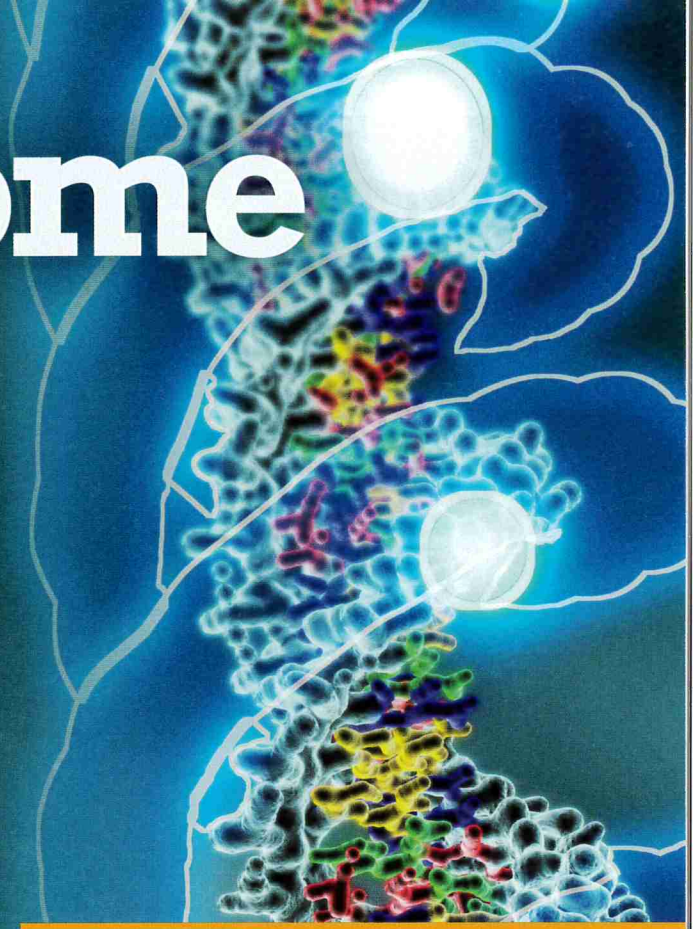
The genome remixed

Epigenetics and human disease



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Genetic researchers Paul Shiels, Laura Monaghan and Ognian Neytchev outline some of the fundamental components of epigenetics and discuss its effect on health

Key words

Epigenetics
Chromatin
Gene regulation
Ageing

AQA: 3.4.2 for definition of genome; 3.8.2.2 Regulation of transcription and translation

Edexcel A: 3.14 (ii) and (iii) Epigenetics; 7.16 Transcription factors

Edexcel B: 7.1 Using gene sequencing; 7.2 Factors affecting gene expression

OCR A: 6.1.1 Cellular control

OCR B: 5.1.2 (f) Epigenetics

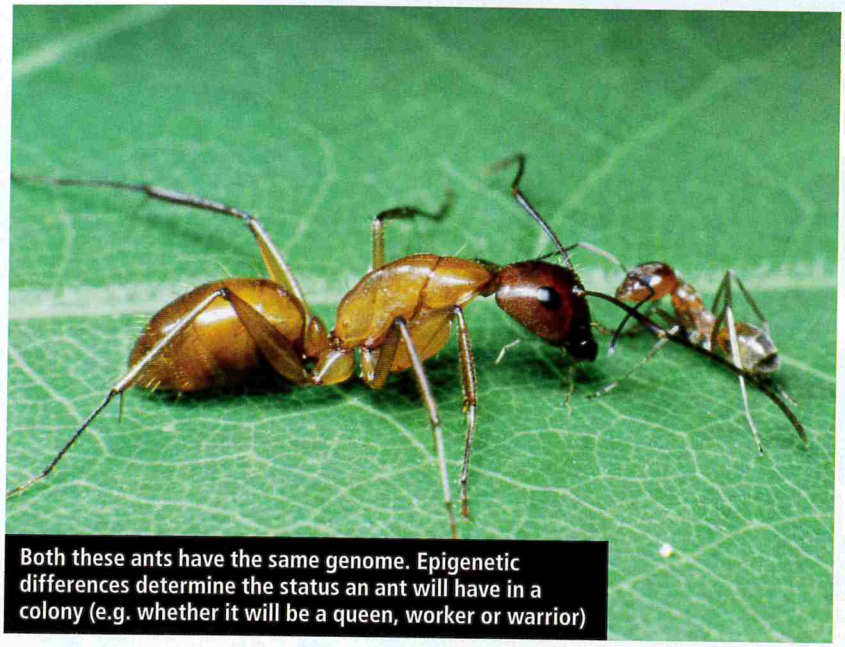
WJEC Eduqas: 2.2.5 (h) Epigenetics

Epigenetics is the study of heritable changes in gene expression that do not involve changes to the DNA sequence itself. But how does this happen and what are its consequences?

The central dogma of molecular biology is that DNA is transcribed into mRNA, which is then translated into protein. However, when you consider that almost 2 metres of DNA encoding approximately 25 000 protein-coding genes is packaged into the nucleus of almost every cell in your body, there is a clear need for gene regulation and control. This regulation — namely which genes are transcribed, at what level, at what time in your life, for how long, and in what cell type — comprises epigenetics.

What is epigenetics?

Epigenetics can seem complex, but by drawing analogies with processes in everyday life, we can begin to put together a picture of the role it plays in our body's functions. The term 'epigenome' means 'on top of the genome'. It is defined as a set of heritable changes that are not coded for in the underlying DNA sequence. Epigenetic changes therefore provide a way of changing the phenotype (how an organism/cell looks or behaves) without changing the genotype (its DNA). They allow the body to respond rapidly to environmental changes, whereas doing so through natural selection would take hundreds of generations and thus be too slow to allow a species to adapt quickly enough. Epigenetic change is like a DJ remixing a song, giving it an upbeat edge, or a sample from a different era, given a revival. A remix is still essentially the original, but by adding a beat, a loop or a scratch, you have changed the way it sounds.



Both these ants have the same genome. Epigenetic differences determine the status an ant will have in a colony (e.g. whether it will be a queen, worker or warrior)

Effects on human health

Epigenetics plays an important role not only in phenotype, but also in many diseases, including cancer, diabetes, kidney disease, psychiatric and neurological disorders. Epigenetic regulation also guides the development of all complex organisms. The DNA sequence is virtually identical in every cell of an organism, and it is through epigenetics that different cell types are generated, each performing its own specialised function. It is important for this differentiation to be stable across time and cell divisions. It would be a disaster for an animal if, for example, cells in its liver suddenly started to 'forget' what they were and became heart or skin cells.

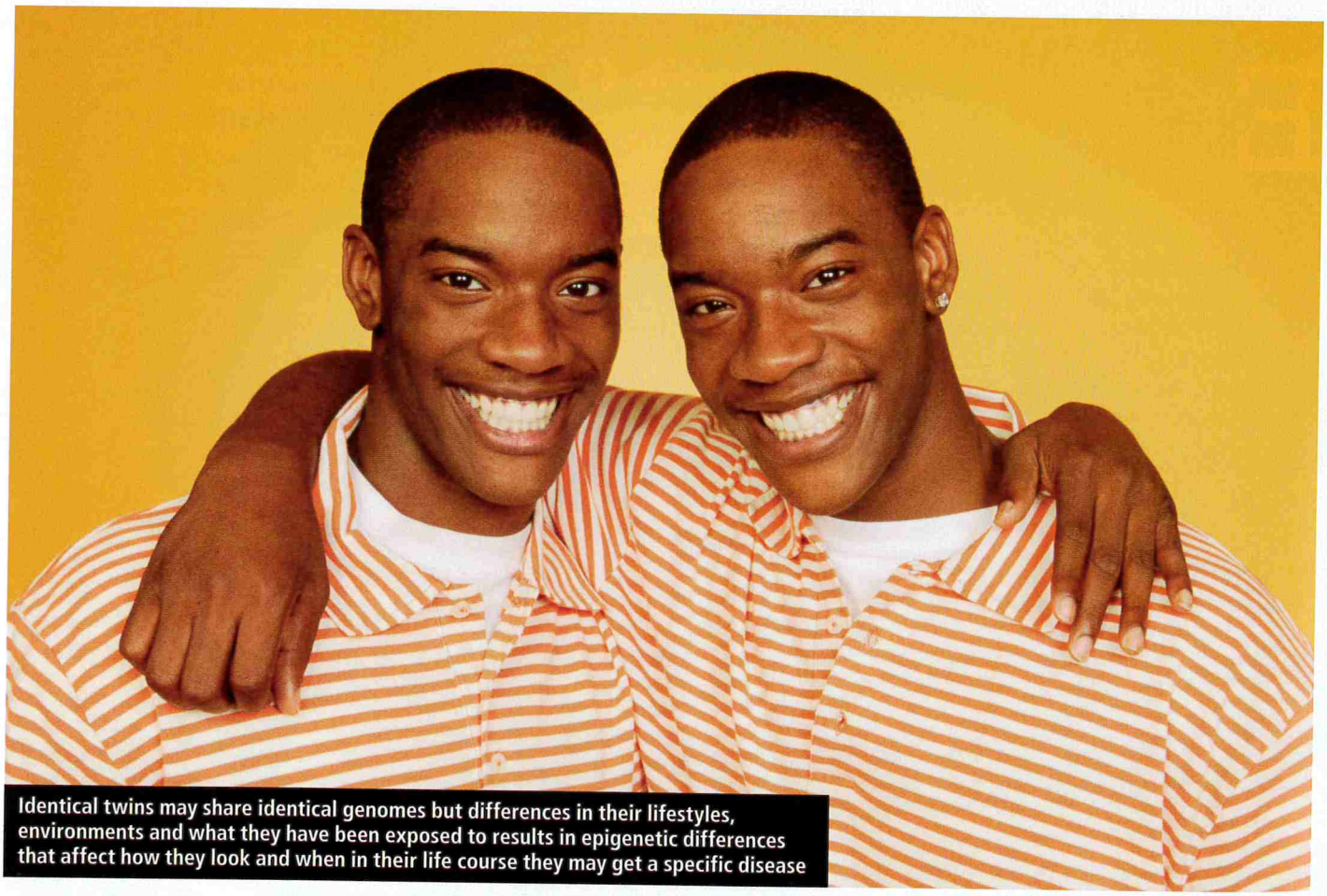
Epigenetics can be responsible for differences between genetically identical individuals. It determines, for instance, the differentiation into separate castes (e.g. worker, warrior, queen) within ant and bee colonies.

An example from mammals is the agouti gene, which controls the production of melanin in hair. When this gene is methylated (an epigenetic mark that we will explore in greater detail later) in a particular strain of mice called *Agouti viable yellow* (A^{vy}), the individual is brown and healthy. When the gene is unmethylated, the animal is yellow and has a higher risk of obesity, diabetes and cancer.

Epigenetics also affects some human characteristics. Differences in lifestyle, environment and life events lead to a divergence of epigenetic modifications that makes identical twins look less and less alike as they age.

Epigenetic mechanisms

A variety of epigenetic mechanisms interact to change the structure of chromatin, affecting gene expression by helping or preventing transcription, which in turn modifies the proteome (the set of



Identical twins may share identical genomes but differences in their lifestyles, environments and what they have been exposed to results in epigenetic differences that affect how they look and when in their life course they may get a specific disease

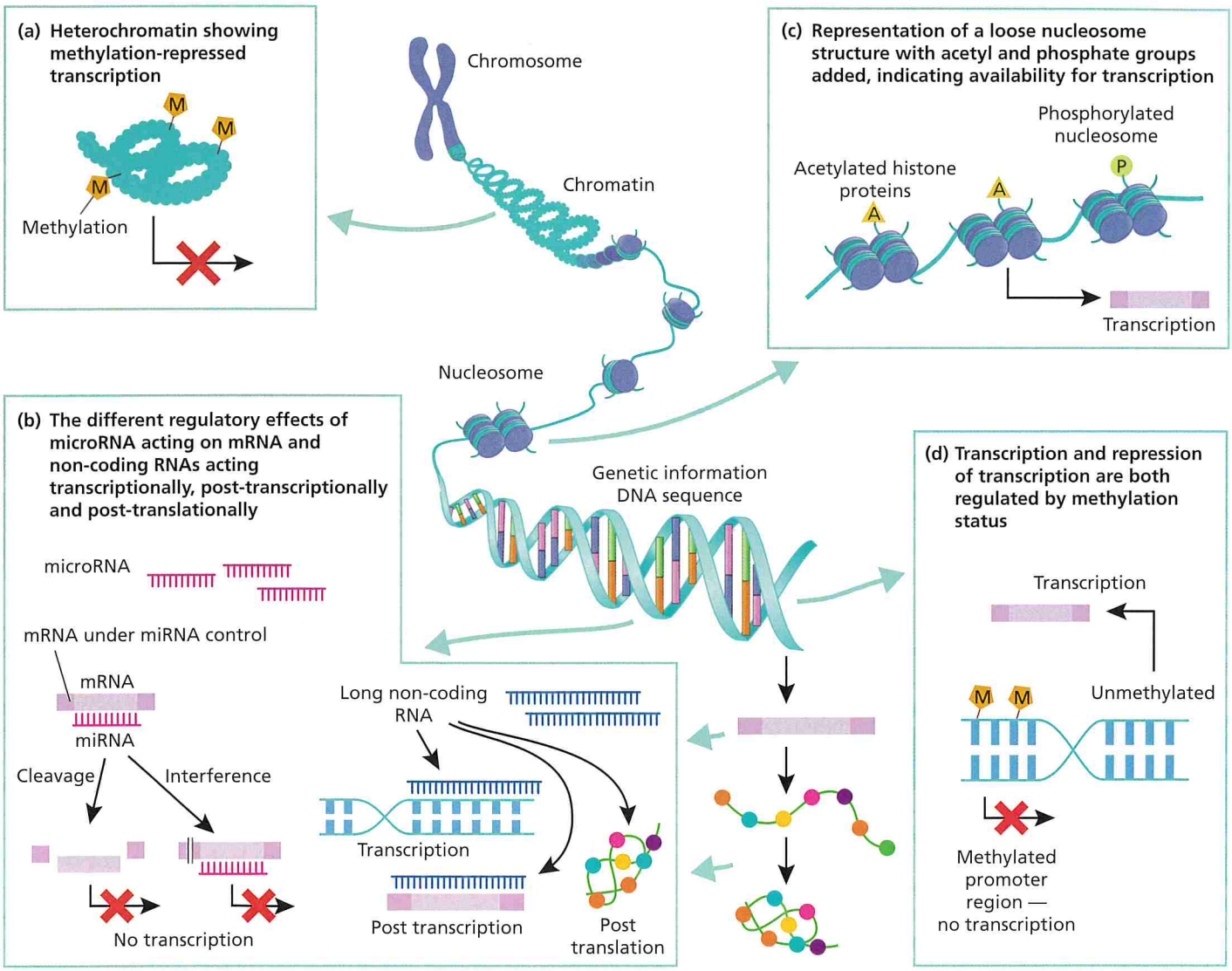
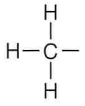


Figure 1 Diagram explaining epigenetic modifications, including DNA methylation, histone modifications and regulation by non-coding RNAs

proteins present in the cell) and changes the cell's behaviour (see Figure 1).

DNA methylation

The main epigenetic modification of DNA consists of adding a methyl group (a carbon bound to three hydrogen atoms) to cytosine residues. If present in the promoter, a switch region for transcription of a gene, DNA methylation can stably switch off transcription.



Methyl group

Histone modification

DNA is associated with **histones** and other proteins that allow the DNA to wrap tightly, like thread around a spool, into smaller structures called nucleosomes. These are in turn packed into chromatin, allowing the 2 metres of DNA to be contained in each of our cells (see Figure 1). Before a gene can be transcribed, the chromatin around that gene must be unravelled to allow access for the transcription machinery. Modification of the histones can alter chromatin structure, 'opening' or 'closing' it in order to allow, or prevent, transcription. Histones can be methylated, as with DNA, as well as a series of other modifications, such as acetylation and phosphorylation. The process, which is catalysed by enzymes, is reversible and changes in response to the environment and the current needs of the cell.

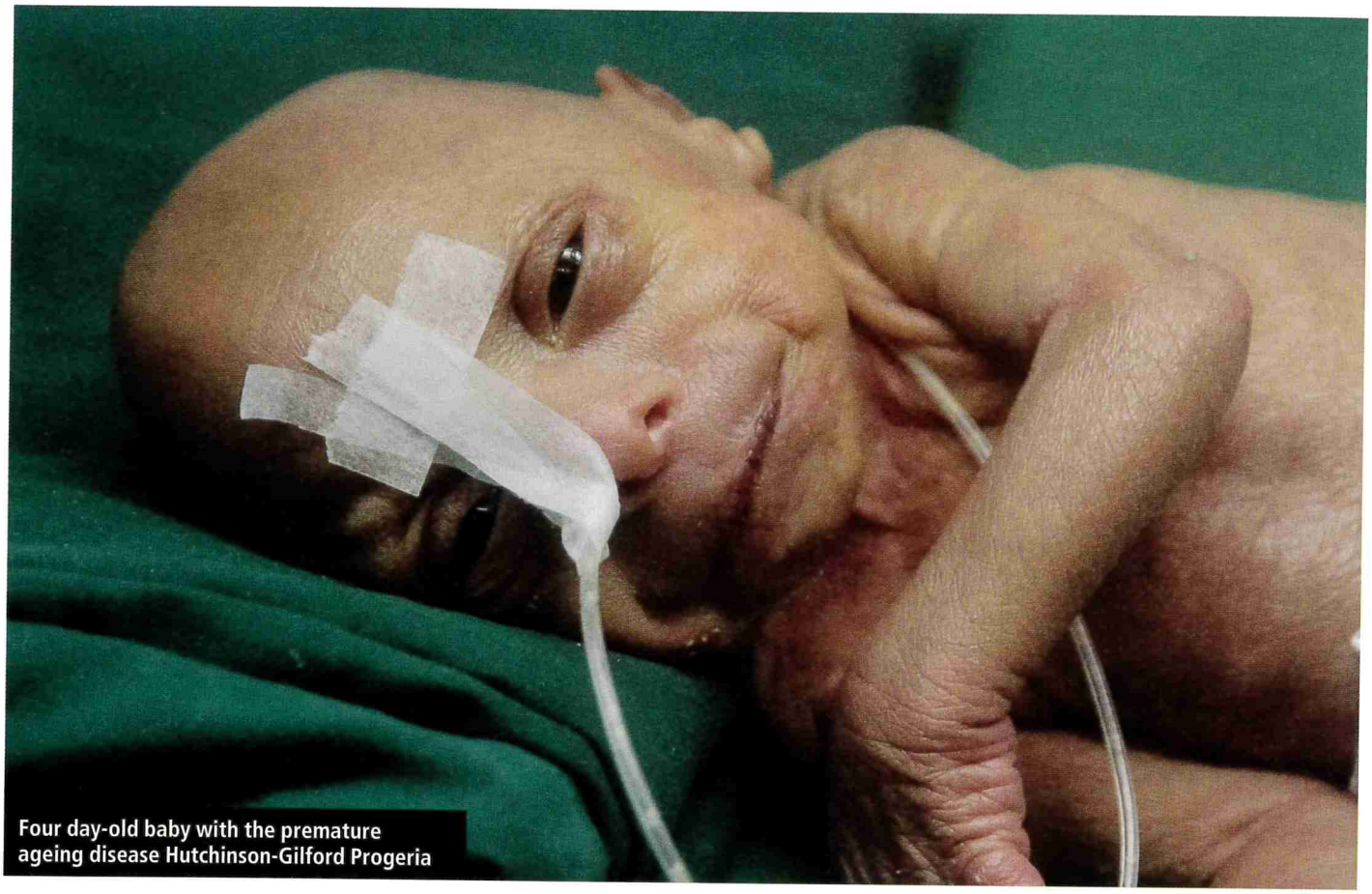
Non-coding RNA

There are small groups of genes that will never be translated into proteins but play a vital role in the regulation of gene expression. These are transcribed

Terms explained

Heterochromatin A tightly packed form of chromatin containing DNA that is not transcribed.

Histones A family of DNA-binding proteins which contribute to chromatin organisation.



Four day-old baby with the premature ageing disease Hutchinson-Gilford Progeria

to produce non-coding RNAs with a variety of functions, such as changing chromatin structure and inhibiting translation of specific genes.

Role in ageing

The process of ageing is highly regulated by epigenetics. As the body ages, a series of factors lead to widespread epigenetic changes. Premature ageing diseases, such as Hutchinson-Gilford Progeria Syndrome, show evidence of epigenetic changes, both in methylation differences and loss of **heterochromatin** structure associated with histones. Sirtuins, a family of enzymes that modify histones, alter chromatin structure during ageing. A loss of function for individual members of this family can lead to chromatin dysregulation, methylation changes, and premature biological ageing. These alterations may be contributing to the significant increase of disease incidence associated with advancing age.

Epigenetic inheritance

There are two types of cell division: mitosis, producing somatic cells to allow for growth, and meiosis, producing gametes from parent cells, for egg and sperm production. Epigenetic traits can be mitotically and meiotically heritable. During mammalian development, DNA methylation is erased and rewritten. This is a little like formatting your computer hard drive and reinstalling the operating system. Unlike formatting a PC, or a smartphone, however, epigenetic reprogramming does not erase everything every time. What is specifically inherited can be affected and modified by the external environment.

Does that mean these epigenetic traits are always passed from one generation to the next? One of the favourite quotes of biologists is 'Nothing in biology makes sense except in the light of evolution', so let's consider this for a moment. Would it be helpful for an animal to pass all its epigenetic traits to its offspring, including higher susceptibility to a variety of illnesses, including heart disease and cancer? While acquired epigenetic traits are heritable, they can also be lost or gained over the life course, thus allowing modification through successive generations in response to a changing environment and not predisposing offspring to continued disease susceptibility.

Types of epigenetic inheritance

There are two types of epigenetic inheritance:

- Intergenerational inheritance: referring to epigenetic changes directly in the developing offspring (such as by affecting the uterine environment). However, as it is the offspring being directly affected, is this a true case of inheritance?
- Transgenerational inheritance: involving a change being transmitted to an individual who has not been exposed to the trigger condition that induces epigenetic change.

Germ cells, which later give rise to sperm and eggs, differentiate early in embryonic development, so, at least in principle, a stimulus at the right time

Further reading

'What is epigenetics?': **www.whatisepigenetics.com/fundamentals**

Time magazine article from 6 January 2010: 'Why genes aren't destiny': **https://tinyurl.com/y97ym68e**

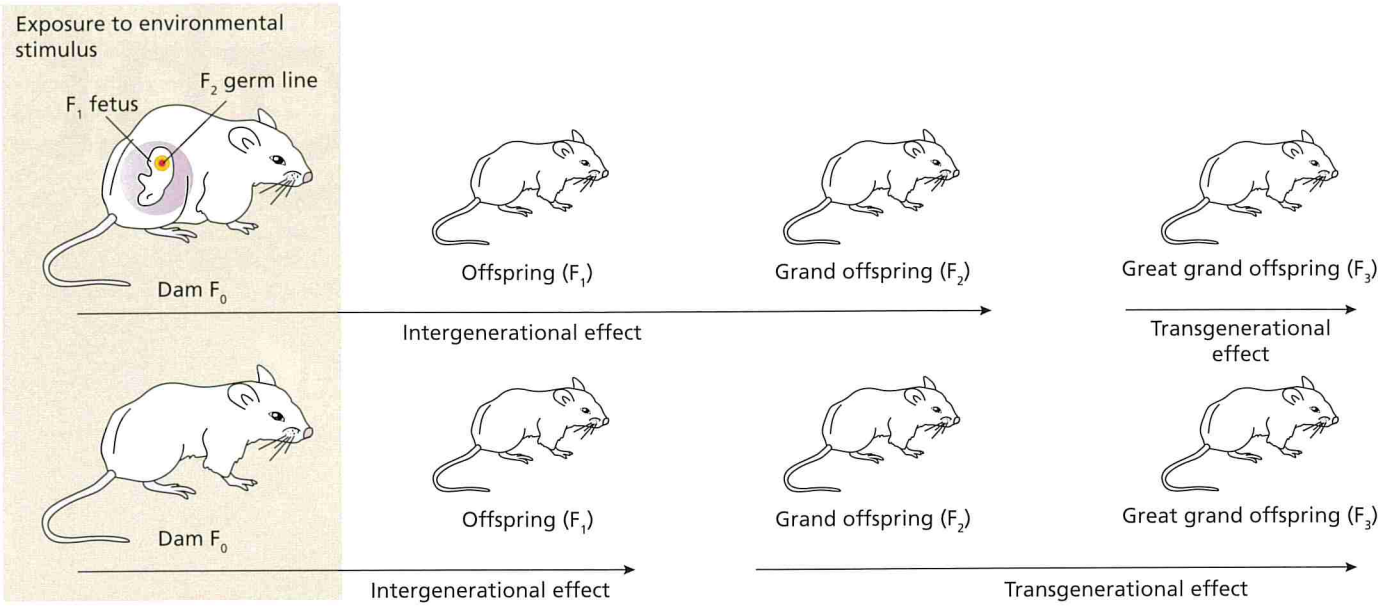


Figure 2 Environmental stimuli can affect germ cells and the developing embryo. For this reason, to indicate 'true' transgenerational inheritance, we must examine a descendant who was not exposed: this would be an F_2, or an F_3 if the initial stimulus was applied to a pregnant female

Box 1 Natural experiments allow scientists to study humans

Överkalix is a small municipality in northern Sweden. Its isolation and the fact that the entire community was registered at the local church mean that researchers have detailed and reliable information on food availability and health of the population across generations. By tracking a group of individuals born at the end of the nineteenth or beginning of the twentieth century and their parents and grandparents, researchers have shown that abundance of food during a particular stage of a male's childhood was negatively correlated with longevity of his children and grandchildren.

The Dutch famine of 1944–45 happened towards the end of the Second World War, when a Nazi embargo led to severe food shortage in western Netherlands. By studying a cohort of women who were pregnant during this period and their children and grandchildren, researchers have shown that famine has a negative impact on the F_1 and, to a limited extent, the F_2 generation (consider, however, that the F_2 generation is still too young to draw conclusions from). The effects include lower birth weight and higher rates of metabolic and cardiovascular problems. A further interesting result was that the negative impact of the famine appeared to vary depending on the pregnancy stage.

A third, more recent, example is the Quebec ice storm of 1998. A series of ice storms in January caused severe damage to the power grid and disruption to transportation, leaving millions of people without electricity, central heating, and with limited food for weeks. Research on a cohort of women who were pregnant during that period found that objective hardship, but not subjective stress, in the mother was associated with a different pattern of DNA methylation in the child.

could directly affect three generations: the mother, the developing embryo in her womb, and the germ cells inside the embryo (see Figure 2).

Epigenetic traits can be inherited and affect the health and wellbeing of subsequent generations. Studies on rats, mice and humans (see Box 1) show both intergenerational and transgenerational effects for factors such as environmental or psychological stress, or poor nutrition in the parent (typically the mother), causing a higher incidence of ill health in the offspring over their life course. We will explore whether there is anything we can do to mitigate this in an upcoming article in Biological Sciences Review.

Points for discussion

- Epigenetic mechanisms become disrupted in disease. What are the different ways this might occur in cancer?
- Think of diseases associated with ageing and investigate the epigenetic mechanisms that alter their progression.
- Why are natural experiments so valuable, compared with observational studies, when it comes to studying humans?

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Key points

- Epigenetic mechanisms regulate gene expression in a stable manner, allowing individuals to differentiate and adapt rapidly to different environments.
- Epigenetic changes are mitotically and meiotically heritable. They can persist for the entire lifespan of an individual and even be transmitted to their offspring.
- Epigenetics plays a key role in normal development, biological ageing, and a variety of diseases, including cancer.