK* activity	Stochastic, elevated by stress 10%–20% in lab strains, 1% in the wild	Self-sustaining loops	Maamar and Dubnau (2005)
Escherichia coli	Utilization of lactose[i]	Lac operon activity	Stochastic, growth in low concentration of inducer Stable under conditions of low inducer concentration	Self-sustaining loops	Novick and Weiner (1957), Cohn and Horibata (1959a,b), Laurent et al. (2005), Ozbudak et al. (2004)
Escherichia coli	Fluffy morphism	Agn43	Probably oxidative stress; phase variation Stable	GATC methylation	Casadesús and Low (2006)
Escherichia coli	Pili (pilin expression)	Pap operon	Changed carbon source, temperature, and spontaneous	GATC methylation	Hernday et al. (2002)

Escherichia coli	Growth rate (persister type II)[ii]	Probably many genes	10^{-4} per cell generation; reversion rate 10^{-3} per cell generation Induced spontaneously and by antibiotic treatment 10^{-6} per generation; reversion rate 10^{-1} per generation	Self-sustaining loop	Balaban et al. (2004), Lewis (2007), N. Balaban (personal communication)
Escherichia coli	Resistance to antibiotics (ampicillin, tetracycline, and nalidixic acid)	Altered regulation of β lactamase cryptic gene, glutamate gene, and decarboxylase gene; possible involvement of DNA methtylase genes	3%–20% survival (depending on concentration of antibiotic) and 50% reversion rate; induced in low and successively increased concentrations of antibiotics	Possibly self-sustaining loops and /or DNA methylation	Adam et al. (2008)
Pseudomonas aeruginosa	Toxin injection	TTSS system	Cell density Stable	Self-sustaining loop	Filopon et al. (2006)
Synechococcus elongates (Cyanobacteria)	Circadian rhythm	Regulatory loop involving key KaiC protein	Induced by light and dark pulses Stability: Number of days	Self-sustaining loop	Kondo and Ishiura (2000)
Protists					
Oxytricha trifallax (Ciliate)	Alteration of gene order: Aberrant rearrangements	Genes that become unscrambled in the somatic macronucleus (i.e., most genes)	Induced by experimental manipulation of injected RNA; stable through asexual cell divisions and also through at least 3 generations following sexual reproduction	RNA-mediated DNA gene rearrangement	Nowacki et al. (2008)
Paramecium aurelia (Ciliate)	Serotypes expressed	Cilia proteins	Induced by changes in pH, temperature, food supply, and salinity Stable	Self-sustaining loop	Landman (1991)

Paramecium aurelia (Ciliate)	Induced tolerance to heat, salt, and arsenic	Not specified	Induced by exposure to high temperature, as well as high salt and arsenic concentrations. Inherited for many generations, fading away gradually. Termed "Dauermodifikationen" (lingering modifications) by Jollos	Not known	Jollos (1921); reviewed in Jablonka et al. (1992)
Paramecium tetraurelia, Stylonchia lemnae, Tetrahymena thermophila **(**Ciliates) (and presumably all other ciilates) [iii]	Various traits related to alternative genetic organization patterns in the macronucleus	In principal, any DNA sequence in the genome	Stable through macronucleus reproduction, both during asexual reproduction and following sexual reproduction. Sequence comparison of maternal (old) and zygotic (new) nuclei leads to the inheritance of maternal, nucleus-guided gene organization, with only occasional reversions to micronucleus-based information	Inherited DNA rearrangement/ editing/programming of the macronucleus, mediated by siRNAs and chromatin modifications (acetylation and methylation of histones)	Garnier et al. (2004), Juranek et al. (2005), Liu et al. (2004), Meyer and Chalker (2007), Taverna et al. (2002), Yao et al. (2003)
Paramecium tetraurelia, Stylonchia lemnae, Tetrahymena thermophila **(**Ciliates) (and presumably all other ciilates) [iii]	Cortical organization	Basal body and cortex proteins	Experimental manipulation (for example, microsurgery), chemical treatments, stress Stable in mitosis and sometimes in meiosis	3D-templating, guided assembly	Grimes and Aufderheide (1991)
Tetrahymena (Ciliate)	Increased insulin binding, increased insulin production, and associated increased glucose uptake; concentration-dependent increase in growth rate following exposure to diiodotyrosine (T_2)	Not specified	Single treatment with insulin significantly increased insulin binding for 664 generations Increase in insulin content following 1 hour of insulin treatment (10^{-6} M) was maintained through ~ 200 generations Increased growth rate was induced by single 24-hour exposure period to diiodotyrosine.	The possibilities of structural inheritance and self-sustaining loop are raised but considered less likely than the involvement of DNA methylation. 5-aza-C treatment (which inhibits DNA methylation)	Csaba (2008), Csaba et al. (1999), Csaba and Kovacs (1990, 1995), Csaba et al. (1982a,b)

			Although it was gradually decreased, the propagation rate of the progeny of the treated ciliates was still significantly higher than that of untreated individuals over at least 500 generations	decreased insulin binding when given before and during exposure to insulin, but not after its application. However, increased insulin binding was detected 24 hours after treatment among the progeny of ciliates treated with either insulin alone, 5-aza-C alone, or 5-aza-C and insulin	
Plasmodium falciparum (Malaria parasite)	Telomere inactivation	Telomere sequences	Induced spontaneously Switch every ~ 15 generations	Chromatin-marking	Roberts et al. (1992)
Volvox carteri	Silencing of *in vitro* CpG-methylated transgene (non-methylated transgene was expressed in 59% of the transformants right after transformation)	*C-ars* reporter transgene	Algae were transformed with a methylated *C-ars* transgene. Methylation and inactivation of the transgene were maintained through more than 100 generations after transformation	DNA methylation	Babinger et al. (2007)
Fungi					
Ascobolus immerses	Transgene inactivation	Any duplicated transgene	Methylation induced pre-meiotically (normal physiological mechanism) Stable	DNA methylation	Martienssen and Colot (2001), Rhounim et al. (1992)

Candida albicans[iv]	Cell morphology, ability to colonize on various substrates, mating properties	Master regulator WOR1	Induced spontaneously; effected by temperature Stable; switch every ~ 10,000 generations	Self-sustaining loop	Huang et al. (2006), Malagnac and Silar (2003), Zordan et al. (2006)
Coprinus cinereus	Methylation pattern	Centromere-linked locus	Inducer unknown Stable when highly methylated	Chromatin-marking, DNA methylation involved	Zolan and Pukkila (1986)
Podospora anserina (Filamentous fungus)	Crippled Growth (CG)	*C*—assumed to be a transmissible self-sustaining cascade involving a Map kinase module	Transformation of normal-growing cells to CG cells is induced by cytoduction, promoting a stationary state and growth on a medium supplemented with yeast extract Stable mitotic inheritance	Self-sustaining loops and prion inheritance	Kicka et al. (2006), Malagnac and Silar (2006), Silar et al. (1999)
Podospora anserina (Filamentous fungus)	[Het-s*] and [Het-s] variants affecting vegetative incompatibility	*het-s*	Stable; low frequency [Het-s] converted to inactive [Het-s*], but the reverse also occurs, albeit at low frequency Spontaneous	Structural inheritance (prion)	Maddelein et al. (2002)
Saccharomyces cerevisiae	Enhanced resistance to starvation on dextrose minimal plates and suppression of inability to sporulate	[β]-prion form of the PrB vacuolar protease	Emerges in deletion mutants for the gene *PEP4* encoding PrA—a protease which activates PrB. [β] can be transmitted by cytoduction. The frequency of its induction is increased as a result of *PrB* over-expression; reversibly repressed on a medium repressing *PrB* expression Stability: indefinite propagation	Prion inheritance, through self-sustaining loops	Roberts and Wickner (2003)

Saccharomyces cerevisiae	Growth phenotype	*FLO* genes near telomere	Spontaneous Switches every ~ 10-15 generations	Chromatin inheritance	Halme et al. (2004)
Saccharomyces cerevisiae	Elongation-related read-through	[PSI]	Varied induction conditions Inheritance is stable	Structural inheritance (prion)	Tuite and Cox (2006)
Saccharomyces cerevisiae	Nitrogen catabolic gene expression	[URE3]	Spontaneous and over expression of [URE3] Stable	Structural inheritance (prion)	Benkemoun and Saupe (2006)
Saccharomyces cerevisiae	Probably ascus formation	$[PIN]^{+}$Rnq1p	Spontaneous and over expression of Sup35 Stable	Structural inheritance (prion)	Benkemoun and Saupe (2006)
Saccharomyces cerevisiae	Expression of experimentally modified GAL network	Gal network	Intermediate inducer concentrations Stable	Self-sustaining loop	Acar et al. (2005)
Saccharomyces cerevisiae	Induction of *GAL1* and *GAL7* by galactose	Gal genes	Induction by galactose; following induction, cells were moved to glucose for 6–7 generations and then moved again to galactose. Induction occurred much more quickly pointing to epigenetic "memory" of past induction	Slow dilution of abundant regulatory gene protein *GAL1*	Zacharioudakis et al. (2007)

Saccharomyces cerevisiae	Anti-suppressor of Sup 35 Glucosamine resistance Control of killer virus expression	ISP^{+}? GR? KI-d? (suspected prions)	Presumably spontaneous and stable	Probably based on structural inheritance	Benkemoun and Saupe (2006), Kunz and Ball (1977), Tallóczy et al. (2000), Volkov et al. (2002)
Saccharomyces cerevisiae	Slow growth and additional requirement for leucine (*Leu^{p}*)	Structural alteration of the mitochondrion	Spontaneous inherited loss of mitochondrial DNA in certain strains yielded derivates exhibiting *Leu^{p}*, and normal growth was switched bidirectionally following cytoduction Difference in colony size between diploids formed by mating, normal-growing strains and *Leu^{p}* strains lasted for more than 100 generations of growth in the absence of leucine	Structural inheritance	Lockshon (2002)
Schizosaccharomyces pombe	Survival of mutant strain lacking the *hcd* region-encoding, highly conserved domain of essential chaperone calnexin	[cif]	Calnexin independence was inherited by 88.7% of spores germinated, following mating of haploid cells of strain lacking the gene coding for calnexin with calnexin-dependent cells. The ability to bypass necessity for calnexin was transmitted by transformation of cell extracts into wild-type naïve strain	Probably prion inheritance	Collin et al. (2004)
Schizosaccharomyces pombe	Reporter transgene silencing and mating type switching	KΔ::ura4 (transgene inserted at K-region)	Transgenically induced Stable for at least 30 mitotic generations after meiosis	Chromatin-organizing factors probably involved	Grewal and Klar (1996)

Schizosaccharomyces pombe	Meiotic telomere clustering and chromatin structure	Interaction of telomeric and subtelomeric regions with Taz1	Normal and stable phenomenon; variation shown by deleting telomere sequences in chromosomes	Chromatin-marking, structural inheritance	Sadaie et al. (2003)
Plants					
Antirrhinum majus (Snapdragon)	Flush/granulated phenotype	*nivea* locus, encoding chalcone synthase	Induced by crossing between 2 lines with insertions in the *nivea* locus The flush/granulated phenotype emerges in a variegated fashion in F_1 and in a more stable manner in F_2	Transposition may be involved; chromatin-marking probably involved	Krebbers et al. (1987)
Arabidopsis thaliana (Mouseear cress)	Reversion of dwarf morphology	*cpr1–1* gene-epiallele interacting with *bal*	Induced by crossing Effect seen in F_2 progeny, but not in F_1	Unknown	Stokes and Richards (2002)
Arabidopsis thaliana (Mouseear cress)	Reversion of dwarf morphology; morphological abnormalities of rosettes and petioles; reactivation of the expression of *GFP* reporter gene	Transgenic loci *E82* and *L91* and their suppressive interaction with *COP1* endogene	Transgenically-induced by crossing *E82* and *L91* lines with plants bearing the trans-silencer locus *C73* At least 5 generations (shorter-term, inherited suppression effects of other transgenic loci are also reported)	Unknown; involvement of RNA-mediated DNA methylation is suggested	Qin and von Arnim (2002)

Arabidopsis thaliana (Mouseear cress)	Delayed flowering	*fwa* (gene-epiallele)	EMS, fast neutron treatment, or *ddm1* induced Very stable inheritance of the trait is reported when the epimutation is induced by treatment of methanesulphonate (EMS) or fast neutrons. Transmission of the trait, that was later segregated away, for 5 generations of self-pollination was observed in progeny of *ddm1* mutants, and the wild-type copy of *ddm1* (required to maintain DNA methylation) was acquired by crossing. Inherited reversion of the trait was reported following transformation of transgenic, direct-repeat sequences flanking the FWA transcription start site, even in the absence of the transgene, accompanied by increased DNA methylation in the repeats	DNA methylation, histone H3 methylation (siRNAs involved)	Soppe et al. (2000), Lippman et al. (2004), Kinoshita et al. (2007)
Arabidopsis thaliana (Mouseear cress)	Dwarfism and constitutive activation of the salicylic acid (SA)-dependent defense response pathway	*bal* locus at the lower arm of chromosome 4	The trait was inherited in progeny of *ddm1* mutants after the mutation was segregated away and the wild-type copy of *DDM1* was acquired through crossing Stability: At least 5 generations	DNA methylation assumed to be involved	Stokes et al. (2002)
Arabidopsis thaliana (Mouseear cress)	Abnormal number of reproductive organs	*SUP*	Induced by various mutagens Stability: At least 5 generations	DNA methylation	Jacobsen and Meyerowitz (1997)

Arabidopsis thaliana (Mouseear cress)	Expression levels of the retrotransposon *At2g10410*	*At2g10410* epiallele	Stable polymorphism of the expression state of *At2g10410* and its methylation state was found in natural populations The expression state was inherited through at least 8 generations of self-fertilization from the accessions Col and Ler. *ddm1*-induced ectopically expressed Ler alleles (that are methylated and silenced in wild-type plants) are meiotically stable even after introduction of the wild-type *DDM1*	DNA methylation	Rangwala et al. (2006)
Arabidopsis thaliana (Mouseear cress)	Increased levels of homologous recombination in soma	Not specified	Induced by UV-C radiation or introduction of flagellin—bacterium-derived elicitor. All members of the population were affected. Stability: At least 4 generations in the case of UV-C radiation. At least 2 generations in the case of introduced flagellin, as tested in 2 different *Arabidopsis* lines	Not specified	Molinier et al. (2006), J. Molinier (personal communication)
Arabidopsis thaliana (Mouseear cress)	Loss of hygromycin resistance in tetraploid (paramutation)	*hpt* transgene	Transgenically induced No effect in F_1; F_2 affected during development	*Trans* silencing involving DNA methylation	Scheid et al. (2003)
Arabidopsis thaliana (Mouseear cress)	Transcriptional activity of transposable elements	Various transposable elements	Retrotransposons as well as DNA transposons were transcriptionally activated in the *ddm1* mutant; in numerous instances, activation was maintained epigenetically through at least 6 generations after removal of the *ddm1* mutation.	DNA methylation, chromatin modifications; RNAi is probably involved	Lippman et al. (2003, 2004), V. Colot (personal communication)

Arabidopsis thaliana (Mouseear cress)	Gain of blue fluorescence, tryptophan and indole-3-acetic (growth regulator) acid deficiency, and morphological abnormalities	*PAI* (gene-epialleles)	T-DNA mutagenesis; *PA1-PAI4* inverted repeat locus was introduced to Col plants by genetic cross to WS plants. Natural variation in methylation state of *PAI* genes between WS and Col plants was discovered Increased methylation of *PAI* genes persisted for at least 6 generations in self-pollinating *PAI*-deletion mutants of the Wassilewskija (WS) ecotype. Mutant traits and modified methylation state were maintained through 2 backcrosses of the mutant with WS plants and 2 generations of self-pollination following crosses of the mutant with wild-type Columbia (Col) ecotype plants De-novo methylation of Col *PAI1* and *PAI2* induced by *PA1-PAI4* was stably maintained and transmitted in the absence of the inducing locus	DNA methylation; involvement of DNA/DNA pairing mechanism is suggested	Bender and Fink (1995), Luff et al. (1999)
Arabidopsis Interspecfic hybrids[v]	Many traits	Multiple loci, both coding and non-coding	Induced by hybridization followed by polyploidization. Stability varies with locus, but many epigenetic variations are stably inherited	Chromatin-marking, DNA methylation; RNAi system also likely involved	Comai et al. (2000), Scheid et al. (2003)

Beta vulgaris (Sugar beet)	Many traits in mitotic, agamospermic, and inbred lines, including single or multiple flower initiation, self-fertility, polymorphism of malic enzyme, and variation in number of chloroplasts, as well as many other traits	*Mm* and *li* loci *Rf1* locus *Me1*	Mode of reproduction (agamoseprmy, hybridization), climatic conditions (low temperature 13–16° C), direction of cross. Stability is variable. In many cases, the variant is transmitted for more than 2 generations	DNA methylation may be involved in the case of chloroplast-number inheritance because there is an effect of the de-methylating chemical 5-azaC	Levites (2000), Levites and Maletskii (1999), Maletskii (1999)
Linaria vulgaris (Common toadflax)	Radial symmetry of flowers	*Lcyc* (gene-epiallele)	At least 2 generations; natural variation in populations	DNA methylation	Cubas et al. (1999), J. Parker (personal communication)
Linum usitatissimum (Flax)	Plant weight and height, peroxidase isozyme pattern, and the seed capsule septa hair number	r-DNA genes and repetitive sequences	Genome-wide alterations that occur in response to specific environments have been described in the inbred flax variety 'Stormont Cirrus.' Growth of plants from this variety in different fertilizer combinations or under different temperature regimes can result in phenotypic differences in the first generation. Certain growth conditions can result in stable inheritance of these differences in subsequent generations obtained by self-fertilization under many different growth conditions. Response of the genome to growth in various environments has also been observed in other flax varieties ('Rembrandt,' 'Hollandia,' and 'Liral Monarch')	Methylation and DNA-repatterning (difference in genomic DNA amount between genotrophs—lines in which 'stable' changes were observed—was measured)	Cullis (2005)

Linum usitatissimum (Flax)	Early flowering, main stem height at maturity, and number of leaves	Not specified, but epimutations in at least 3 independent, non-random loci are assumed to be involved	Germinating seeds were treated with 5-azaC In selfed early-flowering flax lines, reduced cytosine methylation was observed in plants up to the 9th generation beyond the generation treated with 5-azaC; reversions were reported Decreasing methylation was also detected in segregants derived by selecting for the early-flowering phenotype in the F_2 and F_3 generations of out-crosses. This selection seems to lead to lower levels of methylation	DNA methylation and possibly associated chromatin remodeling	Fieldes and Amyot (1999), Fieldes et al. (2005)
Lycopersicon esculentum (Tomato)	Inhibition of normal ripening and development of a colorless, mealy pericarp	*KeSPL-CNR* (gene epiallele)	Spontaneous epimutation Very stable inheritance—only 3 individual revertants from more than 3,000 plants grown since 1993 were observed	DNA methylation	Manning et al. (2006)
Lycopersicon esculentum (Tomato)	Wild type *sulf*$^{+}$ homozygote plants have pure green leaves and shoots; paramutant *sulf*^{pura} homozygotes have pure yellow leaves and shoots; *sulf*^{vag} homozygotes have yellow-green speckled leaves and shoots (paramutation)	*sulf* (gene epialleles)	The wild type allele *sulf*$^{+}$ is altered in *sulf*$^{+}$/*sulf*^{pura} heterozygotes, by paramutation, either to a *sulf*^{pura} allele or to a *sulf*^{vag} allele. The wild-type allele *sulf*$^{+}$ is altered in *sulf*$^{+}$/*sulf*^{vag} heterozygotes by paramutation to a *sulf*^{vag} allele The first *sulf* mutant originated after x-ray treatment of tomato plants of the variety "Lukullus" in 1949. Since 1956, these lines were kept by selfing green heterozygotes (i.e., the sulf epialleles have been kept for more than 50 years) *sulf*$^{+}$ is stable in the homozygous condition,	Several molecular mechanisms of paramutation have been discussed, but a decision has not been obtained; DNA and/or protein methylation at the paramutation sites were suggested Heterochromatization of the paramutant sites (there are indications that the	Hagemann (1969, 1993), Hagemann and Berg (1977), Wisman et al. (1993), R. Hagemann (personal communication)

			but in *sulf*$^{+}$/*sulf*^{pura} heterozygotes it becomes unstable and paramutates to *sulf*^{pura} or to *sulf*^{vag}. These newly arisen paramutant *sulf* alleles can be kept in heterozygotes with *sulf*$^{+}$ for more than 5 generations. There are groups of *sulf*^{pura} and *sulf*^{vag} alleles that have similar traits but differ in their paramutation activity. The *sulf*^{pura} group consists of alleles with all possible degrees of paramutagenicity between 0.5% and 100%. The *sulf*^{vag} alleles have a lower paramutagenicity; its maximum is about 12% Another *sulf* mutant, SC148, was isolated following in-vitro regeneration of leaf explants. SC148 paramutagenic effect depended on the tomato line to which it was crossed	location of the *sulf* locus is close or within heterochromatin) Involvement of transposable elements and homing processes is suggested	
Melandrium album (White campion)	Bisexuality	Decrease in CG methylation in many loci	Induced by treatment with the DNA methyltransferase inhibitor 5-azacytidine The bisexual trait was transmitted to 2 successive generations, but only when androhermaphrodite plants that harbored both male and bisexual flowers were used as pollen donors in crosses either with wild-type females or with progeny of androhermaphrodite plants. Bisexuality was inherited through the male parent only	DNA methylation	Janoušek et al (1996)

Nicotiana tabacum (Tobacco)	Loss of kanamycin resistance	Nos_{pro}, which controls the expression of *nptII* (which, in turn, allows selection of transformed genes on kanamycin) and *nos* transgenes; *nos* is a synthase of nopaline, which is used as a screening marker	Transgenic silencing in doubly transformed plants Stability: At least 2 generations; weaker transgenic silencing accompanied with gradual loss of methylation at the Nos_{pro} locus was observed, even after the paramutable and paramutagenic alleles had segregated away from each other	DNA methylation	Matzke et al. (1989), Matzke and Matzke (1991)
Nicotiana tabacum (Tobacco)	Loss of hygromycin resistance	*Hpt* transgene	Transgenic silencing Substantial silencing of the *hpt* transgene persisted for 2 generations after it was introduced to plants transformed with the 271 silencing locus; 271 was crossed out as a result of backcrossing to untransformed tobacco	DNA methylation	Park et al. (1996)
Nicotiana tabacum (Tobacco)	Requirement of leaf cell for cytokinin	Not specified	Subculturing in media containing successively lower concentrations of cytokinin 10^{-2} per cell generation	Unknown; DNA methylation suggested	Meins (1986, 1989a,b), Meins and Thomas (2003)
Oryza sativa (Rice) Hybridization between cultivars [v]	Not specified, but CpG methylation patterns showed inherited cultivar specificity	Methylation state of cytosine in various CCGG sites across the genome	Methylation patterns segregated in a Mendelian fashion after crossing between Nipponbare and Kasalath cultivars Differential methylation was inherited over at least 6 generations; low frequency changes in the extent of methylation	DNA methylation	Ashikawa (2001)

Oryza sativa (Rice)[v]	Influence of alteration in CCGG methylation on introgression phenomena, such as plant form, disease resistance, flowering time, and yield-component traits, is hypothesized	Methylation state of cytosine in various CCGG sites across the genome	Inheritance of modified methylation patterns was observed in introgression lines RZ1, RZ2, and RZ35 derived from hybridization between parental cultivar Matsumae rice and local accession of *Zizania latifolia* Griseb Modified methylation patterns in comparison to the parental cultivar Matsumae were inherited through the 9–11th selfed generations of introgression lines	DNA methylation	Dong et al. (2006)
Oryza sativa (Rice)	Two mutant lines were obtained following high-pressure treatment given to seeds: The first had awnless kernels and an apparently reduced number of tillers, and the second was characterized by a significantly increased number of tillers and slender awnless kernels	Stress (drought)—responsive genes epialleles *S2* and *S3* and various unspecified methylation sites across the DNA	Induced by high-pressure treatment given to seeds Alteration in DNA methylation patterns and morphological differences are reported to be inherited stably in the mutant lines for 3–6 generations of self-reproduction following high-pressure treatment	DNA methylation	Shen et al. (2006)
Oryza sativa (Rice)	Induced dwarfism Resistance to pathogens	General change in DNA methylation involved; Xa21G promoter	Induced by 5-azaC; inherited for more than 9 generations	DNA methylation involved	Akimoto et al. (2007), Sano et al. (1990)
Petunia hybrida (Petunia)	White-flowering, paramutation-like (trans) effects in some cases	*An3* epiallele and the transposon *dTph1*	Mutants of *an3* (a locus containing a gene coding for an enzyme required for the synthesis of anthocyanin pigments) were generated by random transposon mutagenesis. Stable *an3* mutants have	Mechanism is not specified, but heritable epigenetic interaction between at least 3 *dTph1*	Van Houwelingen et al. (1999)

			nearly white flowers, whereas unstable *an3* mutants contain insertion of either the *dTph1* or *dTph2* transposons and have nearly white flowers with colored revertant sectors. S205 is an unstable allele of *an3*, but it can also undergo heritable transformation to the suppressed epiallele S205* following exposure to other *an3* alleles, such as T3463 in a heterozygous cell. The suppressed state induced by this heterozygosity was transmitted through at least 3 generations of self-fertilization. S205* produced fewer wild-type-sized excision products and did not confer this state to the unstable S205 allele in the heterozygote	copies in 2 homologous chromosomes is reported. An effect of epigenetic mechanism on DNA recombination, which is involved in transposon excision and/or break, is suggested	
Triticum aestivum (Wheat)	Cytosine methylation pattern	Glutenin gene	Inbreeding Stability: At least 2 generations	Chromatin-marking; DNA methylation involved	Flavell and O'Dell (1990)
Triticum aestivum (Wheat)	Longer productive spikes, larger seeds, and other quantitative traits	*Hl1* and *pc* loci	Nicotinic acid (001–0.1% NA), stable for 57 generations	Unknown	Bogdanova (2003)
Wheat synthetic hybrids[v]	Many traits	About 13% of the genome	Hybridization; formation of synthetic amphiploids. A rapid phase of extensive epigenomic changes was followed by a stabilized phase in which variations were consolidated. The re-patterning was targeted to the same genomic and chromosomal regions upon repeated formation of amphiploids	DNA methylation and protein marking; presumably RNAi system involved	Levy and Feldman (2004)

Triticale (stable wheat-rye hybrid)	Increase in stature, number of tillers, changed time of ripening	Not specified	Induced by 5-azaC treatment Stability: At least 2 generations	Chromatin-marking; DNA methylation involved	Heslop-Harrison (1990)
Zea mays (Maize)	Reduced pigmentation (paramutation)	*b1* gene-epiallele	Paramutagenic *B'* epiallele arises spontaneously from *B-I* allele at a frequency of ~1% to 10% Very stable: When *B'* epiallele is crossed to *B-I*, only *B'* are observed, with more than 100,000 plants tested in 50 years of study, independent of whether it is homozygous or heterozygous with other alleles	Chromatin inheritance. *B'* and *B-I* epialleles are distinguished by the methylation state of a regulation region located ~100 kb upstream to the transcription start site. siRNAs-directed chromatin modification is involved	Alleman et al. (2006), Chandler (2007), Chandler et al. (2000), Coe (1966), Stam et al. (2002)
Zea mays (Maize)	Reduced pigmentation (paramutation)	*r1* (complex loci); several paramutagenic and paramutable haplotypes were observed	Paramutation found in wild-type populations. Transmissibility depends on epiallele identity: heterozygotes of paramutable and paramutagenic haplotypes produce the lowest expression levels; paramutable homozygotes show intermediate expression levels; high expression levels are observed in cases of heterozygotes of paramutable and non-paramutable haplotypes. Environmental influence: Exposure to varied light durations and temperature levels during the early development of seedlings of heterozygotes bearing the paramutagenic *R* results in heritable effects on kernel pigmentation	DNA methylation: hypermethylation characterizes certain sites in paramutagenic, but not paramutable or "neutral" haplotypes. Chromatin inheritance is suggested	Chandler et al. (2000), Mikula (1995), Walker and Panavas (2001)

			Stability is variable: The number of generations of homo/heterozygosity influences the levels of pigmentation and expression of the haplotype. When paramutable *R-r:std'* is exposed to repeated generations of paramutation, its seed pigmentation levels continue to decrease. In contrast, hemizygous *R-r:std'* or *R-r:std'* with alleles that do not participate in paramutation reverts significantly towards normal expression in the first generation, and expression continues to increase in subsequent generations		
Zea mays (Maize)	Reduced, light-dependent pigmentation (paramutation)	*pl* gene-epiallele	Paramutation arises spontaneously in plants bearing the genotype *B-I*/*B-I*, *R-r*/*R-r*, *Pl-Rh*/ *Pl-Rh*, *C1*/*C1* Stability of inheritance varies with allelic identity and paramutation intensity: Most lightly pigmented *Pl'* plants show high mutagenicity and are "very stable" In crosses between *Pl'* and paramutable *Pl-Rh* homozygotes, only weakly-pigmented *Pl'* are recovered *Pl'* states with intermediate levels of pigmentation frequently change to lower but not to higher expression states and are capable of changing *Pl-Rh* to *Pl'* *Pl'* states that confer only slightly less color than *Pl-Rh*, are metastable, and can change for lower or fully expressed state	Involvement of heritable alterations in chromatin structure are suggested	Chandler et al. (2000), Hollick et al. (1995, 2000), Hollick and Chandler 1998

Zea mays (Maize)	Reduced pericarp color but dark pigmentation at the point of silk attachment (paramutation)	*P1* gene-epiallele	Spontaneous change of the paramutable *P1-rr* to *P1-pr* occurs at a frequency of ~1 x 10^{6}. Following crossing of certain sublines to the inbred A188 subline, kernels display increased frequencies of somatic mutations. Paramutagenic state *P1-rr'* was induced by transformation of P1.2b::GUS transgene In the case of the paramutation *P1-rr*, DNA methylation of the *p1* gene was found to be fully penetrant for at least 5 generations of self-pollination or crossing to non-paramutant *P1-ww* plants after the modified trait was recognized in 2 parental plants; variability in methylation was inversely correlated to variability in pigmentation conditioned by *P1-pr*, and variability in transcript levels of the *p1* gene in progeny were also correlated. The P1.2b::GUS transgene, which contains a 1.2 kb-long enhancer fragment of *P1-rr* allele, induces a heritable suppressed state of the *P1-rr* allele, termed *P1-rr'*. Paramutational morphology was transmitted for 2 generations with *P1-rr'* in the absence of the transgene that had segregated away following crossing. The epiallele *P1-rr'* exhibited variable levels of heritable paramutagenicity ranging from 0 to >90% among the progeny and that depended on crossing. *P1-rr'* and the spontaneously occurring *P1-pr* epiallele commonly produce kernels with similar color patterns correlated with increased DNA methylation, and with a pattern similar to that of *P1-rr'*.	DNA methylation; chromatin inheritance is suggested	Cocciolone et al. (2001), Das and Messing (1994), Rajandeep et al. (2007), Sidorenko and Peterson (2001), Sekhon et al. (2007)

			The spontaneously generated epiallele *P1-rr** produces white pericarp, white cob, and shows hypermethylation of cytosine residues in exon 1 and intron 2 regions of the gene. Introgressed *Ufo1* factor in *P1-rr** plants was associated with reversion of cob pigmentation and was directly correlated with DNA demethylation in intron 2		
Zea mays (Maize)	Weakly spotted kernels resulted from silencing of the regulatory transposon *MuDR*, which is able to catalize the excision of the element *Mu1* at the *a1-mum2* reporter gene	*MuDR* transposable element	The silencing effect of the locus *Muk* on *MuDR* was maintained for at least 4 generations, even when *Muk* has segregated away following crosses: *Muk*/- ; *MuDR(p1)* (*MuDR* on the long arm of the chromosome 2L)/—weakly spotted plants were crossed as female to the minimal *Mutator* line tester containing *a1-mum2* but not *MuDR* to give F_1 generation. Weakly spotted kernels from F_1, F_2, and F_3 were crossed to *a1-mum2* minimal *Mutator* line tester to generate subsequent generations	DNA methylation; siRNAs are involved in maintaining heritable methylation states in *Mu1* and *MuDR* elements	Lisch et al. (2002), Slotkin et al. (2003), Slotkin et al. (2005)
Animals					
Caenorhabditis elegans (Nematode)	Small and dumpy appearance	RNAi of *ceh-13*	The modified morphology was induced by feeding the worms with bacteria expressing double-stranded RNA targeting *ceh-13*. It was transmitted for over 40 generations	Chromatin remodelling (specifically histone acetylation/ deacetylation) probably involved RNAi	Vastenhouw et al. (2006), N. Vastenhouw (personal communication)

Caenorhabditis elegans (Nematode)	Silencing of green fluorescent protein (GFP)	RNAi of *gfp* transgene	The modified morphology was induced by feeding the worms with bacteria expressing double-stranded RNA targeting the transgene *gfp*. It was transmitted for over 40 generations	Chromatin remodelling (specifically histone acetylation/ deacetylation) probably involved RNAi	Vastenhouw et al. (2006), N. Vastenhouw (personal communication)
Caenorhabditis elegans (Nematode)	Various effects, not reported	RNAi of 13 genes	The modified phenotypes were induced by feeding the worms with bacteria expressing double-stranded RNA targeting specific genes. They were transmitted for at least 10 generations	Chromatin remodelling (specifically histone acetylation/ deacetylation) probably involved RNAi	Vastenhouw et al. (2006), N. Vastenhouw (personal communication)
Daphnia pulex (Water flea)	Expression of *G6PD* S and N variants	*G6PD* locus or its regulator	Spontaneous and induced changes in gene expression in meiotic parthenogens. Glucose induced the S form in some clones; presence of S form is related to stressful conditions. The spontaneous rate of reversion between the 2 forms was 1 in 10 and 1 in 2. Clones responded to selection	Not known	Ruvinsky et al (1983a,b, 1986)
Diaphanosoma celebensis (cladoceran)	Earlier first reproduction, higher number of offspring	Not reported	The natural estrogen E2 was given to neonates younger than 24 hours in concentrations of 10, 100, and 1,000 µg/L. These cladocerans and their F_1 and F_2 progeny were effected, but not the F_3 font	Parallel effect of E2 on the parents and the two subsequent generations is suggested	Marcial and Hagiwara (2007)
Drosophila melanogaster (Fruit fly)	Modifying ability of Y chromosome	Imprintor gene interaction	Transient effect of imprintor gene Stability: At least 11generations	Chromatin marks	Dorn et al. (1993)
Drosophila melanogaster	Ectopic outgrowth in	*Kr* (*Kr*$^{If-1}$ allele),	A sensitized isogenic strain bearing allele	Chromatin	Ruden et al. (2003),

(Fruit fly)	eyes	*vtd*^{3} (TrxG mutation)	*Kr*$^{If\text{-}1}$ was generated. Flies of this strain respond to reduced levels of active Hsp90 heat shock proteins with enhanced development of eye ectopic outgrowth. In this case, they were fed with geldanamycin—a potent and specific Hsp90 inhibitor. Ectopic outgrowths were induced, and progeny were selected for eye anomaly and then bred for 13 generations in the absence of the drug. The percentage of flies with ectopic outgrowth increased in each successive generation and reached a plateau of about 65% by the F_6 generation, and this was maintained until the experiment was terminated at the F_{13} generation Ectopic outgrowth was also obtained in flies bearing the TrxG mutation *vtd*^{3}. *vtd*^{3} was not necessary for maintenance of ectopic outgrowth for 5 generations of selection for this trait, as indicated by the increasing percentage of *vtd*$^{+}$/ *vtd*$^{+}$ flies bearing it	inheritance: Flies selected for ectopic outgrowth were fed with histone deacetylase inhibitor, thus reducing outgrowth in progeny	Sollars et al. (2003)
Drosophila melanogaster (Fruit fly)	Red eye-color resulting from activation of mini-*white* reporter transgene or activation of *lacZ* reporter transgene	Transgenic *Fab-7* flanking *lacZ* and mini-*white* reporter transgenes; transgenic/ endogenous *Fab-7* is a regulatory element that can be switched into repressing or activating mode during embryogenesis and	The transgenic line FLW1 carries a heat shock-inducible GAL4 driver, regulating expression of the GAL4-dependent *lacZ* reporter flanked by the *Fab-7* and mini-*white* gene Most FLW1 flies that were exposed to a heat shock-induced burst of GAL-4 during embryogenesis were red-eyed and showed strong *β-gal* staining, indicating derepression of reporter transgenes in transgenic *Fab-7*. Flies with the most strongly pigmented eyes were repeatedly	Probably chromatin inheritance; short-term H4 hyperacetylation may act as a heritable epigenetic tag	Cavalli and Paro (1998, 1999)

		is involved in the formation of spatially restricted expression patterns of homeotic genes	selected and crossed to generate 3 subsequent generations through which the derepression was maintained. Both derepression and activation were reversible. Reactivation of *Fab-7* was transmitted through 4 generations in the absence of GAL-4 protein: After GAL-4 pulse had been induced in embryos of the line bearing the GAL-4 transgene, this transgene was segregated away by crossing to a GAL-4-less transgene. High eye pigment levels were observed in GAL-4-less progeny and transmitted for 4 generations following crossings between the most heavily eye-pigmented flies Flies bearing derepressed endogenous and transgenic *Fab-7* were backcrossed with flies bearing the equivalent genotype but with *Fab-7* in a silenced mode		

Drosophila melanogaster (Fruit fly)	Red eye-color resulting from derepression of mini-*white* reporter gene cloned downstream to transgenic *Fab-7* Suppression of wing deformations resulted from derepression of the gene *sd,* located downstream to the insertion site of *Fab-7* on the X chromosome	Activation state of endogenous and transgenic *Fab-7* elements containing CMM (cellular memory modules) sequences	Intercrossing of strongly mini-*white* derepressed (red-eyed) flies yielded up to 60% derepression through 4 subsequent generations. Silencing was restored after derepressed flies had laid eggs at higher temperatures For about 4 years, stable inheritance of derepression was seen in >50% of the flies. 2 stocks that carry the same genotype, both in terms of transgene as well as the endogenous *Fab-7* locus, differ in their activation state Derepressed state of *sd* was inherited, but stability became lower and harder to detect since flies grow poorly at temperature of 29°C, at which *sd* derepression is visible	Chromatin inheritance; inherited physical *Fab-7* interchromosomal association enhancing PcG silencing is reported in female embryos, as well as is inherited loss in *sd*-derepressed flies	Bantignies et al. (2003), G. Cavalli (personal communication)

Drosophila melanogaster (Fruit fly)	Susceptibility to tumorigenesis	Several alleles cause heritable epigenetic alterations associated with increased/ decreased tumorigenesis induced by the mutant $hop^{Tum\text{-}l}$. Heritable epigenetic variation in the *ftz* promoter was observed	*hop* locus encodes JAK kinase in *Drosophila*. $hop^{Tum\text{-}l}$ mutants have hyperactive JAK kinase expression (a protein involved in regulation of developmental processes), hemocytic defects, and increased tumor susceptibility. The *Krüppel* mutation Kr^1 induced increased tumorigenicity that was transmitted to F_1 and F_2 flies with no Kr^1 allele. This epigenetic effect decreased in F_3. In $hop^{Tum\text{-}l}$ flies with the Kr^1 mutation, increased methylation was found in the enhancer of *ftz*, which encodes a homeodomain protein required for embryonic patterning. Crossing male flies from this type with $hop^{Tum\text{-}l}$ females resulted in maintenance of the increased methylation in the *ftz* enhancer, even in the absence of Kr^1. Tumorigenesis was dramatically increased in $hop^{Tum\text{-}l}$/+ flies that were treated either with DNA-methyltransferase inhibitor 5-aza-dC or with histone deacetylase inhibitor TSA. Tumorigenicity was also found in F_1 progeny of 5-aza-dC/TSA-treated wild-type flies with $hop^{Tum\text{-}l}$ females	DNA methylation, chromatin inheritance	Xing et al. (2007)
Ephestia kuehniella (Moth)	Reversion of shortened antennae and associated mating disadvantage	*Sa*	*sa* mutants are characterized by short antennae and reduced mating success. These traits were suppressed by exposure of the larva and pupa to lithium ions, alternate electrical fields, or higher temperatures (25°C). The sensitive stage for the temperature suppression occurs during the late 5^{th} instar larval and pupal phases of the life cycle	Possibly chromatin inheritance; wild-type moths, suppressed *sa* moths, and non-suppressed *sa* moths differed from each other in the band-patterns of protein fractions of	Pavelka and Kondelova (2001)

			sa suppression (denoted sa^{WT}) induced by high temperature treatment was maintained in progeny of the sa^{WT} crossing for up to 5 generations of intra-population crossing, although the moths were kept at the non-suppressing temperature of 20°C. Suppression of the traits was incompletely inherited from the mother but almost fully inherited from the father. When rare *sa* moths emerged from these cultures and were mated with *sa* individuals, most progeny showed the *sa* phenotype	sperm and spermatophore	
Homo sapiens (Humans)	Cardiovascular mortality and diabetes susceptibility	Assumed to be imprinted tandem repeat upstream of INS-IGF2-H19 region	Differential effect of food availability during childhood growth of fathers, mothers, grandfathers, and grandmothers Stability: At least 2 generations	Possibly methylation; imprinting transmitted through the male germline	Kaati et al. (2002, 2007), Pembrey (2002)
Homo sapiens (Humans)	Angleman and Prader Willi syndromes	15q11-13 region	Effect seen in F_1 and F_2; a spontaneous imprinting effect. Paternal grandmother imprint failed to be erased in the father. Imprinting defects may be induced when conception involves intracytoplasmic sperm injection or hormonal treatment	DNA methylation is involved	Buiting et al. (2003), Zoghbi and Beaudet (2007)
Mus musculus (Mouse)	Probability of developing coat color, obesity, and susceptibility to diabetes and cancer	A^{vy} (gene-epiallele); probably other loci too	Affected by diet Stability: At least 2 generations of Agouti epigenotype; three generations of cumulative obesity-effect, which is ameliorated by methyl supplementation	DNA methylation (DNA methylation may be a secondary mark constituted through chromatin modification or RNA	Blewitt et al. (2006), Cropley et al. (2006), Morgan et al. (1999), Waterland et al. (2007), Wolff et al. (1998), Waterland et al. (2008)

				based inheritance mechanism	
Mus musculus (Mouse)	Probability of kinked tail shape	*Axin-fused* (gene-epiallele) and IAP transposable element	The spontaneous rate of inactivation was 6%, that of reactivation 1%; injection of hydrocortisone during spermiogenesis in males reduced the penetrance of the fused phenotype Later work showed that methyl donor supplementation of female mice before and during pregnancy resulted in reduced *Axin-fused* methylation in tail genomic DNA and in reduced incidence of tail-kinking. At least 2 generations	DNA methylation of retrotransposon that activates cryptic promoter by integration in the gene (maternal and paternal transmission)	Belyaev et al. (1981a, 1983); Rakyan et al. (2003) Waterland et al. (2006), D. Martin (personal communication)
Mus musculus (Mouse)	White-spotted tail and feet; paramutation	*Kit*	Kit^{tm1Alf} mutation was engineered by inserting a 3 kilobase *lacZ-neo* cassette downstream of the initiator ATG site of *Kit* gene coding for a tyrosine kinase receptor. The paramutant traits induced by the allele Kit^{tm1Alf} was transmitted to Kit^{tm1Alf}-less mice through 2 generations of outbred crossing of paramutants to wild-type mice. These traits have also been observed in Kit^{tm1Alf}-less mice for 6 generations of inbred crossing between paramutants obtained so far Paramutant traits were also induced and inherited following microinjection of either total RNA from Kit^{tm1Alf} heterozygotes or of *Kit* specific microRNAs into fertilized eggs. Paramutant traits were maintained among Kit^{tm1Alf}-less mice for at least 6 generations	RNA inheritance; RNAi is involved	Rassoulzadegan et al. (2006), M. Rassoulzadegan (personal communication)

			and were lost after 2 generations of outbred crossing		
Mus musculus (Mouse)	Reduced body weight, reduced level of proteins involved in sexual recognition, and possibly higher mortality between birth and weaning	Not specified, but epimutation is connected to Major Urinary Protein (*MUP*) and Olfactory Marker Protein (*OMP*) genes	Mouse nuclei at the one cell stage were exposed to an altered cytoplasmic environment by transferring them to eggs of a different genotype. 96% of nucleocytoplasmic hybrid males raised from these cells, as well as more than 50% of first generation mice following their crossing to wild-type females, showed altered traits. Preliminary results suggest that the altered traits can be transmitted to the second generation, obtained by backcrossing	Not known, probably DNA methylation	Roemer et al. (1997)
Mus musculus (Mouse)	Tendency to develop tumors	Elevated expression of LF (an estrogen responsive protein) and C-*fos*	Induced by diethylstilbestrol; apparent in the F_1 and F_2 generations	Probably chromatin-marking, including DNA methylation	Newbold et al (2006)
Mus musculus (Mouse)	Glucose intolerance	Not specified	Feeding betel nut in standard feed for 2–6 days. Glucose intolerance was found in 4 of 25 male and in 1 of 22 female F_1 offspring, with significant hyperglycaemia in F_1 males born to hyperglycaemic but not to normoglycaemic mothers. In the F_2 generation 4 of 23 males and 1 of 16 females, and, in the F_3 generation, 1 of 16 males and 0 of 20 females, were glucose intolerant	Not known	Boucher et al. (1994)

Mus musculus (Mouse)	Repression of the recombination of the *LoxP* element	Transgenic *LoxP* and surrounding chromosomal sequences	Recombination between *LoxP* sequences is mediated by Cre recombinase. *Sycp1- Cre* is a transgenic construct, including *Cre* and the promoter fragment from the *Sycp1* gene, exclusively active at the leptotene to early pachytene stages of male meiosis. Mice bearing the transgenic elements *Sycp1-Cre* and $ROSA26^{flox}$, which is a reporter locus activated by Cre-mediated *LoxP* excision, were created. *LoxP* was excised with high efficiency in pachytene spermatocytes of males bearing $ROSA26^{flox}$ and their derivatives generating $ROSA26^{del}$ genotype. The next generation's females bearing $ROSA26^{wt/del}$ were crossed with $ROSA26^{flox/flox}$ males, but, surprisingly, a sharp decrease in excision of *LoxP* in the male alleles was observed, despite maintenance of the *Sycp1-Cre* transgene. *LoxP* methylation following exposure to Cre during meiosis was found, and an inhibition effect of *LoxP*-CpG methylation on Cre recombination was confirmed *in vitro* *LoxP* methylation (and methylation of the surrounding chromosomal region) in meiotic cells expressing Cre was also observed in another transgenic locus, $Rxr\alpha^{AF1}$, which contains a single *LoxP* site. Once established as a result of *Sycp1-Cre* presence, the methylated state was maintained through at least 3 successive generations of breeding in the absence of Cre transgene. Methylation modification was also seen in somatic tissues. Transvection could also be mediated by wild-type *ROSA26* allele with no *LoxP* element: wild-type *ROSA26* that had been exposed to the recombinase activity, seem to have modified DNA methylation in subsequent generations	DNA Methylation; association between recombination and methylation in pachytene spermatocytes is plausible	Rassoulzadegan et al. (2002)

Mus musculus (Mouse)	Genome stability	Many	Induced by irradiation Stability: At least 3 generations	Chromatin methylation	Barber et al. (2002), Dubrova (2003)
Mus musculus (Mouse)	Cardiac hypertrophy	The microRNA miR-1, known to be involved in regulation of cardiac growth	MiR-1 was injected into fertilized eggs. The resultant heart hypertrophy was transmitted in 90% of the mice for at least 3 generations in crosses between either females or males from the treated group and normal partners. Increased levels of miR-1 RNA were detected in the spermatozoa of F_1 and F_2 generations	RNA inheritance	Wagner et al. (2008)
Myzus persicae (Peach potato aphid)	Loss of insecticide resistance	Probably amplified resistance genes	Stable inheritance of lost resistance in clones that have amplified DNA	DNA methylation	Field et al. (1989)
Rattus norvegicus (Rat) [vii]	Modified serotonin content in immune cells	Not specified	Intramuscular administration of β-endorphin during the 19th day of pregnancy led to decreased serotonin content in the peritoneal monocyte-macrophage-granulocyte group and in blood lymphocytes. Observed in 7-week male F_1 offspring of treated mothers Four weeks after delivery, F_1 females had increased serotonin content in the peritoneal lymphocytes, in the mast cells, and in blood lymphocytes, but reduced serotonin content in blood granulocytes and monocytes. Mast-cell serotonin content in 7-week-old F_2 males was significantly lower than controls without further treatment. β-endorphin treatment also provoked sensitization of the grandsons' blood and thymic lymphocytes to repeated endorphin treatment	Not known	Csaba et al. (2005)

Rattus norvegicus (Rat)	Increased expression of genes coding for metabolic factors	Methylation states of *PPARα* and *GR* promoters in the liver	F_0 females were fed a protein-restricted diet (90 g/kg casein) through pregnancy. They were mated with males fed a purified AIN-76A diet (200 g/kg casein) during lactation. Hypomethylation of both GR_{10} and PPARα promoters was observed in liver of F_1 and F_2 males Trends towards higher mRNA expression (p<0.1) in F_1 and F_2 males' livers were observed in cases of *GR_{10}*, *PPARα*, and *AOX*. Significantly higher mRNA levels (p<0.5) was observed in the case of PEPCK	DNA methylation	Burdge et al. (2007), G. Burdge (personal communication)
Rattus norvegicus (Rat)	Altered glucose homeostasis	Not reported	F_0 females were fed with a low-protein diet from day 1 of pregnancy through lactation. Adequate unrestricted diet was given to both their mates and their pups after weaning. Some of the F_1 daughters of malnourished rats were mated with control males and maintained on adequate diet throughout gestation and lactation. This process was repeated to form the F_3 generation Increased fasting plasma glucose levels were observed in F_3 females compared to control females; decreased plasma glucose levels 30 minutes after glucose load levels were measured in F_1, F_2, and F_3 males. F_3 male insulin levels were higher than controls at fasting and 30 minutes after the glucose load. F_3 males also showed higher insulin to glucose ratio at 30 min	Not specified, but the authors point to preliminary evidence for involvement of DNA methylation in F_1 animals	Benyshek et al. (2006), D. C. Benyshek (personal communication)

Rattus norvegicus (Rat)	Decreased spermatogenic capacity (cell number and viability), increased spermatogenic cell apoptosis and subfertility, higher incidence of tumor development, immune system abnormalities, and prostate and kidney diseases, elevated serum cholesterol levels, premature aging phenomena, and male mating disadvantage	Methylation pattern of 15 different DNA sequences; reduced expression of *ankyrin 28*, *Ncstn*, *Rab12*, *Lrrn6a*, and *NCAM1* found in vinclozolin group as well as increased expression of *Fadd*, *Pbm1b*, *snRP1c*, and *Waspip*	Gestating rats were intraperitoneally treated with vinclozolin (antiandrogenic endocrine disruptor) or methoxychlor (estrogenic endocrine disruptor) between embryonic days 8 and 15 (gonadal sex determination). The aforementioned traits were observed in, inbred (sibling breeding was avoided) F_1–F_3 offspring of the vinclozolin treated rats (more than 90% of all F_1–F_3 males had reduced spermatogenic activity). Offspring of out-crossing between vinclozolin F_2 males and wild-type untreated females had an increase in spermatogenic cell apoptosis and a decrease in sperm number and motility. In contrast, the reverse outcross between F_2 vinclozolin females and wild-type control males demonstrated no effect on spermatogeic cells, suggesting transmission of the heritable effect through the male germline F_3 male and female offspring of vinclozolin F_0 females were checked for mate attractiveness and mate preference. Both vinclozolin-treated and control females preferred control rather than vinclozolin-affected males, while males from both lineages exhibited no preference for female type. 15 different DNA sequences were confirmed to have altered methylation patterns and these patterns were transmitted to F_1–F_3 offspring of vinclozolin-treated F_0 females. Expression pattern of several genes was altered in the testis of F_1-F_2 vinclozolin group. More than ten-fold decrease in expression level of *NCAM1* was identified in the brains of F_3 vinclozolin affected males relative to control. Altered expression of *MHC* genes in brain and testis of 3 generations of vinclozolin-affected rats was also reported. Increased spermatogenic cell apoptosis was observed in F_1–F_2 offspring of gestating females treated with methoxychlor	DNA methylation	Anway et al. (2005, 2006a, 2006b), Chang et al. (2006), Crews et al. (2007)

Vulpes vulpes (silver fox)	Piebald spotting	Activation state of *Star* gene	*Star* (semidominant allele) activated in ~ 1% of domesticated animals; inherited for more than 2 generations. Spontaneous in tamed foxes raised in fur farms; hormonal stress suggested [vi]	Possibly heritable chromatin modification	Belyaev et al. (1981b), Trut et al. (2004)

Note: The species in each category are ordered alphabetically.

[i] Similar systems have been described for arabinose-utilization in *E .coli* (Khlebnikov et al. 2000) and for lactose operon in *Salmonella enterica typhimurium* (Tolker-Nielsen et al. 1998).

[ii] Probably occurs in many pathogens (Lewis 2007).

[iii] It seems that all ciliates show cortical inheritance and guided assembly of cortical structures (Frankel 1989). Ciliates have a silent micronucleus and an active macronucleus, from which noncoding sequences are excised and coding sequences are amplified. Following conjugation or autogamy, a new, zygotic macronucleus is formed from the fused meiotic product of the micronucleus, and the old, maternal macronucleus degenerates. The complex processes, guided by the maternal nucleus, which lead to the inheritance of chromosomal rearrangement patterns in the zygotic nucleus, seem characteristic of all ciliate species (Meyer and Chalker 2007).

[iv] Similar phenomena are found in *C. galborata*, *C. tropicalis*, *C. parpsilosis,* and in the basiomycetes fungus *Crystococcus neoformans*.

[v] Interspecific plant hybrids—and sometimes hybrids between cultivars—display epigenetic variations that are heritable across generations. When hybridization is followed by polyploidization, this seems to be a normal and invariant genomic response. In *The Biological Journal of the Linnean Society* 82(4) (Allen 2004), many examples of the epigenomic effects of hybridization in plants, including maize, wheat, rice, cotton, and sunflower, are reviewed.

[vi] There are similar, older studies of transgenerational effects following administrations of hormones and drugs in a variety of mammals. These studies, which did not include molecular data, were reviewed by Campbell and Perkins (1988).

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