What Is a Recessive Allele?

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ONE of the commonly misunderstood and misinterpreted concepts in elementary genetics is that of dominance and recessiveness of alleles. Many students in introductory courses perceive the idea that the dominant form of a gene is somehow stronger than the recessive form and, when they are together in a heterozygote, the dominant allele suppresses the action of the recessive one. This belief is not only incorrect but it can lead to a whole series of further errors. Students, for example, often erroneously conclude that because the dominant allele is the stronger, it therefore ought to become more common in the course of evolution.

There are other common misconceptions, among them that:

1) Dominance operates at the genotypic level.

2) Allelic families must have some order of dominance among the members.

3) Dominance is an all-or-none phenomenon.

4) The dominance relationship depends on some mysterious, unknown and perhaps unknowable force rather than on molecular and physiological events subject to exploration and explanation.

Gregor Mendel recognized that "hybrids," i.e. the F_1 generation of a cross between two purebred parents differing in one or more characteristics, are seldom exactly intermediate in appearance between the parents. In some cases, he says:

> [w]ith some of the more striking characters, those, for instance, which relate to the form and size of the leaves, the pubescence of the several parts, &c., the intermediate, indeed, is nearly always to be seen; in other cases, however, one of the two parental characters is so preponderant that it is difficult, or quite impossible, to detect the other in the hybrid. (Mendel 1950, p. 7)

Turning to the results of his own work, he continues:

> In the case of each of the seven crosses the hybrid-character resembles that of one of the parental forms so closely that the other either escapes observation completely or cannot be detected with certainty . . . . [T]hose characters which are transmitted entire, or almost unchanged in the hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the dominant [dominirende], and those which become latent in the process recessive [recessive]. The expression "recessive" has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrids, but nevertheless reappear unchanged in their progeny . . . (Mendel 1950, p. 8)

Two important concepts are presented here: (1) Statements about dominance and recessiveness are statements about the appearance of characters, about what is seen or can be detected, not about the underlying genetic situation; (2) The relationship between two alleles of a gene falls on a continuous scale from one of complete dominance and recessiveness to a complete lack thereof. In the latter case, the expression of both alleles is seen in either of two ways in the heterozygote.

The actual situation is, however, somewhat more complicated than Mendel knew. Here, three propositions will be briefly analyzed: (1) There exists a full spectrum of possible relationships between two alleles of a gene. (2) The nature of the relationship sometimes depends upon the level of analysis used. (3) The cause of the relationship can sometimes be analyzed in great detail. For the last of these, we will return to one of Mendel's cases, that of the wrinkled pea.

The Spectrum of Relationships

Generally, textbooks speak of four types of dominance-recessiveness relationships: (1) complete dominance, (2) codominance, (3) partial or incomplete dominance, and (4) lack of dominance, although some do not differentiate among all these categories, particularly the last two. Complete dominance occurs where the offspring of a mating between two differing, purebred strains "resembles that of one of the parental forms so closely that the other either escapes observation completely or cannot be detected with certainty" (Mendel 1950, p. 7). In more modern terms, there is complete dominance when the phenotype of the heterozygote cannot be distinguished from that of the dominant parent. A classic example is the case of the round and wrinkled peas where the round heterozygotes are as round as the round homozygotes (Mendel 1950).

Codominance exists when the phenotypic expression of both alleles is clearly and separately seen in the heterozygote. A good example here is the human

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blood type AB, the phenotype produced by the simultaneous action of the alleles I^A and I^B. Partial or incomplete dominance exists if the heterozygote shows a phenotype more or less, but not exactly, intermediate between the two parental phenotypes, as where pink carnations result from the mating of red flowered with white flowered plants (Klug & Cummings 1986). Finally, if the heterozygote's character state is precisely intermediate between that of the two parental character states, we may even speak of a lack of dominance. The differences among these relationships—codominance, partial or incomplete dominance, and lack of dominance—are small and may not be worth emphasizing in introductory courses.

Two important ideas follow from an understanding of these relationships between pairs of alleles. First, the dominant-recessive relation may be considered as on a scale from complete to nonexistent (Strickberger 1985). Second, it is sometimes possible to calculate the degree of dominance exercised by each allele as in the form:

$$\text{Degree of Dominance} = \frac{(\text{Heterozygous value}) - (\text{recessive value})}{(\text{Dominant value}) - (\text{recessive value})}$$

(Stansfield 1977). As a simple example, consider a pair of purebred plant lines where one averages one meter in height and the other three. Assume that the heterozygotes resulting from a cross of these two lines average 2.5 meters in height. The heterozygotes are closer in height to the tall parents: The allele producing the greater height exerts 2.5-1/3-1 or 3/4 of a complete dominance effect on the height of the heterozygotes. Contrary to the belief among some inexperienced students, the dominance-recessive relationship is neither inevitable nor absolute. The relationship neither has to exist (and often indeed does not) nor must the dominant allele always completely prevent the expression of the recessive one.

The Level of Analysis

Since dominance and recessiveness refer essentially to an organism's phenotype, we should not be surprised that the relationship may be different at different levels of analysis between phenotype and genotype. This is well illustrated in the human autosomal recessive condition usually called Tay-Sachs disease or, more descriptively, GM_2-gangliosidosis B variant (McKusick 1988, entry no. 27280). The cause of this condition is the virtual absence of an enzyme, hexoseaminidase A (Hex A) in the affected homozygotes (Thompson & Thompson 1979). The normal allele is conventionally designated as TS; the one which, in the homozygous state, causes the disease is designated as ts. Carriers (heterozygotes, genotype TS/ts) have usually 40–60 percent of the enzyme activity of normal, homozygous persons (genotype TS/TS) (Bergsma 1979). In everyday life, health, longevity and fertility the heterozygotes cannot be distinguished from the normal homozygotes. The homozygotes ts/ts die in infancy or early childhood (McKusick 1988).

Is, then, Tay-Sachs disease caused by a recessive allele? Since the gross phenotypes of the heterozygotes and homozygote normals cannot be distinguished, it is so by Mendel's criterion. Yet, the heterozygotes are easily distinguished from the homozygote normals (and from the affected persons) by a relatively simple serum enzyme test (Thompson & Thompson 1979). Whether the allele yielding the "normal" phenotype is dominant relative to the allele causing the disease depends upon the level of analysis.

When alleles of a gene are compared by DNA nucleotide sequencing, no two alleles are in a recessive-dominant relationship. At this level of analysis every heterozygote must differ from either homozygote since, by the very definition of "allele," the base sequences of the two homologous chromosomes must differ in some way. Again, the dominant-recessive relationship is not one fundamental to the nature of genes but depends upon the level of analysis and the degree of detail to which we know the genetic situation. One might well argue that the concept of the relationship disappears entirely at the level of the DNA (or RNA) base sequences.

The Causes of Dominance

A heterozygote may display in its phenotype the action of one of its pair of alleles for any of several reasons. Sometimes the recessive gene may not direct the synthesis of an RNA or protein product; sometimes the gene product is defective or markedly low in activity. In other cases, especially those where the recessive allele, when homozygous, produces the normal phenotype, the dominant allele may be producing a structural protein incapable of proper function by itself or with the product of the recessive allele.

A case of the last type where, for structural reasons, the abnormal allele acts as a dominant relative to the normal allele is illustrated by Ehlers-Danlos syndrome type IV (McKusick 1988, entry no. 13005). The normal allele directs the synthesis of a normal polypeptide. This polypeptide is combined with others to form the collagen molecule of connective tissues. The abnormal allele causes the production of an abnormal polypeptide that prevents proper formation of the whole collagen protein from the polypeptide subunits. Superti-Furga and Steinman (1988)

have demonstrated a deletion of the DNA coding for the alpha subunit of one type of collagen in the fibroblasts of at least one patient with this condition. As might be expected in a heterozygote, both normal and abnormal forms of the corresponding mRNA were present. The collagen formed by the assembly of correct and incorrect subunits had a reduced thermal stability, was secreted less efficiently and was processed abnormally in the cell. This seems to explain the unusually extensible and weak connective tissue found in this form of the Ehlers-Danlos syndrome.

The Case of the Wrinkled Peas

Perhaps the most common reason for the recessive action of one allele relative to another is that an allele yields either no product or a product with very little or no activity. Even if a relatively or completely inactive protein is produced, it often does not interfere with the action of a normal protein. Thus the heterozygote exhibits only the character due to the allele directing the production of the functioning protein. The allele yielding the functioning product is completely dominant because its product is the only one of the two affecting the phenotype.

This relationship between an allele yielding a functional protein and one that does not is well illustrated by Mendel's (1950) famous case of the wrinkled (genotype rr) and round (genotypes RR or Rr) peas. This case has now been analyzed to an exquisite level of detail. The wrinkling of the peas in the recessive homozygous plants appears to result from a relatively high concentration of the sugar sucrose in the developing seed. This, in turn, causes an increased water content and stretched seed coat. When the usual drying occurs, wrinkling results.

The relatively high sugar concentration is due to a defect in starch-branching enzyme I (SBEI) whose normal function is to produce a branch-chain form of starch (amylopectin). Some straight-chain starch (amylose) is also produced. When SBEI is deficient, some sucrose is not converted to starch and an excess accumulates (Fincham 1990). Bhattacharyya et al. (1990) have shown by cloning that the mRNA transcribed from the r allele is longer than that from the R allele and is also less abundant. The difference is due to an extra 800 DNA base pairs inserted into the r allele. The sequence with this insert produces a poorly functioning or nonfunctional SBEI molecule.

When tested against the genomic DNA from plants of either homozygous genotype (RR or rr), a particular segment of the dominant, normal allele hybridized with a single DNA segment. Somewhat surprisingly, however, the corresponding segment from the recessive allele hybridized with 30 or more short fragments in the DNA from plants of either genotype.

That the gene fragment derived from rr plants would bind to 30 or more sequences in the DNA of plants of either genotype indicates that the extra piece of DNA in the r allele might be an inserted fragment, similar or identical to fragments inserted elsewhere in the genome. Indeed, the piece was shown to have inverted tandem repeats and to be flanked by a tandem duplication eight base pairs long, two items commonly found in and around inserted fragments. Sequence analysis of the terminal repeats showed them to be quite similar to those of transposable elements that are capable of becoming inserted into genes of maize, snapdragon and parsley.

However, the size of the inserted element in the r allele is too short to carry the usual apparatus needed for excision and transposition to another gene. The inserted sequence of DNA nucleotides does not appear to be a complete movable element. Similar inserted sequences in maize can only move if a full-sized version, constituting a complete transposable element, is also present on the same chromosome. But the full-sized version does not appear to exist in wrinkled peas, making the insertion essentially a permanent one. (Were it to be excised, a part of the tandem repeats would likely be left behind, probably causing a frameshift mutation and leaving the allele still nonfunctional). Quite possibly, a part of what was originally a transposable element was lost by mutation long ago.

We cannot now be certain that Mendel's wrinkled peas had the same genetic arrangement as those studied by Bhattacharyya et al. (1990), although it seems very likely that they did. If so, we have finally learned, a century and a quarter later, just what caused the F_1 plants bred from Mendel's pure round and pure wrinkled stocks to look like their round parents. More importantly, we now have further justification for thinking that the dominant-recessive relationship between alleles does not involve any direct interaction between them or, as one of my students put it, "One allele does not sit on the other and tell it to be quiet."

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