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Short Review

The evolution of dominance

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The evolution of dominance has been subject to intensive debate since Fisher first argued that modifiers would be selected for if they made wild-type alleles more dominant over mutant alleles. An alternative explanation, put forward by Wright, is that the commonly observed dominance of wild-type alleles is simply a physiological consequence of metabolic pathways. Wright's explanation has gained support over the years, largely ending the debate over the general recessivity of deleterious mutations. Nevertheless there is reason to believe that dominance relationships have been moulded by natural selection to some extent. First, the metabolic pathways are themselves products of evolutionary processes that may have led them to be more stable to perturbations, including mutations. Secondly, theoretical models and empirical experiments suggest that substantial selection for dominance modifiers exists during the spread of adaptive alleles or when a polymorphism is maintained either by overdominant selection or by migration-selection balance.

Keywords: balanced polymorphism, deleterious mutations, dominance modifiers, metabolic pathways, overdominance, patchy environment.

The puzzle of dominance

The basis of dominance relationships has generated a long-standing and contentious debate in genetics and evolutionary biology. Sixty years after the extensive debate between Fisher and Wright on the origin of dominance (Provine, 1986), the extent to which dominance levels have been modified by evolution is still being explored (Savageau & Sorribas, 1989; Grossniklaus *et al*., 1996; Porteous, 1996; Mayo & Bürger, 1997; Otto & Bourguet, 1999). The evolution of dominance was proposed initially by Fisher (1928) to explain the observed partial or complete dominance of wild-type alleles to the overwhelming majority of deleterious mutations. He suggested that most deleterious mutations were originally codominant and became progressively recessive through the accumulation of modifier alleles at other loci. Wright (1929, 1934) challenged this explanation, arguing that the strength of selection on modifiers of dominance is exceedingly small, in the order of the mutation rate. Instead Wright advocated a physiological explanation for dominance, based on the idea that many metabolic pathways have a safety margin that allows them to function despite small changes in the component enzymes. The interchange between Fisher and Wright on dominance had far-reaching ramifications: Fisher and Wright were essentially arguing over the power of selection (Provine, 1986). Fisher viewed the evolution of dominance as vindicating his view that minute selective pressures on a given trait could achieve important effects given sufficient time. Wright instead argued that extremely weak selection pressures are very likely to be overwhelmed by other effects of the gene on fitness or by the effects of random drift, in line with Wright's general view of evolution.

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Wright's theory of dominance has since gained favour among biologists for several reasons. Kacser & Burns (1981) developed a detailed and modern version of Wright's physiological explanation, based on metabolic control theory. The key consequence of this theory is that most enzymes have little influence on the flux through a pathway unless their activity level decreases to become limiting. Therefore, although the absence of an enzyme might be devastating, halving the enzyme activity is likely to have little effect on the overall metabolic flux. Consequently, mutations will generally have a much more severe effect when homozygous than when heterozygous. Furthermore, strong evidence has accumulated that mutation rates per year per base pair are very low, ranging between 10^{-8} and 10^{-11} in eukaryotes (reviewed by Drake *et al*., 1998). These findings confirm Wright's claim that most mutations would be exceedingly rare and, hence, would not generate much selection for dominance. Fisher's explanation for dominance subsequently received two substantial blows. The first came from Charlesworth (1979), who noted that Wright's model, but not Fisher's, could explain the observation that wild-type alleles are more dominant when paired with lethal mutations than with minor-effect mutations. The second criticism was made by Orr (1991), who argued that dominance must be an inherent attribute of wild-type alleles rather than an evolved phenomenon. He could show that wild-type alleles in a haploid organism display dominance in artificially constructed diploids, even though dominance had little or no previous opportunity to evolve. A similar argument was given by Haldane (1939) who found that despite a decreased intensity of selection for dominance in self-fertilized populations, dominance is often more common in inbred than in outbred plant species.

Consequently, the widespread occurrence of recessivity is now accepted to be a by-product of the kinetic structure of

enzymatic pathways rather than the outcome of evolutionary modification (Keightley, 1996; Porteous, 1996). Does this mean that dominance relationships do not evolve? In fact the physiological basis of dominance is not necessarily at odds with its potential evolution (Mayo & Bürger, 1997) and the question still remains: to what extent has dominance evolved?

Selection on metabolic pathways

One question that has arisen repeatedly is whether or not dominance of the wild-type is an inevitable consequence of the kinetic structure of enzymatic pathways. Several authors (Cornish-Bowden, 1987; Savageau & Sorribas, 1989; Savageau, 1992; Grossniklaus *et al*., 1996) have examined more complex metabolic pathways and concluded that dominance of the wild-type is not always the case.

Cornish-Bowden (1987) showed that pathways in which all enzymes are present in barely sufficient amounts (i.e. with no safety margin) are theoretically possible. In such systems, relatively small changes in one enzyme concentration would create large changes in the concentration of one or more intermediate metabolites and could therefore be lethal. Cornish-Bowden (1987) pointed out that the fact that such pathways do not naturally occur must be a consequence of selection, not mathematics. Savageau & Sorribas (1989) showed that experimental and theoretical biochemical systems can be sensitive to small changes in enzyme amounts. They rejected Kacser and Burns's theory as a general explanation for dominance relationships, claiming instead that natural selection has made biochemical systems less prone to the influence of altered enzyme levels (Savageau & Orribas, 1999). Finally, Grossniklaus *et al*. (1996) recently found that in randomly constructed pathways with non-linear enzyme kinetics, the end-product flux can be quite sensitive to changes in enzymatic activity. They concluded that 'the phenomenon of dominance cannot be a trivial "default" consequence of physiology but ….[must] have been moulded by natural selection'.

Haldane (1930) was the first to argue that biological systems evolved in such a way as to provide metabolic systems with greater safety margins. He wrote: 'If A1 A1 can just oxidize all of a certain substrate as fast as it is formed, its inactivation will produce a zygote A1a which can only oxidize about half. If now A1 mutates to A2, which can oxidize at twice or thrice the rate of A1, if necessary, no effect will be produced, i.e. A1 A2 and A2 A2 zygotes will be indistinguishable from A1 A1. But A2a will be normal. Hence A2a zygotes will have a better chance of survival than A1a and A2 will be selected'. Indeed, a safety margin may be selectively favoured even when mutant alleles are not present. Wright (1929) observed: 'Because of extreme environmental disturbances [a margin of safety] is advantageous'. An example of selection favouring excess enzyme activity in the face of environmental fluctuations was provided by Forsdyke (1994). He noted that the heat-shock response is induced by a sudden change in various physical or chemical features such as an increase in temperature. The response is detected as a rapid increase in the intracellular concentrations of evolutionarily conserved heat-shock proteins, and is accompanied by a decrease in the concentrations of most normal proteins. Therefore, selection may have favoured excess enzyme activity under normal conditions to ensure sufficient enzyme activity when protein concentrations have decreased following a heat-shock response.

To test whether or not a margin of safety has been selected for will be a difficult task as its existence today is no more than the consequence of past selection pressures. Moreover, the benefits of having dominant wild-type alleles may have driven the evolution of increased margins of safety (as proposed by Haldane), or they may simply be an incidental outcome of selection to maintain cell function under extreme environmental circumstances (as suggested by Wright and Forsdyke). Whatever the origin of this margin of safety, its occurrence explains why in most metabolic pathways deleterious mutations are naturally recessive. To further investigate the evolution of metabolic pathways will, therefore, require us to focus on cases where margins of safety are not already in place, as is the case for some dominant lethal mutations responsible for a number of human disorders (Wilkie, 1994) and for some adaptive mutations (Bourguet & Raymond, 1998).

Selection on modifiers of dominance

A separate avenue of research has explored those conditions under which modifiers of dominance would be selected for appreciably. The original modifier model proposed by Wright (1929) assumes that the primary selected locus is held at a mutation-selection balance between the favoured allele A and a mutant allele a. Wright studied the dynamics of a dominance modifier allele M that suppresses the fitness loss of Aa heterozygotes (s, selection coefficient, h, dominance level; $s > 0$, $0 \leqslant h \leqslant 1$):

	AA	Aa	aa
MM	1	1	$1 - s$
Mm	1	1	$1 - s$
Mm	1	$1 - hs$	$1 - s$

Results from this and subsequent models have found that the selective advantage of the modifier allele M need only be very small, of the same order of magnitude as the mutation rate in most cases (Wright, 1929; Haldane, 1930; Ewens, 1966; Feldman & Karlin, 1971; Bürger, 1983a,b,c).

A second category of models (Haldane, 1956; Parsons & Bodmer, 1961; Ewens, 1966; O'Donald, 1967; Bürger, 1983a,b,c; Wagner & Bürger, 1985) tracks the evolution of dominance when alleles at the primary locus evolve towards a new equilibrium. Results show that, when a favourable allele spreads through a population, selection on a modifier can be very efficient. However, the sweep of the favourable allele may occur too fast for the evolution of dominance to proceed very far. Furthermore, modifier alleles that alter the dominance level of an advantageous allele may not be present within a population during this window of opportunity, and, even if present, their frequency may not increase sufficiently before fixation of the advantageous allele (Haldane, 1956).

A third class of models has been developed, based on the idea that dominance is more likely to evolve when heterozygotes are

maintained at high frequencies for extended periods of time. This situation may occur when the primary selected locus constitutes a selectively maintained polymorphism. Although this is the most favourable situation for the evolution of dominance it has remained the least explored theoretically (but see Clarke, 1964 and Charlesworth & Charlesworth, 1975). Recently Otto & Bourguet (1999) have analysed the complete two-locus model (with one selected locus and one modifier locus) suggested by Feldman & Karlin (1971). This study examined the strength of selection on dominance modifiers when a balanced polymorphism is maintained either by overdominant selection or by migration-selection balance. At an overdominant equilibrium, a modifier allele that increases heterozygote fitness can always invade a population. While rare, the modifier allele will experience selection of a strength comparable to that at the primary selected locus. The spread of a modifier that increases dominance is hastened by tighter linkage while the modifier is rare but is hampered once the modifier becomes common. This occurs because, at the end of the selection process, the increase in frequency of the modifier depends on the spread of the haplotype which has the smaller selection coefficient. When a polymorphism is maintained by migration between patches in which different alleles at the primary locus are favoured, a modifier that increases the fitness of heterozygotes in each patch is positively selected for when rare. Even if the modifier increases heterozygote fitness in one patch and decreases it in the second patch, the modifier can invade, as long as it increases a weighted average of the heterozygotes fitness. Again, the strength of selection is comparable to that at the primary selected locus. Interestingly, the evolution of dominance causes the locally deleterious allele to become more recessive in each patch, increasing the fitness of the heterozygotes. This, in turn, causes heterozygotes to become more frequent and increases the opportunity for dominance evolution in a self-reinforcing process. Therefore, the evolution of dominance should be expected whenever a substantial polymorphism is maintained by either overdominance or migration.

Spatial heterogeneity and selection for dominance

A large study of butterfly mimicry has given several examples of evolutionary modification of dominance (reviewed by Mayo & Bürger, 1997). However, the industrial melanism in the peppered moth *Biston betularia* is still one of the best model cases. In Britain the melanic form of this moth became more common because light-coloured individuals were counter-selected in industrial areas where soot blackened the tree trunks. In the mid-1800s during the early stages of selection, melanic forms were rare and presumably heterozygotes. However, these early specimens were not completely black; instead they contained many more white markings than heterozygous melanic forms in this century, suggesting that increased dominance of the melanic form evolved over this time period (Haldane, 1956). Mayo & Bürger (1997) have suggested that selection of the modifier occurred during the spread of the adaptive melanic allele. Mani (1980) showed that spatial variation in selection (probably caused by varying degrees of industrialization) better explains the observed frequency distribution of the melanic allele. Therefore, selection of dominance modifiers probably occurred when the melanic form was maintained at an intermediate frequency rather than during a straight sweep of this adaptive allele.

Consequences of man-made changes such as pesticide resistance represent an excellent situation to study how dominance may evolve. First, the genes and resistance alleles involved are often known, including some loci that alter dominance relationships. Secondly, the selection pressure on the primary allele can sometimes be estimated (Lenormand *et al*., 1999). Finally, resistance alleles, which are positively selected for in treated areas, are often counter-selected in untreated areas due to associated fitness costs. The resulting balanced polymorphism increases the possibility of selection for dominance modifiers. Dominance relationships of pesticide resistance have been investigated in the mosquito *Culex pipiens*. In this species, there is a positive correlation between the dominance of the insecticide resistance conferred by insecticide resistance alleles at the acetylcholine esterase gene and the amount of this enzyme (Bourguet *et al*., 1997). The data suggest that the expression of the acetylcholine esterase gene is regulated by either neighbouring or distant sites. In this system, dominance levels are likely to evolve because (1) heritable variation in acetylcholine esterase activity was found, (2) pesticide applications are heterogeneous in space, providing a patchy environment with treated and untreated areas (Lenormand & Raymond, 1998), and (3) insecticide-resistant alleles at the acetylcholine esterase locus are associated with important fitness costs (Chevillon *et al*., 1997).

More generally, alleles that confer an advantage in a new environment (e.g. a new parasite, climate, or chemical challenge) may often be associated with a fitness cost in the previous environment (e.g. Carrière *et al*., 1994, and Bergelson & Purrington, 1996). Furthermore, such environmental changes usually occur, at least initially, in limited regions, creating spatial heterogeneity in selection. Hence, I believe that adaptation may often result in balanced polymorphisms offering an opportunity for the evolution of dominance.

Conclusions and perspectives

The debate over whether the general recessivity of deleterious mutations represents the result of the selection of modifiers has been largely resolved (Mayo & Bürger, 1997). There is a consensus that mutant recessivity usually arises as a side-effect of the margin of safety built into most metabolic pathways. However, whether or not this safety margin results from natural selection remains controversial. Moreover, the metabolic control theory may not be generalized to include the many genes that are not coding for metabolic enzymes. Finally, theoretical models indicate that in particular cases, such as when an adaptive allele spreads through a population or when a polymorphism is selectively maintained, the selection pressure for dominance modifiers can drive them to high frequencies and sometimes to fixation.

Therefore, although Wright's explanation has gained favour over the years, there is growing evidence that an evolutionary model is also needed to explain the entire range of dominance relationships that are currently observed. As dominance evolution was thought to be ineffective, relatively few empirical

studies have been undertaken. To better understand this phenomenon and its extent, further studies are needed, for example, research should be undertaken into how modifiers of dominance act. Geneticists have focused their attention on suppressors and enhancers of phenotypic mutations. Although these mutations are generally deleterious, their fitness impact (s) and the dominance of their fitness effect (h) have not always been estimated and the influence of the suppressors on s and h are rarely determined. Besides, the outcome of theoretical models also depends on parameters such as the linkage of the dominance modifiers with the primary locus, their own fitness costs, and their initial frequency in natural populations. Little is known concerning the occurrence and frequency of dominance modifiers in natural populations (but see Alvarez & Zapata, 1996). Therefore, although dominance levels are suspected to have evolved in response to visual predation in Lepidopteran species and to pesticide treatments in some pest species, the spread of such modifiers remains to be studied. New experiments could be performed to determine whether, and to what extent, these modifiers are selected for. Only empirical studies will bring us closer to assessing the importance of natural selection on dominance relationships.

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