BASIC

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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.

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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.

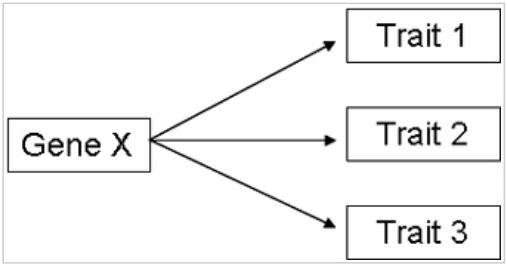

Figure 1: Diagram of pleiotropy.
A pleiotropic gene is a single gene that controls more than one trait.

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 2: A chicken with the frizzle gene

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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Phenotype Variability: Penetrance and Expressivity

By: Ilona Miko, Ph.D. (*Write Science Right*)

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Sometimes, identical genes will produce different expression patterns. Why? Geneticists are now examining the "penetrance" and "expressivity" of genotypes and their phenotypes.

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Dominance relationships between alleles for a given trait can impact phenotypic ratios, but interactions between different genes can also impact phenotype. Such traits that result from the interaction among multiple genes and their environment are called complex traits. So, given a specific trait, how can we tell whether it is complex? One way to recognize a complex trait is through inconsistent inheritance patterns in successive generations. For example, a dominant trait might skip an entire generation yet be expressed in the subsequent generation. How is this possible? The answer to this question lies in the concepts of penetrance and expressivity.

Penetrance

When studying the relationships between genotype and phenotype, it is important to examine the statistical occurrence of phenotypes in a group of known genotypes. In other words, given a group of known genotypes for one trait, how many identical genotypes show the related phenotype? You might be surprised to learn that, for some traits, the phenotype might not occur as often as the genotype. For example, say everyone in population W carries the same allele combinations for a certain trait, yet only 85% of the population actually shows the phenotype expected from those allele combinations. The proportion of genotypes that actually show expected phenotypes is called penetrance. Thus, in the preceding example, the penetrance is 85%. This value is calculated from looking at populations whose genotypes we know.

In fact, large population studies are necessary for measuring penetrance, and studies of penetrance help us predict how likely it is that a trait will be evident in those who carry the underlying alleles. In general, when we know that the genotype is present but the phenotype is not observable, the trait shows incomplete penetrance. Basically, anything that shows less than 100% penetrance is an example of incomplete penetrance. Therefore, although the penetrance of a trait is a statistically calculated value based on the appearance of a phenotype among known genotypes, incomplete penetrance is simply a qualitative description about a group of known genotypes.

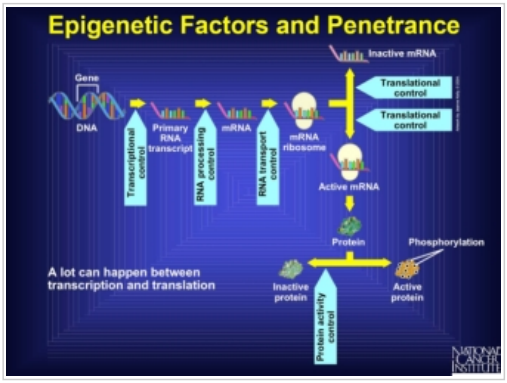

Figure 1: Epigenetic factors.

Genes can affect the final protein product of another gene by interfering during the transcription and translation process. Jeanne Kelly/National Cancer Institute.

Figure Detail

A specific example of incomplete penetrance is the human bone disease osteogenesis imperfecta (OI). The majority of people with this disease have a dominant mutation in one of the two genes that produce type 1 collagen, *COL1A1* or *COL1A2*. Collagen is a tissue that strengthens bones and muscles and multiple body tissues. People with OI have weak bones, bluish color in the whites of their eyes, and a variety of afflictions that cause weakness in their joints and teeth. However, this disease doesn't affect everyone who has *COLIA1* and *COLIA2* mutations in the same way. In fact, some people can carry the mutation but have no symptoms. Thus, families can unknowingly transmit the mutation from one generation to the next through someone who carries the mutation but does not express the OI phenotype.

Incomplete penetrance examples such as OI demonstrate that even monogenic diseases do not have predictable expression patterns in a population. Is there a way to explain this unpredictability? Let's think about it. If two people have the same dominant mutation in *COL1A1*, why might only one of them actually display OI symptoms? Could it have to do with other genes that rescue the bad effect of a mutated collagen gene? Could it be that those who have OI simply express more mutated collagen than the person who is unaffected? To consider the possible explanations for incomplete penetrance, we have to remember how many steps there are between gene transcription and protein expression.

Note that the expression of other genes, such as transcriptional or translational regulators, can influence the final effect of a gene product. Anything that interferes with the pathway from transcription to protein activation is known as an epigenetic factor. Indeed, there are multiple points at which another gene product can intervene in the stages prior to the production of a protein. Interference at these stages might stop production entirely, create an altered form of the protein that might never be active, or do any number of other things that renders the gene silent. So, the final stage of an active protein reflects many different processes that lead to the amino acid sequence and ultimate protein shape, all of which can be interfered with by other genes. Furthermore, some genes can up- or downregulate rates of transcription, which changes the total amount of protein produced. Thus, genes that affect the final form and expression amount of another gene can be influential in the formation of the phenotype derived from the regulated gene (Figure 1).

So, if so many different possible modification points for a gene product exist, how can we narrow down the question of what causes incomplete penetrance? Interestingly, some scientists have actually tried to do this by observing how the genetic mutations that cause OI affect mice. These investigators inserted a mutated form of *COL1A1* into mice and bred them so that they all contained this mutation. The mice were affected in similar ways to those with human OI: Many had severe bone weakness and multiple bone fractures, even at birth. In fact, when the researchers examined the mouse bones closely, they found that 70% of mice with the mutated *COL1A1* gene showed evidence of OI (bone fractures); however, the remaining 30% appeared completely

normal. In these mice with no OI phenotype, there was the same amount of *COL1A1* expression as in those mice that did show the phenotype. Furthermore, the investigators used a purebred strain of mice that had little variability in their genomes to begin with. This means that the genetic context in which *COL1A1* was expressed did not vary among the mice studied. Yet, despite the fact that all the mice had extremely similar genomes and all of them expressed the same amount of *COL1A1*, 30% of them did not show any OI phenotype. These results continue to be perplexing.

Therefore, even the powerful experimental techniques currently available cannot explain penetrance. The two most popular explanations for incomplete penetrance, genetic background and variable expression levels, did not explain the lack of phenotype in 30% of the mice (Pereira *et al.*, 1994).

Expressivity

Individuals with the same genotype can also show different degrees of the same phenotype. Expressivity is the degree to which trait expression differs among individuals. Unlike penetrance, expressivity describes individual variability, not statistical variability among a population of genotypes. For example, the features of Marfan syndrome vary widely; some people have only mild symptoms, such as being tall and thin with long, slender fingers, whereas others also experience life-threatening complications involving the heart and blood vessels. Although the features of Marfan syndrome are highly variable, all people with this disorder have a dominant mutation in the gene coding for fibrillin 1, *FBN1*. However, it turns out that the position of the mutation in the *FBN1* gene is correlated with the severity of the Marfan phenotype. Researchers found that a mutation in one *FBN1* position is prevalent in families with severe symptoms, whereas a mutation in another position is prevalent in families with less severe symptoms. These findings are an encouraging clue as to how specific defects in the fibrillin 1 protein can account for the variable expressivity in Marfan syndrome (Li *et al.*, 2008).

Another example of expressivity at work is the occurrence of extra toes, or polydactyly, in cats. The presence of extra toes on a cat's paw is a phenotype that emerges in groups of cats who have interbred for generations. In fact, there are several well-known groups of these cats, such as those on Key West Island (known as "Hemingway's cats"), as well as those in breeding clusters in the eastern U.S. and shores of the British Isles (Figure 2). The first to report on this phenomenon was C. H. Danforth, who studied the inheritance of polydactyly among 55 generations of cats. He observed that the polydactyly phenotype showed "good penetrance, but variable expression" because the gene always causes extra toes on the paw, but the number of extra toes varies widely from cat to cat (Danforth, 1947). Through his breeding studies, Danforth found that although a dominant allele underlies the cause of polydactyly, the degree of polydactyly depends on the condition of adjacent layered tissues in the developing limb; that is, the expression of genes in tissues surrounding tissue that will become the toe determines the degree of polydactyly (Willier, 1974).

Figure 2: Hemingway's cat with polydactyly.

Because the gene for polydactyly always causes extra toes in cats, but the number of extra toes varies between individuals with the gene, polydactyly is considered an example of variable "expressivity."

Future Directions

The relationship between genotype and phenotype is not simple. Sometimes, dominant alleles can be silenced by other genes that minimize the appearance of the phenotype. In other cases, gene expression can be changed in subtle ways, yet it can have a large impact on phenotype. The exact causes of penetrance and expressivity are still not well understood. The more we learn about the molecular mechanisms governing genetic regulation, the more we can formulate and test hypotheses about how this variability arises.

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