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PERSPECTIVE

When genes move, genomes collide

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The ultimate test of whether two diverged populations are, in fact, good species is whether they will maintain their distinctness in sympatry [1, 2]. This requires the action of one or more reproductive isolating mechanisms. Identifying traits and alleles that underlie reproductive isolation has therefore been a major focus of speciation genetics research [3, 4]. In addition to informing the basis of reproductive isolation, alleles underlying interspecific incompatibilities can provide information concerning how functional evolutionary divergence unfolds.

The genus *Mimulus* has long served as a model for the study of reproductive isolation [5, 6]. Much of this work has focused on *Mimulus guttatus* and *M. nasutus*. These recently diverged species have broadly overlapping geographic ranges, and—when sympatric—*M. nasutus*' ancestry frequently introgresses into *M. guttatus* [7–9]. Because hybridization and introgression in this species pair are common, the genetic mechanisms preventing their fusion is of great interest. In this issue, Zuellig and Sweigart [10] map the genetic basis of an inviability phenotype that only manifests in F2 *M. nasutus* × *M. guttatus* hybrids.

Zuellig and Sweigart [10] identify the precise alleles of hybrid seed inviability in a pair of recently related and naturally hybridizing species of *Mimulus* (Fig 1A). After two bulked segregant analyses to identify the incompatibilities, and some impressive snooping in the unassembled portion of the *M. guttatus* reference genome, Zuellig and Sweigart identify 2 genes involved in the defect: *hl13* (Migut.M02023) and *hl14* (Migut.O00467). These genes are duplicates of plastid transcriptionally active chromosome 14 (*pTAC14*)—a gene known to be essential for proper chloroplast development in *Arabidopsis thaliana* [11]. A functional copy of *pTAC14* is found on chromosome 14 (*hl14*) of both the *M. guttatus* reference genome and the *M. guttatus* studied samples, but the gene is missing from *M. nasutus*' chromosome 14. In contrast, both species have a syntenic copy of *pTAC14* (*hl13*) on chromosome 13, but the *M. guttatus* allele includes a frameshift mutation and is not expressed. As a result, some F2 hybrids and advanced backcrossed seedlings will be homozygous for the nonfunctional *M. guttatus*' copy of *pTAC14* at *hl13* and *M. nasutus*' null allele on chromosome 14; these individuals will lack a functional *pTAC14* gene, leaving them unable to photosynthesize and therefore inviable (Fig 1B).

The idea that divergent resolution of gene duplicates could result in the inviability of hybrids inheriting null alleles has been long hypothesized by theory [12–16]. The results are an intuitive consequence of gene movement and meiotic segregation. Moyle et al. [12] first formalized this model of stepwise gene movement leading to hybrid incompatibility—first a gene is duplicated, then it loses function in its original location, and, effectively, the only remaining copy is in a different chromosome. The nature of Mendelian segregation ensures hybrid defects that affect only a proportion of hybrids (in this case no F1 is affected, while one-sixteenth of the F2s are).

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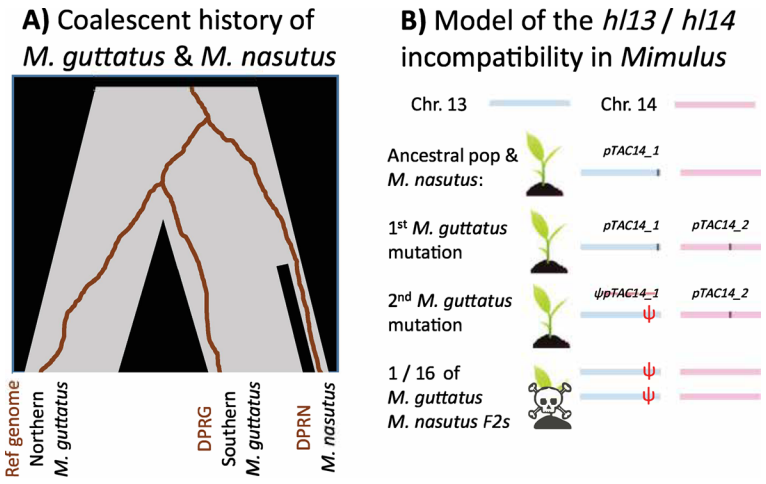

Fig 1. The history of the *M. guttatus*–*M. nasutus* species pair, and the evolution of the *hl13*/*hl14* incompatibility. (A) Southern *M. guttatus* populations (including the sample DPRG studied by Zuellig and Sweigart) are more closely related to *M. nasutus* (sample DPRN) than to northern *M. guttatus* (including the *M. guttatus* reference genome). Nonetheless, DPRG is more similar to the reference strain at *hl13* and *hl14*—the loci underlying the hybrid incompatibility identified by Zuellig and Sweigart—than *M. nasutus* (shown by the brown coalescent genealogies). (B) Zuellig and Sweigart found that (1) *pTAC14* was ancestrally located in chromosome 13 in *Mimulus*, (2) a copy moved to chromosome 14 in *M. guttatus*, and (3) the initial copy then lost function in *M. guttatus*. While all F1s are viable, one-sixteenth of F2s inherit a chromosome 14 without *pTAC14* and a chromosome 13 with a nonfunctional *pTAC14*. Because *pTAC14* is a critical photosynthetic gene, these seedlings are inviable.

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Previous studies also have lent support for this model. In the *Drosophila simulans*–*D. melanogaster* species pair, the transposition of the gene *JYalpha* from the fourth to the third chromosome in *D. simulans* causes sterility in the hybrid males [17]. A similar result has been found between accessions of the selfing plant *A. thaliana* from Columbia (Col) and Cape Verde Island (Cvi)—the histidinol-phosphate aminotransferasegene exists on chromosome 1 but not chromosome 5 in Cvi, and on chromosome 5 but not chromosome 1 in Col, and F2s lacking histidinol-phosphate aminotransferasegene are inviable [18]. Unlike *M. guttatus* and *M. nasutus*, none of these species pairs hybridize in nature.

The results from Zuellig and Sweigart have three important implications, each offering new research directions. First, this study will allow researchers to ask how incompatibility due to gene movement contributes to genome variation and differentiation in natural populations. For example, future studies and/or reexamination of genomic patterns of introgression between these species [9] could examine whether *M. nasutus*' ancestry is elevated around *hl14* and depleted around *hl13* in sympatric *M. guttatus*, as would be expected if incompatible alleles are selected against upon introgression [19–21]. Additional directions could address how *hl13/hl14* acts in concert with the other reproductive isolating mechanisms and mapped incompatibilities (e.g., [22]) to prevent the fusion of these species in sympatry.

Second, both the process of duplication of *pTAC14* and nonfunctionalization are plausibly neutral, suggesting that reproductive isolation may have arisen by a neutral process. In fact, Zuellig and Sweigart find no strong evidence that natural selection is responsible for either *pTAC14*'s duplication or degeneration, and as such the authors suggest that this incompatibility has a neutral origin. While this hypothesis is plausible, it clearly needs more scrutiny. Further study of the effects of the alternative functional copies, and additional population genomic studies of the history of selection on *hl13* and *hl14*, could inform the evolutionary question of how and why genes relocate.

Finally, the recency of the split between these species and the extensive natural variation in *M. guttatus* mean that the *hl13/hl14* incompatibility provides an excellent opportunity to identify the factors shaping the alternative resolution of alternative paralogs. This question is particularly interesting because of the evolutionary history of the species' split; the *M. guttatus* population studied by Zuellig and Sweigart is more closely related to *M. nasutus* than it is to the *M. guttatus* reference genome with which it shares *hl13* and *hl14* alleles [8]. This observation—that the gene trees underlying hybrid incompatibilities do not match the population tree—may seem counterintuitive, but is potentially consistent with recent results from theoretical population genetics [23].

Overall, Zuellig and Sweigart's results provide empirical evidence that the evolution of gene duplicates might be involved in reproductive isolation in young species that hybridize in nature. Systematic efforts like Zuellig and Sweigart's will reveal to what extent gene movement is a prevalent force in the formation of species. More generally, their study provides a map route to understand what is the role of hybrid incompatibilities in keeping naturally co-occurring—and potentially hybridizing—species apart.

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