# Epigenetic Epidemiology

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REVIEW

# Epigenetic epidemiology

Eva Jablonka

Traditionally, when a disease persists in a population over several generations, it is attributed either to genetic continuity (the inheritance of defective genes) or to environmental continuity (the persistence of adverse conditions or infectious agents). However, during the last two decades, there has been an accumulation of observations that do not slot neatly into either of these categories. It has become clear that the health and general physiology of animals and people can be affected not only by the interplay of their own genes and conditions of life, but also by the inherited effects of the interplay of genes and environment in their ancestors. These ancestral influences on health depend neither on inheriting particular genes, nor on the persistence of the ancestral environment.

The studies that have revealed heritable effects that do not depend on DNA sequence variations have used several different methodologies and had a variety of aims. Some have followed the biological consequences of particular habits or environments in families or communities, tracking the effects that the conditions of life of the parents have on the physiological state of subsequent generations.[1–4] Others have been based on a molecular approach, focusing, for example, on genomic imprinting (in which the expression of a gene depends on whether it was inherited from the mother or the father),[5] or on prion diseases.[6] Yet another type of study has centred on the role in cancer[7] and other complex diseases[8] of cell-heritable defects that are not known to be associated with DNA sequence variations. The range of physiological and behavioural processes that these studies have addressed is thus very wide, and the transmissible effects they have revealed involve several distinct mechanisms operating at different levels of biological organization. This is probably why inherited non-genetic influences on disease have not been considered systematically under one conceptual umbrella. However, the growing volume of information about this type of inheritance suggests that the time may now be ripe for this kind of systematization. What we already know suggests that recognizing non-genetic heredity could be important for understanding the causes of diseases.

The transmission from one generation of entities to the next of phenotypic variations that do not depend on differences in DNA sequence has come to be known as epigenetic inheritance. When the entities are cells, epigenetic inheritance is identical with cell heredity, and involves the mechanisms that underlie the transmission of alternative phenotypes in somatic cell lineages with identical genotypes, as well as (sometimes) the transmission of epigenetic variations through the germ line. When the entities are organisms, inheritance may involve additional, higher levels of organization, such as those through which parental hormonal states are re-constructed in the progeny, or through which the parents' behaviour is reproduced by their offspring. Definitions of epigenetic inheritance, as well as additional related terms referred to in this paper, are presented in the Glossary. The existence of the various types of non-genetic inheritance with obvious relevance to human health led Jablonka and Lamb to predict that their common features would lead to the emergence of a new branch of study—*epigenetic epidemiology*.[9,10] Provisionally, epigenetic epidemiology might be defined as 'the part of epidemiology that studies the effects of heritable epigenetic changes on the occurrence and distribution of diseases'.

When so defined, epigenetic epidemiology includes both cell-to-cell transmission of epigenetic variants during an individual's lifetime, and trans-generational (between generation) inheritance. The latter category includes the study of effects that were environmentally induced in parents and are then transmitted for one or more generations of descendants, as well as stochastic fluctuations in developmental pathways (developmental noise) that have persistent effects in the next generation or generations. In both cases, differences that were established during the development of their ancestors can, in theory, result in two genetically identical individuals, living in exactly the same environment, having different phenotypes and passing these phenotypes to their offspring. In reality, of course, teasing apart the interacting genetic, environmental, and epigenetic effects that lead to heritable differences between individuals is a very difficult undertaking. This is why so much of our current understanding of the molecular aspects of epigenetics that may be significant in epidemiology stems from experimental studies in non-human organisms.

## Epigenetic inheritance systems (EIS)

The first person to realize the importance of cellular epigenetic inheritance for medicine and epidemiology was Robin Holliday. In a series of papers published during the last 25 years, he has argued that the inheritance of epigenetic defects, such as defects in DNA methylation (which he called epimutations), can underlie cancer,[11] ageing changes,[12] parentally-induced heritable morphological abnormalities caused by teratogens,[13] and various types of sporadic diseases.[14] Some of Holliday's pioneering ideas have since been vindicated—cancer epigenetics, for example, is now a flourishing and important field of study

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(e.g. see refs 7,15), and the role of epigenetic defects in some complex diseases is beginning to be uncovered (e.g. see ref. 16). Naturally, the recent advances in molecular biology and the discovery of new types of mechanisms underlying the inheritance of cellular states have extended the study of heritable epigenetic variations beyond Holliday's original suggestions.

At present, four different cellular EIS are recognized.[17] Very briefly, these are:

1. Self-sustaining metabolic loops, which through positive feedback enable the long-term perpetuation of alternative cellular states.[18,19]
2. Chromatin-marking systems such as those involving DNA methylation,[20,21] DNA-binding proteins,[22] and cell-heritable histone modifications, which are all closely mechanistically and functionally interrelated.[23]
3. Structural inheritance, which involves three-dimensional architectural templating, such as that seen in complex membranes systems and cortical structures,[24,25] and in the self-perpetuating activities of prions.[6]
4. The system of RNA interference (RNAi), which allows the amplification and transmission between cells of small RNA molecules capable of suppressing gene activity.[26–29]

These EIS all enable information to be transmitted to daughter cells, although the fidelity of transmission is usually not as great as with genetic inheritance. Indeed, one of the characteristics of cellular epigenetic inheritance is that changes tend to be reversible. In addition to the cellular EIS, information affecting mammalian development can be passed on through the uterine environment,[30,31] through milk,[31,32] and through behaviour,[32–34] and the transmission of this information can lead to functional changes in the offspring that lead to similarity between them and their parents (commonly but not always, their mothers).[32,34] Transmitting developmental information and resources through one channel does not, of course, preclude transmission through other channels. Some important characteristics of transmission through cellular and organismal EIS, which seem particularly relevant for epidemiological studies, are summarized in Table 1.

## Epigenetic inheritance and human health

It is impossible to review here the vast literature on all the processes and issues that might be relevant for epigenetic epidemiology. Instead, I will simply point to the types of studies that suggest that including a consideration of the role of epigenetic inheritance could be informative in epidemiological investigations.

There are certain areas of medicine where the importance of epigenetic inheritance is not in doubt. Cancer is one of them. Nearly 50% of the genes that when mutated in the germline cause familial cancer are hypermethylated and epigenetically

**Table 1** Transmission of phenotypes through epigenetic inheritance systems (EIS)

| Type of EIS | Evidence for transmission through mitosis? | Evidence for transmission between generations? | Transmission through mother, father, both? | Horizontal as well as vertical transmission? |
|---|---|---|---|---|
| **Cellular** | | | | |
| *Chromatin marking* | | | | Unlikely unless mediated through cellular EIS |
| (i) DNA methylation | Yes (20,21,51) | Yes (9,45,46) | Both (46) | |
| (ii) Proteins marks | Yes (22) | Yes (9,47) | Both (47) | |
| (iii) Histone modifications | Yes (23) | NR[a] | NR | |
| **Cellular** | | | | |
| *Structural* | | | | |
| Membranes, cortical structures, prions | Yes (6,24,25) | Yes (6,24,25) | NR in mammals | Yes (6) |
| **Cellular** | | | | |
| *Self-sustaining loops* | Yes (18,19) | NR | NR | Possible, but not reported |
| **Cellular** | | | | |
| *RNAi* | Yes (25) | Yes (27,29) | Female, possibly male (28,29) | Yes |
| **Organismal** | | | | |
| *Physiological* | Possible for some types of metabolic programming (38) | Yes (30) | Mainly female (30). Males (4), only through germ cells | Possible, if embryos cross-transplanted |
| **Organismal** | | | | |
| *Behavioural* | Possible if involves changes in cellular EIS | Yes (31–34) | Female and male (31–34) | Yes, when fostered by parents with different habits (34) |

Numbers in brackets refer to relevant articles in the reference list.

[a] Not reported.

inactivated in sporadic cancers of the same type.[7] Furthermore, heritable cancers often show a mutation in one gene and an epimutation in its wild type allele, which is consistent with the two-hit model that suggests that both alleles of tumour suppressor genes have to be functionally impaired for the cell to progress along a tumourigenic path.[35–37] Diseases that are due to aberrant genomic imprinting, such as Prader-Willi and Angelman syndromes, are also known to be caused either by mutations at the imprinted locus or by epimutations in the same chromosome region.[38] There is an interesting relationship between aberrant imprinting and cancer—in several of the human diseases that are due to loss of imprinting, such as Beckwith-Wiederman syndrome, there is heightened susceptibility to cancer. Since imprinted genes are expressed only from one chromosome (either maternal or paternal, depending on the gene) a change in the pattern of imprinting—loss of imprinting—either inactivation of the active allele, or reactivation of the inactive one—may lead to local cancerous change. This has indeed been found for several different cancers, and it has been suggested that epigenetic loss of imprinting in many common cancers may be one of the initial events playing a causal role in the progression of the disease.[37]

A related issue is the association of epimutations with some age-related diseases. It seems inevitable that with age there will be gradual accumulation of abnormal epigenetic marks that lead to general failure of cells and organs, and epigenetic changes, such as changes in DNA methylation, are known to occur with age.[12,39,40] Since many age-related diseases are likely to be affected by multiple loci, unravelling the contribution of epigenetic changes will often be difficult. However, some cases may be simpler. For example, most people are heterozygous for several recessive deleterious alleles with major effects (such as alleles for Tay-Sachs disease, or cystic fibrosis), and it is possible that with age, the normal allele of such genes acquires epimutations that in some cell lineages suppress or lead to a reduced or abnormal pattern of activity. Heterozygous carriers may therefore develop variable and mild symptoms of the disease. Since age-related epimutations may also occur in the germ line, some parental-age effects may be due to inherited epimutations, and such effects might accumulate in lineages where reproduction has persistently occurred late in life.[39]

Many other diseases (including for example asthma, schizophrenia, diabetes, and inflammatory bowel diseases), which do not show Mendelian segregation in families, nevertheless have a heritable component. The manifestation of these complex diseases is very variable, and is influenced by environmental factors as well as by general ageing processes.[41] However, often the particular environmental factors that influence them have not been identified, and variability is commonly seen even in identical twins reared together, where genetic differences are assumed to be almost non-existent, and environmental differences are assumed to be minimal. Although it is possible to explain many of the observations about these complex heritable diseases as the effects of yet-to-be-identified modifier genes (when there is genetic variability), or unidentified environmental variability (when there is no genetic variation), Petronis has argued that more notice should be taken of the key role that epigenetic inheritance may play in their development.[16] His own analysis of genetic and molecular studies of inflammatory bowel disease points to the involvement of the chromatin marking EIS in the origin and persistence of Crohn's disease and ulcerative colitis.[8] Petronis believes that the complete curability of some complex diseases (e.g. see ref. 42) is more compatible with an epigenetic interpretation of the disease's progression than it is with genetic explanations. Similarly, the high levels of discordance for some complex genetic diseases in identical twins point to the possibility that induced or chance changes in the epigenetic state of somatic cells during development may be important in the establishment of the diseases and their persistence.

## Transgenerational epigenetic inheritance

If epigenetic differences between individuals contribute to the variability seen with complex diseases, how, why and when do these differences originate? Some may be caused by heritable cellular modifications that occur during the development of individuals, either through chance events or as a result of the activities of various environmental agents, and the evidence of this in the case of various cancers is persuasive.[7,15,35–37] However, it is also clear, especially from animal studies, that some changes are initiated in the parental generation or even earlier generations.[1,9] Consequently, the patterns of transmission of complex hereditary diseases may reflect the activities of non-mutagenic environmental agents and nutritional conditions on gene expression in ancestral generations, as well as the effects of the DNA that individuals actually inherited.

Although both male and female parents can transmit epigenetic defects that lead to susceptibility to a complex disease, unlike the genetic case, symmetry of transmission is *not* inherent in the mechanisms of epigenetic heredity. Transmissibility may therefore be often biased by the sex of the transmitting parent (Table 1). Such asymmetry may indicate that there is an epigenetic component in the inherited susceptibility to a complex disease. When the mother is the major transmitter, there are multiple possible routes of transmission: through the uterine environment, the placenta, or milk; through early maternal behaviour towards the infant; and also through the egg, via any of four cellular EIS outlined earlier. When the transmission bias is paternal, several of these possibilities are excluded: transmission can only be through the sperms' chromatin marks, and possibly through the RNAi system or through prions (as yet there are no examples), as well as through paternal behaviour.[34] When both mother and father influence disease risk equally, this does not exclude the transmission of epigenetic variations; it may point to the involvement of chromatin marks, which are most likely to be transmitted equally by both parents.

It is known from human epidemiological studies and from the experimental manipulation of animals that conditions during the prenatal period, especially maternal nutrition, can have long-term effects on health. These long-lasting effects have been attributed to 'metabolic programming', or 'metabolic imprinting', which may adapt offspring to the conditions they are experiencing.[1,3,43] Metabolic programming can involve persistent change in cell number, in metabolic activity, in endocrine and immune functions, and in organ structure,[3,43]

and it is recognized that it may be associated with induced heritable changes in the epigenetic state of cells which later in life affect gene expression.[4] However, Pembrey has suggested that changes in epigenetic marks brought about by parental conditions may persist for longer than a single generation.[44] He pointed out that the finding by Kaati and his colleagues[4] that a grandfather's diet can affect the diseases contracted by his grandchildren could mean that changes in DNA methylation or other chromatin marks, which were induced in the grandfather's germ-line cells, were transmitted to his grandchildren.

There are, of course, molecular features that can point to the possibility that the heritable component of a disease is epigenetic rather than genetic. The first and most obvious is the absence of DNA sequence changes in the gene(s) known to affect the disease phenotype, and the presence of epigenetic modifications of the same gene (e.g. see ref. 38). Work on isogenic lines of both mammals and insects has shown that genetic identity does not preclude heritable epigenetic differences, and that such epigenetic variation can persist and be selected over several generations.[45–47] Second, when a disease can be reversed or prevented by agents known to affect EIS (such as 5-azacytidine, which inhibits DNA methyltransferase, or dietary factors such as folic acid, B12 and betaine that affect methyl metabolism), it is reasonable to suspect that epimutations may be significant in the establishment and persistence of the disease.[48,49] Third, when the heritable component of disease susceptibility is associated with chromosome regions with DNA sequences that are known to be good carriers of epigenetic marks, such as retroviral elements, repetitive sequences, imprinting boxes, and certain CpG sites, the heritable variation may be an epimutation.[9,50,51]

## Where do we go from here?

Once one or more cellular EIS have been identified as having a role in disease susceptibility, questions about the effects and the transmissibility of the epigenetic variants, as well as about the population resources that need to be explored, have to be answered. Epidemiologists may ask: what kind of information needs to be gathered in human populations and through research on model animals? Biologists studying the mechanisms of epigenetic inheritance may ask: how stably are changed epigenetic states transmitted? Are they transmitted through the germ line, and if so for how many generations? How can they be reversed? Is it possible to identify the inducing signals or environmental agents that lead to the heritable variants, or are they the result of developmental noise? Do the epigenetic changes affect the stability of DNA inheritance?

Many of these questions have been asked, but in very few instances have even partial answers been obtained. So far, most studies have focused on the DNA methylation EIS, because the methylation pathway is fairly well understood, and DNA methylation levels are relatively easy to determine and manipulate. However, it is clear that DNA methylation is related to the chromatin-marking mechanisms that involve histone modification and various non-histone proteins, and it is likely that it is the synergetic interactions between these components that establishes and stabilizes states of gene expression.[52,53] In addition, the chromatin-marking EIS may be parts of self-sustaining regulatory loops at the tissue and organ levels, so cell heredity may confer further stability on already established, higher-level, physiological self-perpetuating states.

The role of transmitted cellular proteins also has to be considered, because, as the prion diseases attest, they may confer heritable properties that result in abnormalities being passed to the next cell or organismal generation. Kuru and bovine spongiform encephalitis (BSE) show that prion diseases can be transmitted horizontally when abnormal proteins from affected people or animals are transferred to another individual via the digestive system, and then convert the normal proteins of that individual into their own aberrant form.[6] In the case of kuru, eating habits were responsible for the perpetuation of the disease within families and social groups, but the possibility that prions are transmitted through the placenta, milk or faeces also has to be considered, as does the possibility of transmission through the germ line. Most importantly, the role of metabolic and physiological stresses in altering a normal protein into a different, self-propagating prion form needs to be clarified. It should not be assumed that all proteins with prion forms necessarily have effects as devastating as those we are aware of at present: some self-templating proteins may have less dramatic but nevertheless significant influences on health.

The possibility that the newly discovered RNAi system has a role in complex diseases and their transmission also has to be kept in mind. Although at present we are not aware of any diseases that are influenced by RNAi, it is not difficult to imagine how environmental agents might affect RNA structure and trigger an abnormal recruitment of the RNAi system. Since RNA interference is often associated with DNA methylation, and an increasing number of studies report its role in normal development,[26] it is probably only a matter of time before a role for RNAi in human diseases is identified.

One of the problems that will have to be tackled in epigenetic epidemiology is the relationship between the genetic component of complex diseases, metabolic programming, and cellular EIS. Almost by definition complex diseases depend on the intricate interplay of genetic and environmental factors that lead to changed epigenetic states, and some of these changes may be initiated during very early development. Some may also be transmitted to later generations. We need to know which complex diseases show metabolic programming in the fetal period and, for those that do, whether they also show trans-generational effects. The mechanisms through which fetal programming may lead to trans-generational effects are obviously important. For example, we need to know if fetal programming involves epigenetic reprogramming of the germ cells, as suggested by Pembrey.[44] If it sometimes does, are there predisposing induced and stochastically generated germ-line epimutations, as well as predisposing germ-line mutations, and are there particular loci that are especially sensitive to this type of modification? It will be necessary to study many birth cohorts, using intensive prenatal and perinatal phenotyping for important pathophysiological factors, as well as obtaining extensive genotypic information. Such cohorts should be the basis for long-term, trans-generational studies. The new molecular methods that allow the expression profile of thousands of genes to be simultaneously observed and studied will greatly broaden and refine the ability to assess phenotypes and relate them to present and past environmental factors, as well as to genotypes.

It is also important to know to what extent trans-generational effects are 'diluted' with the passage of generations. A similar question is whether or not there are cumulative environmental effects, with both the effect on descendants and the extent of the transmissibility increasing when several successive generations are exposed to the same external or internal physiopathological conditions (e.g. persistent extreme diets, persistent late reproduction). Another unaddressed and hence unanswered question is the effect, if any, of transmission through one sex for several generations on the transmissibility of epigenetic marks. On the average, an autosome spends 50% of its time in a male and 50% in a female, while an X chromosome spends two-thirds of its time in females. In every large population, most chromosomes will have spent only one or a few consecutive generations in the same sex. However, just by chance, a few chromosomes will have spent a large number of generations in a single sex (i.e. they were transmitted through males only, or though females only, for many consecutive generations). Whether and how such single-sex history of transmission affects the epigenetic marks that these chromosomes carry and the meiotic transmissibility of these marks is an open and unexplored question, which would be very interesting (and technically feasible) to study.

Studying the gene expression profiles of descendants of genetically similar individuals who developed in different conditions may help to tease out epigenetic and genetic effects on the development of phenotypes. However, since epigenetic effects may have varied sources and modes of transmission (Table 1) it is important to determine how many channels or routes of transmission are involved in the heritable component of a given disease. Finding that one particular route of transmission is operative may not be enough, because additional mechanisms may also be involved. Animal studies along the lines of the work done recently with isogenic lines (lines where genetic differences between individuals are minimal) of mammals and insects[45–47] can potentially show if, and how, parental effects are transmitted to descendants. For example, by exposing individuals in an isogenic line to a variety of treatments over several generations (such as extreme diets), and by testing and comparing gene expression profiles in them and their offspring, it should be possible to evaluate the effects that ancestral conditions have on descendents. If the treated parent is a male and the offspring inherit its pattern of gene expression, it is likely that the variation was transmitted through the sperm. If the treated parent is a female, egg and embryo transfers and cross-fostering between mothers from different conditions will be necessary to establish whether the route of transmission is through the gametes, placenta, milk and/or behaviour. Conducting such experiments in genetically *different* isogenic lines may help answer the question whether the inheritance of particular epimutations is line-specific (because only some lines have the type of DNA sequences that can carry 'stubborn' epigenetic marks). For such animal studies to have relevance for human health, epidemiologists and biologists who use model animals such as mice or rats will have to collaborate closely and focus their joint research on those aspects of life (such as various extreme diets, toxicants and pollutants, as well as age) that affect humans and that can be profitably studied in the 'model' mammals.

Information about loci that are likely to carry stubborn epigenetic marks may come from another type of animal studies: the study of the epigenetic reprogramming defects in cloned mammals.[54] The epigenetically changed loci in these sick animals may point to chromosome regions that are particularly liable to persistent epigenetic changes in other mammals, including humans.

Human identical twins who are discordant for complex genetic diseases may also help to disentangle the relationship between genetic and epigenetic effects. Identical twins start life with identical genes, and hence it is expected that their patterns of gene expression will, in general, be very similar. Discordance points to a difference, and if it stems from a difference in chromatin and gene activity, it should be possible to detect this by comparing gene expression profiles from the relevant tissue in the twins. If the offspring of discordant identical female twins display the same discordant phenotypes as their mothers, this could be caused by transmitted paternal genetic differences, or by genetic differences resulting from meiotic re-shuffling of the mother's genes, but it can also be the result of the transmission of the maternal epigenetic differences that were associated with their discordant phenotypes. Unravelling the roles of the parental genes and maternal epimutations will require comparison of gene expression profiles, chromatin profiles, and extensive genotyping of large numbers of twins.

Although investigations are still at an early stage, it seems that understanding epigenetic inheritance is going to be important in finding effective treatments for complex diseases and for reducing their incidence. At present, a lot of work is focused on manipulating the methylation pathway by using dietary supplements or inhibitors of DNA methylation,[48] and a profile of the methylation status of genes in the tissues of healthy and sick people is being worked out in the hope that it will be useful for diagnostic purposes.[7,15,55] There are also attempts to get at the profile of other components of chromatin, so as to better understand the biochemical phenotype of genes. Effective disease prevention and treatment will have to overcome the inertia caused by the persistence of epigenetic effects that are the result of exposure to toxicants and pollutants in earlier generations: removing present offending environmental factors may not be enough—it may need active and specific compensation for past epigenetic programming.[49] For example, special supplements may have to be introduced into the diet of children whose ancestors' history was one of persistent starvation. Knowledge about effective treatments will come from integrated physiological and molecular studies in which the agents that might be responsible for the generation of an altered epigenetic state are systematically examined, and the intracellular and intercellular routes of transmission are investigated.

Theoretical models that describe the establishment and spread of epigenetic variations are needed to focus research questions and point the way for future studies. By using considerations similar to those used for studying culturally transmitted variation,[56] it may be possible to show how epigenetic inheritance can contribute to the covariance between relatives. Kisdi and Jablonka (unpublished) suggest that comparing different pairs of relatives for whom the genetic contribution is the same, but the epigenetic contribution is likely to be different (because the number of opportunities for independent meiotic/early-embryo reset is different), may allow preliminary

estimates of the variance contributed by epigenetic inheritance, as well as preliminary estimates of epigenetic transmissibility, or 'memory'. Another type of theoretical model that may be applicable is the existing models of environmentally-induced maternal effects.[57] Such models show the population-wide effects of past legacies, and may allow better understanding of dynamic changes in populations over time.

Including the study of heritable epigenetic variants, their mechanisms of transmission, and the gene–environment interactions that produce them, will add an extra dimension to epidemiological research. Despite the complications that the epigenetic aspects introduce, I believe that as the new field of epigenetic epidemiology develops it will enrich the study of epidemiology, and eventually lead to a better understanding of the causes and patterns of distribution of diseases in human populations.

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## Glossary

**Chromatin** The complex of DNA, RNA, small chemical groups and proteins that make up chromosomes.

**Chromatin mark** The non-DNA part of a chromosomal locus that affects the nature and stability of gene expression.

**Stubborn mark** A chromatin mark that is not easily reset during early embryogenesis and gametogensis, and therefore leads to persistent, cell-heritable epigenetic effects.

**Histone modifications** Chemical modifications (e.g. methylation, acetylation) of particular amino acids in the histone proteins around which DNA is bound; modifications alter the accessibility of the chromosomal region to proteins that participate in the regulation of gene expression.

**DNA methylation** Modification of DNA by the addition of a methyl group ($-CH_3$) to some of the bases; in eukaryotes most of the modified bases are cytosines.

**CpG site** A DNA site at which cytosine (C) is followed by guanine (G); p denotes the phosphate groups, so that the C is at the 5′ position relative to the G.

**Epigenetic inheritance** The transmission, from one generation to the next, of phenotypic variations that do not require a variation in DNA base sequence. Epigenetic inheritance in the wide sense includes cellular inheritance, and also organismic (physiological and behavioral) reconstruction of developmental and behavioral legacies.

**Cellular epigenetic inheritance** The inheritance from one cell generation to the next of phenotypic variations that do not depend on variations in DNA base sequence. Epigenetic variation are therefore transmitted through mitosis, and sometimes also through meiosis.

**Epimutation** A heritable abnormality in phenotype that is not the result of a change in DNA base sequence (for example, a variation n the methylation pattern of a chromosome).

**Genomic imprinting** The dependence of the expression or transmission of a gene, a chromosome region, a whole chromosome, or a chromosome set, on the sex of the parent form which it was inherited.

**Loss of imprinting** The loss of a parent-of-origin effect on the expression of a normally imprinted gene; it may lead to developmental abnormalities and is associated with some cancers.

**Horizontal transmission** The transmission of entities (e.g. genes, epimutations) between individuals that do not have a genealogical parent-child relationship. Horizontal transmission may occur between individuals belonging to different lineages and even different species.

**Isogenic line** A line of sexually reproducing organisms that are genetically nearly identical, being homozygous for most loci. Different isogenic lines have different sets of homozygous alleles.

**Metabolic programming** A change in metabolism, usually occurring early in development, that leads to self-sustaining, long-term, physiological change.

**Prion** A proteinacious infectious agent that propagates via three dimensional templating mechanisms. Prions can be transmitted *vertically* from mother cell to daughter cell (for example, in yeast), as well as *horizontally*, as with BSE.

**RNAi (RNA interference)** The suppression, via the processed products of an RNA transcript, of the expression of the transcribed gene from which the transcript originated, as well as any homologous-enough RNA gene-product. The suppression may occur at the level of transcription, post-transcriptional RNA processing, or translation.

**Vertical transmission** Transmission from parents to child.