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Pleiotropy: One Gene Can Affect Multiple Traits

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How can a mutation in one single gene cause a disease with a wide range of symptoms? This situation is referred to as pleiotropy, and it has been identified in a wide range of species, even humans.

Aa Aa Aa

During his study of inheritance in pea plants, **Gregor Mendel** made several interesting observations regarding the color of various plant components. Specifically, Mendel noticed that plants with colored seed coats always had colored flowers and colored leaf axils. (Axils are the parts of the plant that attach leaves to stems.)

Mendel also observed that pea plants with colorless seed coats always had white flowers and no pigmentation on their axils. In other words, in Mendel's pea plants, seed coat color was always associated with specific flower and axil colors.

Today, we know that Mendel's observations were the result of **pleiotropy**, or the phenomenon in which a single **gene** contributes to multiple phenotypic traits. In this case, the seed coat color gene, denoted *a*, was not only responsible for seed coat color, but also for flower and axil pigmentation (Fairbanks & Rytting, 2001).

The term pleiotropy is derived from the Greek words *pleio*, which means "many," and *tropic*, which means "affecting." **Genes** that affect multiple, apparently unrelated, phenotypes are thus called pleiotropic genes (Figure 1). Pleiotropy should not be confused with **polygenic** traits, in which multiple genes converge to result in a single phenotype.

Examples of Pleiotropy

In some instances of pleiotropy, the influence of the single gene may be direct. For example, if a mouse is born blind due to any number of single-gene traits (Chang *et al.*, 2002), it is not surprising that this mouse would also do poorly in visual learning tasks. In other instances, however, a single gene might be involved in multiple pathways. For instance, consider the **amino acid** tyrosine. This substance is needed for general **protein** synthesis, and it is also a precursor for several neurotransmitters (e.g., dopamine, norepinephrine), the hormone thyroxine, and the pigment melanin. Thus, mutations in any one of the genes that affect tyrosine synthesis or **metabolism** may affect multiple body systems. These and other instances in which a single gene affects multiple systems and therefore has widespread phenotypic effects are referred to as indirect or secondary pleiotropy (Grüneberg, 1938; Hodgkin, 1998). Other examples of both direct and indirect pleiotropy are described in the sections that follow.

Fruit Flies and the Vestigial Gene

In the fruit fly *Drosophila*, the **vestigial** gene plays a critical role in wing **development**. In fact, if these flies are **homozygous** for the **recessive** form of the vestigial gene (*vg*), they will develop short wings, and they will be unable to fly as a direct result. Along with regulating wing development, the *vg* gene is also pleiotropic. Indirectly, the gene changes the number of **egg** strings in a fly's ovaries, alters the position of bristles on a fly's scutellum, and decreases the length of a fly's life (Caspari, 1952; Miglani, 2002).

Chickens and the Frizzle Trait

In 1936, researchers Walter Landauer and Elizabeth Upham observed that chickens that expressed the **dominant** frizzle gene produced feathers that curled outward rather than lying flat against their bodies (Figure 2). However, this was not the only phenotypic effect of this gene — along with producing defective feathers, the frizzle gene caused the fowl to have abnormal body temperatures, higher metabolic and blood flow rates, and greater digestive capacity. Furthermore, chickens who had this **allele** also laid fewer eggs than their wild-type counterparts, further highlighting the pleiotropic nature of the frizzle gene.

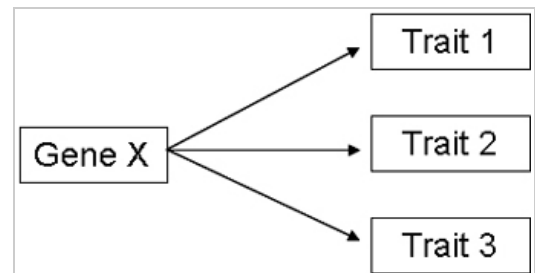


Figure 1: Diagram of pleiotropy.

A pleiotropic gene is a single gene that controls more than one trait.

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Figure 2: A chicken with the frizzle gene

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Pigmentation and Deafness in Cats

Approximately 40% of cats with white fur and blue eyes are deaf (Hartl & Jones, 2005). An initial hint at the link between pigmentation and deafness was the observation that white cats with one blue eye and one yellow eye were deaf only on the blue-eyed side. Interestingly, this phenomenon isn't exclusive to cats; for example, Waardenburg syndrome is a disorder that acts in a similar manner in humans. Because the gene responsible for both of these phenotypes affects pigmentation as well as the ability to hear, the gene is pleiotropic. Research continues into the exact mechanisms by which this gene affects hearing. For instance, in mice, experiments involving pigment cells have shown that pigmentation plays a role in maintaining fluid in ear canals. Animals that lack the pigment also lack ear canal fluid, which causes their ear canals to collapse. In turn, this collapse contributes to degeneration of the auditory nerves, which results in deafness (Sunquist, 2007).

Antagonistic Pleiotropy

Not all instances of pleiotropy are so straightforward, however. For example, in humans, the *p53* gene directs damaged cells to stop reproducing, thereby resulting in cell death. This gene helps avert cancer by preventing cells with DNA damage from dividing, but it also suppresses the division of stem cells, which allow the body to renew and replace deteriorating tissues during aging (Rodier *et al.*, 2007). This situation is therefore an example of antagonistic pleiotropy, in which the expression of a single gene causes competing effects, some of which are beneficial and some of which are detrimental to the fitness of an organism. The idea of antagonistic pleiotropy is central to the theory of aging proposed by American biologist G. C. Williams in 1957. In particular, Williams suggested that while some genes, like *p53*, increase the odds of successful reproduction and fitness early in life, they actually decrease fitness later in life. Moreover, because the gene's harmful effects appear after reproduction is complete, the gene is not eliminated through natural selection.

Yet another example of antagonistic pleiotropy can be found in *Drosophila*. In their research, scientists Carla Sgrò and Linda Partridge (1999) observed that flies with high fecundity early in their lives also had decreased lifespans. Based on these observations, Sgrò and Partridge suggested that aging in *Drosophila* evolved in response to the damaging effects of reproduction earlier in life. It is still not known exactly which genes determine this fecundity–mortality connection. Nevertheless, this example highlights the idea that antagonistic pleiotropy can be a trade-off between beneficial and detrimental effects.

Pleiotropy in Humans

As touched upon earlier in this article, there are many examples of pleiotropic genes in humans, some of which are associated with disease. For instance, Marfan syndrome is a disorder in humans in which one gene is responsible for a constellation of symptoms, including thinness, joint hypermobility, limb elongation, lens dislocation, and increased susceptibility to heart disease. Similarly, mutations in the gene that codes for transcription factor TBX5 cause the cardiac and limb defects of Holt–Oram syndrome, while mutation of the gene that codes for DNA damage repair protein NBS1 leads to microcephaly, immunodeficiency, and cancer predisposition in Nijmegen breakage syndrome.

One of the most widely cited examples of pleiotropy in humans is phenylketonuria (PKU). This disorder is caused by a deficiency of the enzyme phenylalanine hydroxylase, which is necessary to convert the essential amino acid phenylalanine to tyrosine. A defect in the single gene that codes for this enzyme therefore results in the multiple phenotypes associated with PKU, including mental retardation, eczema, and pigment defects that make affected individuals lighter skinned (Paul, 2000).

The phenotypic effects that single genes may impose in multiple systems often give us insight into the biological function of specific genes. Pleiotropic genes can also provide

us valuable information regarding the [evolution](#) of different genes and gene families, as genes are "co-opted" for new purposes beyond what is believed to be their original function (Hodgkin, 1998). Quite simply, pleiotropy reflects the fact that most proteins have multiple roles in distinct [cell](#) types; thus, any genetic change that alters gene expression or function can potentially have wide-ranging effects in a variety of tissues.

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