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the hidden things

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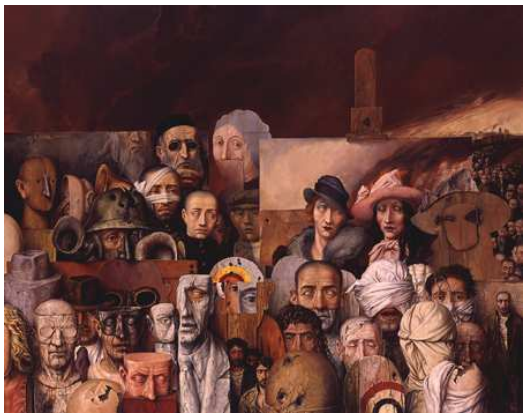
Nature has its secret ways. During the course of the 19th century, the Augustinian friar Gregor Mendel worked out the basics of genetic inheritance as he crossbred pea plants. About a century later, it has become obvious that the inheritance of a given trait is in fact not so straightforward. What is more, there seems to be growing evidence that a given trait can actually be handed down generations – even skipping generations – without it being frankly dictated by a gene; a notion which, in the realm of biological dogmas, is like a crack at the base of a sturdy building. The concept is not really new but scientists may have strengthened it following studies on folate metabolism – one of whose major protagonists is methionine synthase reductase, or Mtrr – by suggesting a mechanism of inheritance that is driven by entities which are not an actual part of a gene, otherwise known as epigenetic inheritance.



The Family, by Samuel Back

wikipedia

What is folate? Folate, or folic acid, is also known as pteroly-L-glutamate and more commonly as vitamin B9. ‘Folate’ or ‘folic’ is derived from the Latin ‘folium’ meaning ‘leaf’, since folates occur naturally and especially in plants that have dark green leaves; the compound received its name in 1941 when it was isolated from spinach. Over the years, it has become apparent that folic acid plays an essential role in nucleic acid synthesis and methionine regeneration – which both play an important part in genetic inheritance. And diets that are poor in folic acid – one of the most common deficiencies in humans – can be at the heart of serious ailments amongst which macrocytic anaemia, intrauterine growth restriction, placental abnormalities, neural tube defects, and perhaps even psychiatric and cognitive disorders.

The first person to discover the link between health and folic acid was the English haematologist Lucy Wills (1888-1964) who travelled to Bombay in 1928 to investigate anaemia in pregnancy, which was prevalent in female textile workers. It became apparent that the poorer populations had diets that were deficient in protein, fruit and vegetables. Wills solved the problem by adding yeast to their diet. It was only years later – in 1941, precisely – that scientists managed to single out the chemical component in the yeast that was lacking in their diet: folic acid. During the 1950s and 1960s, folate metabolism was finally elucidated, and one of its reactions was later shown to be particularly important in DNA synthesis. And who says DNA synthesis says genes, and hence development and inheritance.

One of the major enzymes to be part of the folic acid cycle is methionine synthase reductase, or Mtrr, which is the actual link between folate metabolism and methionine cycles, in other words: development. Indeed, folic acid carries methyl groups that are relayed downstream and ultimately used for DNA methylation. Mtrr uses the methyl groups from the folic acid cycle to form methionine which, in turn, is a precursor of S-adenosylmethionine, or SAM, the methyl donor for many cellular substrates including

proteins, RNA and DNA. Mtrr is therefore essential for the normal progression of the folate and methionine cycles, without which the expression of genes would be seriously hindered.

DNA methylation has an important role in the expression of genes since it operates as a sort of on/off switch. When such a system is impeded, it is not difficult to understand that a wide spectrum of phenotypes can suffer. A diet that is deficient in folic acid can cause this but the same sort of effect can occur if Mtrr is mutated. Indeed when scientists knocked out Mtrr in mice, it caused extensive DNA demethylation and abnormalities such as developmental drawbacks, neural tube defects, placental defects and placental lethality. This demonstrated that DNA methylation per se is an important epigenetic determinant in gene expression and DNA stability.

The intriguing part was that Mtrr deficiency could lead to the appearance of the same congenital malformations in wild-type progeny up to five generations down the line. How? What was it that was maintaining information that was passed on from parents to children in a non-Mendelian manner? One plausible explanation is that DNA methylation is inherited; in other words, the on/off switch is passed down to offspring. Up to now, it had been thought that these switches were wiped away "after use" so to speak, and hence never transmitted to future generations. But it now seems that, much like when you forget to wipe away all the chalk marks on a blackboard, some of the switches remain and are relayed to progeny through the germline. Furthermore, it seems that once an epigenetic defect is generated, it may never completely revert back to the way it was in its ancestors – which has important evolutionary repercussions.

So, what this demonstrates is that a given trait which is transmitted from generation to generation may not only be genetic, but also epigenetic which adds a spicy ingredient to the world of inheritance. And that, in the case of folic acid, the ingredient can actually be caused by a diet deficiency, i.e. something purely environmental, or even societal. It is believed that disorders such as depression or obesity can be passed on in the same way. There is still a long way to go to understand how such a mode of inheritance works and the weight it may have in passing on certain unfortunate traits. However, studying Mtrr to gain a better understanding of epigenetic transmission should prove to be informative on the inheritance of developmental disorders between generations. And, in the long run, perhaps in the treatment of congenital anomalies in humans.

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Methionine synthase reductase, *Mus musculus* (Mouse) : Q8C1A3

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