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Evidence for Fisher's dominance theory: how many 'special cases'?

Sylvain Billiard* **and Vincent Castric***

Université Lille Nord de France, USTL, GEPV, CNRS, FRE 3268, F-59650 Villeneuve d'Ascq, France

Dominance, its genetic basis and evolution has been at the heart of one of the most intense controversies in the history of genetics. For more than eighty years the existence of dominance modifiers, genetic elements controlling dominance–recessivity interactions, has been suggested as a theoretical possibility, but the modifier elements themselves have remained elusive. A recent study of the self-incompatibility locus in flowering plants provided the first empirical evidence for such genetic elements: small non-coding RNAs that control dominance–recessivity by mediating methylation of the promoter of the recessive allele. Theory has shown that several biological situations are favorable for the evolution of dominance modifiers. We argue that the elucidation of this mechanism of dominance opens up new research avenues that could lead to uncovering dominance modifiers in other genetic systems, such as genes controlling Batesian and Müllerian mimicry or host–parasite interactions, thereby shedding light on the generality of the proposed mechanism.

An apparent consensus about the mechanisms underlying dominance

Dominance, one of the earliest genetic phenomena elucidated in the classical investigations of Mendel [1], occurs when phenotypic expression of one of the two alleles in a heterozygous locus is masked. Dominance (Glossary) is one of the most basic properties of inheritance mechanisms and determines the way in which traits are expressed in the progeny by linking genotype to phenotype in heterozygous individuals. It is thus of major evolutionary importance for the dynamics of adaptation [2]. However, the genetic basis and evolution of dominance have been among the most highly debated topics in evolutionary genetics (reviewed in [3]). In the 1920s the issue strongly divided Sir Ronald A. Fisher and Sewall Wright, the two founding fathers of population genetics. Fisher [4] proposed that observed dominance relationships are the result of the evolution of dominance modifiers, in other words genetic elements controlling dominance interactions between alleles at other genes. Although Wright [5] did not fully dismiss the possibility that such genetic elements might indeed exist, he proceeded to quantify the expected intensity of selection on them and showed that, at least in the case of recessive deleterious mutations, it is expected to be of the same order of magnitude as the mutation pressure, in other words 'decidedly small', and thus unlikely to be of substantial evolutionary importance. Fisher's dominance modifier theory was claimed to have been falsified by the observation that wild-type alleles tend to be dominant even in *Chlamydomonas,* which spends most of its life cycle as a haploid and in which selection on heterozygote genotypes would thus be inefficient [6] and by experimental evidence on the heterozygous effects of mutations affecting viability in *Drosophila* [7]. Soon after the appearance of Fisher's initial paper, Wright [5,8] and Haldane [9] proposed an alternative general physiological mechanism based on enzymatic activity, in which dominance would be a simple by-product of the typical saturating shape of the relationship between gene activity and the phenotype. This model has been extensively reviewed elsewhere, and readers are referred to [3] and [10] for a more detailed description. Importantly, this elegant explanation accounts for dominance and its evolution without needing to invoke the hypothetical 'dominance modifiers' proposed by Fisher [4], and notably accounts for the early observation that most deleterious mutations tend to be recessive. Subsequently, several experiments verified key predictions of this theory, such as the negative relationship between selective effect and dominance of mutations in yeast [11,12].

Over the years, Wright's [8] physiological explanation and its modern formulation [13] has gained favor, and now becomes so widely accepted that it has practically achieved the status of a paradigm [6]. In fact, Fisher agreed that any factor altering the expression level of a given enzyme could

Glossary

Balancing selection: a variety of selective processes by which multiple alleles are actively maintained at high frequencies in a population.
Batesian mimicry: a phenomenon whereby a harmless palatable mimic species has evolved to imitate the warning signals of a poisonous model species directed at a common predator.
Codominance: a genetic phenomenon whereby neither of the two alleles in a heterozygous genotype is masked at the phenotypic level. Codominance can result in either intermediate phenotypes (such as for quantitative traits) or in equal expression of both alleles (such as in SI genes).
Dominance: a genetic phenomenon whereby phenotypic expression of one of the two alleles in a heterozygous locus is masked.
Dominance modifier: a genetic element controlling dominance–recessivity interactions between alleles at another locus.
Dominance-recessivity interactions: An allele A is dominant with respect to a recessive allele B when, at the phenotypic level, genotype AB more closely resembles genotype AA than genotype BB.
Müllerian mimicry: a phenomenon whereby two or more harmful species have evolved identical warning signals to advertise their toxicity to a common local set of predators.
Overdominance: a situation whereby heterozygous individuals have a higher fitness than homozygous individuals.

Corresponding author: Billiard, S. (sylvain.billiard@univ-lille1.fr)
* alphabetical order.

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indeed be considered as dominance modifier [14], implying that Wright's physiological theory would be compatible with many observed cases of dominance evolution. Hence, the issue of dominance has generally been thought of as being resolved and hardly worth further consideration [15]. But beyond this apparent consensus a central question pertaining to Fisher–Wright dispute remains unresolved, namely are there in fact biological situations in which genetic elements function to control dominance–recessivity interactions between alleles at other genes? In other words, do dominance modifiers *per se* exist, and if so what is their molecular nature and how ubiquitous are they?

82 years after Fisher: a dominance modifier has been identified!

A recent landmark paper [16] provided the first empirical evidence of a type of genetic element that can indeed be considered to be a dominance modifier *per se*. Embedded within the gene cluster controlling self-incompatibility (SI) in *Brassica*, a *trans*-acting small RNA acting as dominance modifier of the gene controlling pollen specificity was identified [16]. SI is a genetic mechanism based on self-pollen recognition and rejection, enabling flowering plants to avoid selfing and enforcing outcrossing (Figure 1). In the Brassicaceae, dominance in pollen is controlled at the mRNA level through monoallelic transcriptional silencing of recessive alleles when present together with a dominant allele in a heterozygous genotype [17]. This silencing is mediated by methylation in the anther tapetum of a 300 bp region spanning the promoter of the recessive allele [18], and this suppresses mRNA production of the recessive allele, but not that of the dominant allele. As a result, the protein from the dominant haplotype (but not that of the recessive haplotype) is deposited at the pollen surface, thereby providing a simple mechanism for the dominance–recessivity interaction. Until recently the genetic elements controlling this methylation remained elusive. It has now been demonstrated that this mechanism is controlled at the genetic level by a *trans*-acting small RNA (Figure 2) [16]. The *trans*-acting small RNA is encoded by a genomic sequence that has high nucleotide similarity to the promoter of the recessive alleles of the pollen gene and is located in the flanking region of dominant alleles. This sequence (dubbed *Smi* for *SP11* methylation inducer [16]) is specifically expressed in the anther tapetum and is processed into 24-nucleotide RNA and is predicted to target the 5' promoter region of recessive alleles. Transformation experiments showed that this small RNA is sufficient to mediate methylation of the promoter of the recessive allele and thereby result in its monoallelic silencing [16]. Although the details of the mode of action of this small RNA remain incompletely described [19], this genetic element corresponds exactly to the type of dominance modifier originally hypothesized by Fisher in 1928. Indeed, Wright's physiological explanation would be ineffective in this case because this small RNA specifically controls the interaction between alleles in heterozygotes without affecting the expression level in homozygotes.

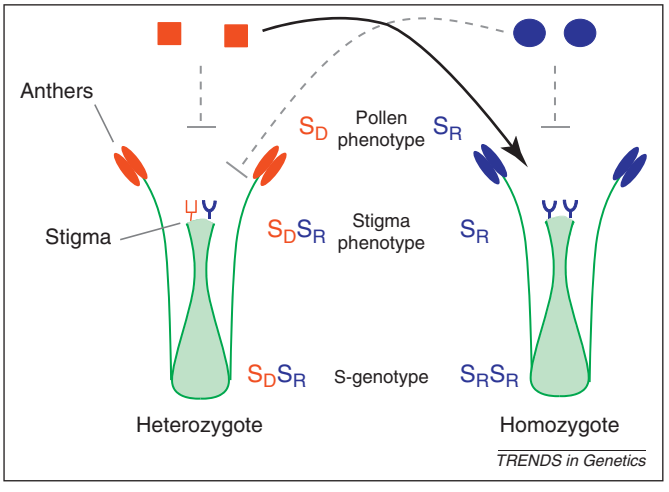

Figure 1. Dominance in sporophytic self-incompatibility in the Brassicaceae. Plants are hermaphrodite and produce both pollen and ovules. The SI phenotype is determined by a single genetic locus and allows the expression of recognition proteins at the surface of stigma and pollen. The genotype of each plant is composed of a combination of S-haplotypes S_D and S_R, which are respectively dominant and recessive in pollen, but codominant in stigma. Plants cannot mate when the form of the pollen (represented as a square or a circle) matches the form of the receptor at the stigma surface. The plant on the left is heterozygous (it has both alleles in its genotype) and displays both stigma receptors, but produces a single type of pollen because S_R is recessive to S_D in anthers. Consequently, both plants are self-incompatible, the homozygous plant cannot fertilize the heterozygous plant, but the heterozygous plant can fertilize the homozygous plant. This arises as a consequence of the dominance of S_D over S_R, which results in the absence of S_R protein deposition on the surface of pollen produced by the heterozygous plant S_D/S_R.

Ubiquitous dominance modifiers?

The functional implications of this discovery have been highlighted by others [16,19–21]. By contrast, the evolutionary implications have been largely overlooked because, to the best of our knowledge, this is the first empirical evidence for a dominance modifier *per se* and hence directly pertains to the Wright–Fisher scientific dispute. Although the paradigmatic physiological explanation proposed by Wright is undoubtedly powerful and remains firmly grounded, this new finding confirms that Wright's explanation does not apply to all observed cases of dominance. Although the mechanism described might be considered merely a special case, we argue that the very possibility that such dominance modifiers exist can be viewed as validating Fisher's intuition. Moreover, it opens up new research avenues aiming at identifying dominance modifiers in other genetic systems, thereby assessing the generality of the documented mechanism. Indeed, recent theoretical work has shown that dominance modifiers *per se* could be favored across a range of biological situations, in particular when masking the phenotypic effect of one allele in a diploid genotype is advantageous, either through greater mating success [22,23] or evasion of host immunity [24].

As appealing as Wright's theory might be, it only addresses a specific category of genes: enzyme-encoding genes involved in metabolic networks. Even so, many genes do not belong to this category, for instance structural genes or genes involved in receptor–ligand interactions. Hence, for all these other types of genes a general theory of dominance is still lacking [11], and we argue that such genes are good candidates in the search for dominance modifiers. More importantly, Wright's primary argument for dismissing Fisher's theory actually revolved around the weakness of natural selection for dominance when heterozygosity is low,

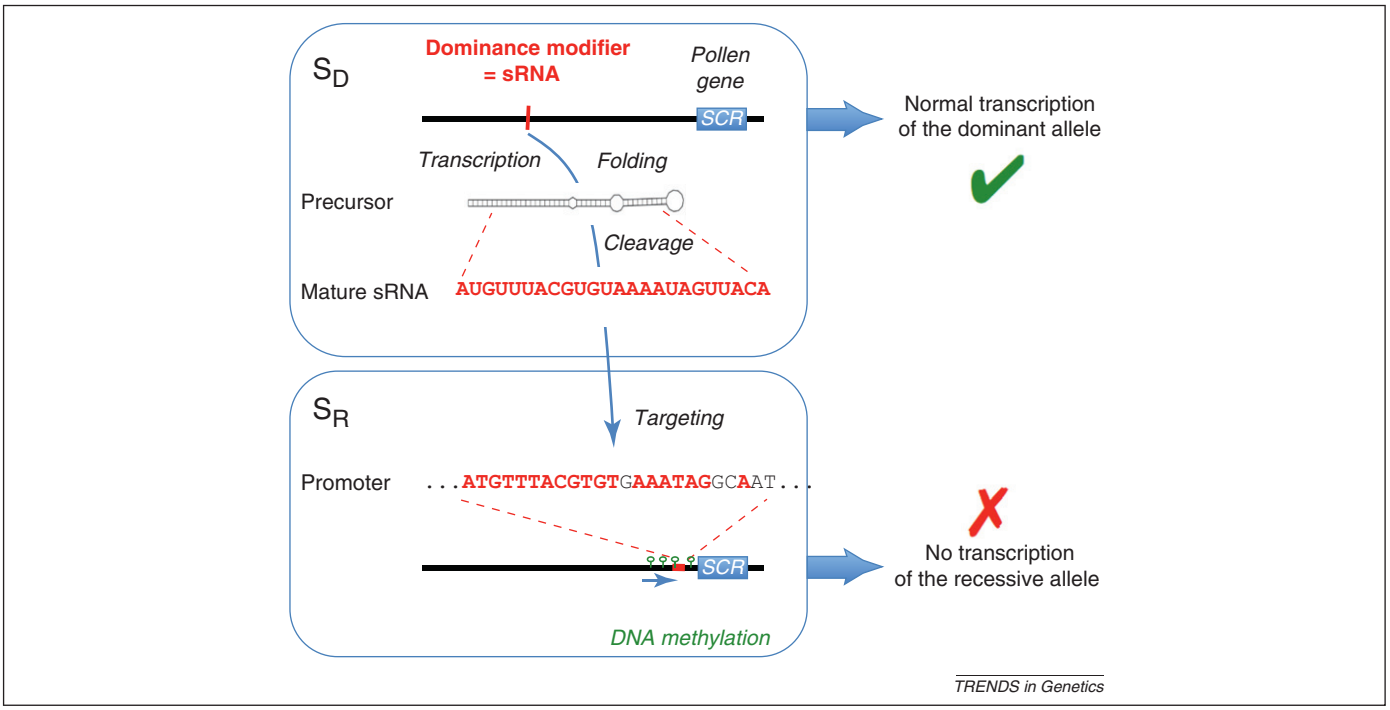

Figure 2. Mode of action of the dominant allele S_D on the recessive allele S_R at the self-incompatibility pollen gene in *Brassica*. The dominant allele S_D prevents the expression of the recessive allele S_R by DNA methylation of the promoter of the pollen gene (*SCR*). A small RNA, the dominance modifier, is present in the S_D haplotype. It is consecutively transcribed, folded and cleaved, giving rise to a mature and functional small RNA (sRNA). This mature sRNA specifically targets a region in the promoter of the pollen gene of the recessive S_R haplotype. The promoter is methylated, and this prevents the expression of S_R, whereas the dominant allele S_D is normally expressed.

and therefore does not cover cases where selection is strong or heterozygosity is high [25]. A variety of processes can lead to either strong selective pressure (such as for instance artificial selection in the course of domestication [26,27]) or high heterozygote frequencies in a population either transiently, during the spread of a favorable allele [28], or permanently because of long-term balancing selection [14]. We believe that the most probable biological conditions under which dominance modifiers have evolved pertain to situations in which balancing selection occurs because the alleles persist at intermediate frequency over a long time period, and below we detail some of these cases.

Two distinct mechanisms of balancing selection, in other words overdominance and selection in heterogeneous but interconnected environments, could allow the maintenance of heterozygosity at a level sufficient to promote substantial positive selection of dominance modifiers [25]. We note however that in two cases [28,29] higher fitness of heterozygotes was assumed to exist *a priori* rather than being based on an explicit modeling of the phenotype; in other words a clearly defined mechanism for dominance is not incorporated into these studies. By contrast, the phenotypic link between genotype and fitness has been explicitly taken into account in at least three model systems. In addition to plant sporophytic self-incompatibility, where theoretical studies [22,23] predicted that natural selection should strongly act on dominance modifiers, and even before they were discovered [16], two other such systems have been investigated. First, codominance resulting in intermediate morphs should be counter-selected at the loci controlling Batesian mimicry in butterflies, hence allowing dominance modifiers conferring either dominance or recessivity to fix in a population [30]. Of course, the genetic basis of this genetic system was unknown at that time, but is now beginning to be deciphered at the molecular level [31–33]. Second, a two-species model of dominance evolution in loci involved in host–parasite interactions [24] showed that codominance is expected to occur in hosts (thereby conferring a wider spectrum for parasite surveillance), whereas it is expected to be counter-selected in parasites (allowing them to remain inconspicuous to the host). In all of the models described above, high levels of heterozygosity might indeed confer the potential for dominance evolution. Surprisingly, such models have only been worked out in detail in a few cases, but there are several other genetic and ecological contexts where balancing selection is also expected to occur. Indeed, we argue that many other systems maintaining diversity either stably or transiently could potentially share the same favorable properties for dominance evolution, but remain to be investigated – these include temporally varying environments, persistent sexually antagonistic variation caused by intra-locus sexual conflict [34,35], mating systems with multiple sexual morphs (gynodioecy, dioecy, heterostyly [36,37]) and, more generally, all systems with negative frequency-dependent selection (i.e. advantage of the rare) acting on different morphs such as dextrality–senestrality in cichlid fishes [38] or color and body size in Anolis lizards [39]. Interestingly, most of these cases entail documented dominance–recessivity interactions between alleles. For instance, dextrality is dominant over senestrality in the scale-eating fish *Perissodus microlepis* [38], and *Orange*, *Yellow* and *Blue* alleles are respectively dominant, intermediate and recessive in male reproductive strategies of Anolis lizards [40], raising the question of which mechanism causes dominance–recessivity interactions in these cases. Many of

Box 1. Multiallelism: an additional level of complexity for the evolution of dominance

Multiallelic genetic systems such as in the case of the human MHC/HLA systems or insect mimicry in animals, and also pathogen resistance and self-incompatibility (SI) in plants, are highly relevant biological models to address the issue of dominance-modifier evolution. First, in two of these systems, dominance interactions have been described, and strict co-dominance was found to be the exception rather than the rule (in pollen in SI [23] and in Müllerian mimicry [32]). Second, they are characterized by high levels of heterozygosity in natural populations. They thus correspond to 'best-case scenarios' where the evolution of dominance is most likely to take place [4]. Finally, these systems typically show a variety of distinct heterozygote combinations. Indeed, although dominance between a pair of alleles involves a single heterozygote genotype, increasing the number of alleles induces a new dimension of complexity, in that dominance interactions involve a network of all possible pairs of alleles.

This additional layer of complexity raises both proximate and ultimate questions. In light of the mechanism discovered [16], two extreme proximate mechanisms can be proposed. First, every pairwise dominance–recessivity interaction between alleles could involve a distinct small non-coding RNA that silences expression of the more recessive allele of the pair but has no impact on the transcription of the other alleles. Alternatively, a single 'master' small RNA in dominant haplotypes could target a wide range of recessive alleles, causing their silencing in a general manner. On the ultimate side, it has been shown in the case of SI that selection against codominance is the main force driving the evolution of dominance [22,23]. Hence, the acquisition of a new small RNA able to target and silence another allele would confer dominance and hence be selected. Similarly, any mutations in a promoter allowing it to be targeted by an already existing small RNA would confer recessivity and hence also be selected. Conversely, any mutation in the promoter causing a haplotype to escape surveillance by a small RNA it was targeted by would restore codominance, and thus will be selected against. Clearly then, because dominance in SI results from the targeting of the promoter of recessive alleles by a small RNA, understanding changes in the dominance network necessitates that we take into account both partners of the interaction, in other words the co-evolution between small RNAs and their targets.

these biological situations show a large range of allele number at a given locus, from two in the case of sex determinism, to dozens in self-incompatibility systems in plants, which raises particular mechanistic and evolutionary challenges (Box 1). It will be interesting to learn from empirical investigations of these systems which molecular mechanisms underlie dominance–recessivity interactions. We anticipate that such studies could reveal a diversity of molecular processes, including both dominance modifiers *per se* as well as cases fitting Wright's physiological theory.

The discovery of a small RNA acting as a dominance modifier comes at a time when small RNAs are becoming increasingly recognized as major players in the regulation of gene expression, and raises the question of how general this mechanism could be for other dominance–recessivity interactions. Although the answer will emerge from detailed empirical studies, possibly on some of the promising biological situations we highlighted above, the details of self-incompatibility itself suggests that dominance modifiers could come in a range of different flavors, each with different mechanistic modes of action. In fact, dominance in pollen is only half of the story, because dominance relationships have also been described between alleles at the gene encoding the pistil phenotype [41], although its molecular basis has not yet been deciphered. Interestingly, dominance in pistils does not involve transcriptional silencing, suggesting that its molecular basis is different from that of pollen, and does not involve small non-coding RNAs [42]. Clearly then, even in this single genetic system, at least two different mechanisms appear to account for dominance, suggesting that a range of distinct mechanisms probably exist throughout Nature.

Concluding remarks: from mechanistic to longstanding evolutionary issues

Overall, although Wright's physiological explanation for dominance has became prevalent, Wright himself acknowledged the possibility that dominance modifiers *per se* could evolve in nature as 'special cases' ('*If for any reason the proportion of heterozygous mutants reaches the same order as that of the* [wild] *type, selection of modifiers of dominance (...) might well become of evolutionary importance*' [5]). For more than 80 years, this ever-recurring issue remained a theoretical but elusive possibility (e.g. [15]). Firm empirical evidence of such modifiers has finally been provided [16] and this discovery enlightens our understanding of the evolution of inheritance systems in general. At the very least, the empirical description of such dominance-modifying elements argues that it is premature to claim that Fisher's theory of dominance evolution has been falsified. Hence, we argue that, in the aforementioned cases, looking for dominance modifiers could lead to promising new discoveries about the underlying mechanisms.

For instance, the discovery of dominance modifiers in the case of self-incompatibility raises the question of how dominance–recessivity interactions first evolved and what types of mutations confer dominance (or recessivity). Interestingly, small non-coding RNAs in plants typically originate from inverted repeats, suggesting a simple mutational mechanism for the biogenesis of a new dominance modifier – either from a portion of the gene being controlled or its promoter (reviewed in [43]). Alternatively, a major role of small RNAs could be to control the activity of transposable elements [44], suggesting that new dominance modifiers can originate from molecular tinkering of pre-existing transposable elements. Interestingly, the self-incompatibility locus in plants is typically enriched in transposable elements [45], and this could have led to the recruitment of new small non-coding RNAs in this genomic region that might later have been selected as dominance modifiers.

In addition, elaboration of the molecular nature of the dominance modifiers will allow the study of patterns of their molecular evolution. The comparison of several dominant S-haplotypes shows that several share a very similar sequence for the small RNA [16], although these S-haplotypes are otherwise highly diverged. This suggests that the functional constraints on the dominance modifier is indeed strong, again undermining the paradigmatic interpretation of Wright's model of dominance – that selection on dominance modifiers *per se* should be weak and thus of little evolutionary importance. Finally, the control of dominance by small RNAs introduces an additional level of

complexity because it entails co-evolution between the dominance modifier (the small RNA) and its target gene. This kind of co-evolutionary process has not been implemented in previous models, but could be particularly important in the case of multiallelic systems (Box 1), and again we argue that a new appraisal of these models will now be necessary.

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