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Genome-Wide Analyses of Hybrid Incompatibility in Drosophila

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Abstract

Recent genome-wide analyses accelerate the identification of hybrid incompatibility (HI) genes. Such analyses in the cross between *Drosophila melanogaster* females and *D. simulans* males are reviewed here. Number of the HI genes was roughly estimated and some of the HI genes have been molecularly identified. More HI genes will be identified not only in this crossing system but also from diverse organisms in the near future.

Keywords: *Drosophila melanogaster; Drosophila simulans;* Hybrid incompatibility; Hybrid inviability; Reproductive isolation; Speciation

Introduction

"Species are groups of actually or potentially interbreeding natural populations, which are reproductively isolated from other such groups" [1] (Biological Species Concept, BSC). Based on the BSC, speciation researchers have been trying to isolate genes responsible for reproductive isolation. Recent genome-wide analyses in Drosophila accelerate the identification of such genes.

Coyne and Orr [2] classified reproductive isolating barriers into three categories: I. Premating, II. Post-mating/pre-zygotic and III. Post-zygotic. Hybrid sterility and inviability are included in category III and seen in the F1 and later generation hybrids; those seen in the descendants are also called hybrid breakdown [3]. Hybrid sterility and inviability are generally the result of epistatic interaction between genes from different species (e.g., hybrid incompatibility; HI), as it has been suggested by Dobzhansky [3] and Muller [4].

Genomic constructions of the F1 and later generation hybrids (and HI genes) are shown in Figure 1. The F1 genotypes are homogeneous, not differing among individuals of the same sex. The majority of the F1 genomes are heterozygous, carrying heterospecific alleles. Therefore, F1 viability/fertility seems to be generally affected by dominant HI genes (Figure 1i). Exceptionally the sex-linked HI genes can be dominant or recessive, because sex-linked genes may be hemizygous in one sex. On the contrary, the genotype of F2 (produced by the sibling cross) or BC1 (produced by the backcross) varies due to recombination. Some genomic regions may be homozygous for alleles from one parental species, and F2 and BC1 viability/fertility seems to be affected by recessive HI genes (Figure 1ii and 1iii). Such difference of HI genes dominance in between F1 and F2/BC1 has been stressed previously [5].

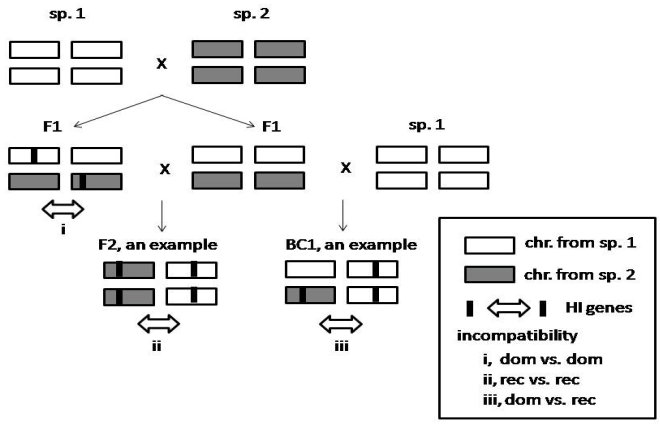

Figure 1: Genomic constructions and HI genes in hybrids (F1, F2, and BC1). Parental species (sp. 1 and sp. 2) are also indicated. chr., chromosome; dom, dominant; rec, recessive.

Drosophila melanogaster and a sibling species, *D. simulans*, have been the model system to elucidate HI genes. The cross between *D. melanogaster* females and *D. simulans* males produce only a sterile female F1; male F1 is lethal later at the larval stage (Figure 2A) [6]. In the present review we do not consider the reciprocal cross for simplicity, where the viable/lethal sex is reversed [6]. Male F1 is rescued if a *D. simulans* mutant of the *Lethal hybrid rescue* (*Lhr*) gene [7] or a *D. melanogaster* mutant of the *Hybrid male rescue* (*Hmr*) gene [8] is used for the cross (Figure 2B). Genome-wide analyses of HI genes in this cross are reviewed here (Table 1).

History

Strategy 1

Coyne et al. [9] conducted pioneering work where they made recessive *D. simulans* HI genes hemizygous over *D. melanogaster* deficiencies in F1 (Figure 2C). Female F1 viability of carriers vs. non-carriers of the deficiency was compared. The HI partner of *D. melanogaster* must be dominant, because the F1 genomes are heterozygous. Matute et al. [10] refined the mapping using more deficiencies (and extended the study to a more distantly-related species, *D. santomea*). These studies resulted in 10 HI gene regions in the 79.4% genome tested.

Strategy 2

Presgraves [11] conducted similar crosses, where he used *Lhr* instead of the wild type *D. simulans* to rescue male F1 (Figure 2D) (for a pilot test see Sawamura [12]). Male F1 viability of carriers vs. non-carriers of the deficiency was compared. The HI partner of *D. melanogaster* can

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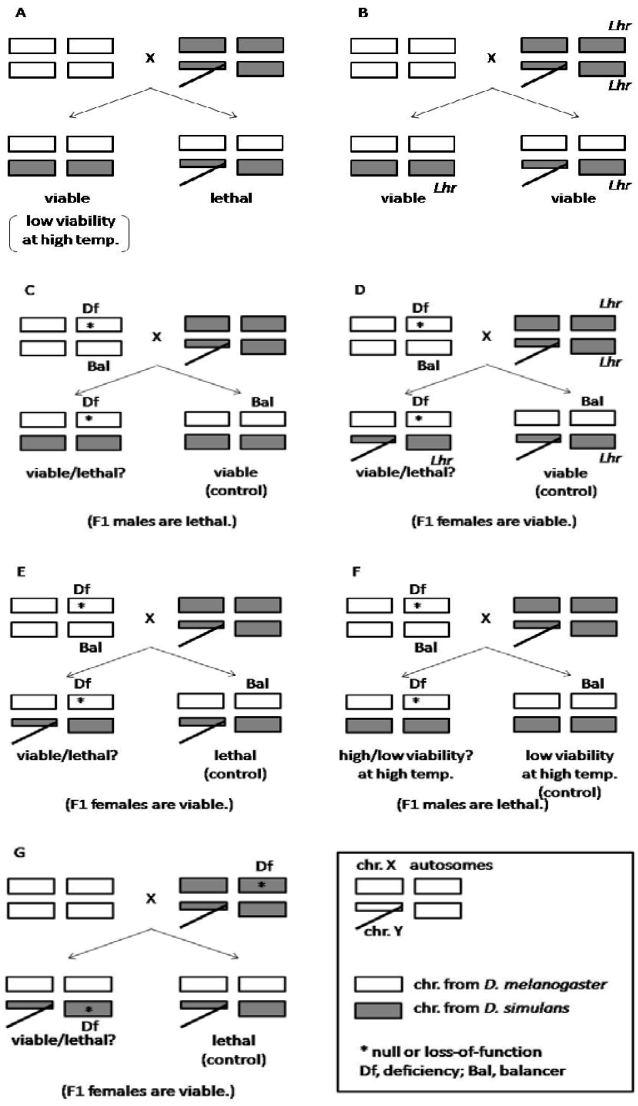

Figure 2: Crosses between *D. melanogaster* females and *D. simulans* males. A, both parents are wildtype. B, *D. simulans* has an *Lhr* mutation. C-F, *D. melanogaster* is heterozygous for a deficiency (Df) and a balancer (Bal). (D, *D. simulans* has *Lhr*.) G, *D. simulans* has newly induced mutations (including Dfs). chr., chromosome.

be recessive if it is X-linked, and the screening is more sensitive than Strategy 1. Presgraves [11] detected 20 lethal and 20 semilethal HI gene regions in the 70% autosome tested, and two have been identified by further studies: *Nucleoporin 96* (*Nup96*) and *Nucleoporin 160* (*Nup160*) [13-15].

Strategy 3

Cuykendall et al., [16] using crosses similar to as Strategy 1, mapped dominant HI gene regions that rescued F1 males when the regions are deleted (Figure 2E). The *D. melanogaster Hmr* is an example of such dominant HI genes; a loss-of-function of the gene rescues male F1 [17]. Of note, Cuykendall et al. [16] preferentially used *D. mauritiana* instead of *D. simulans*, because hybrids can be rescued easier.8, [18] Cuykendall et al. [16] did not detect major HI genes but detected multiple minor-effect HI genes in the 89% autosome tested.

Strategy 4

Female F1 is viable at low temperature (e.g., 18C) but die at the late pupal stage or just after eclosion at high temperature (e.g., 25C) (Figure 2A) [19,20]. Deficiencies of dominant HI genes are expected to rescue the female F1 (Figure 2F). Although the effect of the *D. melanogaster Lhr* was not detected in male F1 (e.g., not rescued by the deficiency) (Strategy 3; see also Barbash et al. [21]), it was detected in female F1 (e.g., rescued by the deficiency) [22]. The data presented in Coyne et al., [9] Matute et al., [10] and Cuykendall et al. [16] can be reanalyzed for female F1 viability rescue by deficiencies. The genome-wide analysis of the dominant HI genes is in progress (KS, T. Hayashi, K. Miura, and Q. Araye, unpublished).

Strategy 5

Until now, it was difficult to screen *D. simulans* mutations because elegant genetic tools like balancer chromosomes were not available in this species. Phadnis et al. [23] overcame this difficulty by inducing point mutations (and deficiencies) in *D. simulans* males and crossing them with *D. melanogaster* females (Figure 2G). Rescued male F1 must have mutations on dominant HI genes. The *D. simulans Lhr* is an example of such genes; a loss-of-function of the gene rescues male F1 [21]. Phadnis et al. [23] used next-generation sequencing of the recovered *D. simulans* mutations and discovered the third gene involved in the F1 inviability: *Suppressor of Killer-of-prune* (*Su(Kpn)*)=*glutathione-S-transferase-containing FLYWCH zinc finger protein* (*gfzf*). More genes will be discovered, because this screening has not been saturated [23].

Strategy	Depicted in	Cross	Viability examined	HI genes examined	Potential HI partner	Number of HI genes	Examples of HI genes
1	Figure 2C	mel Df/Bal ♀ x sim + ♂	Df/sim ♀(down) vs. Bal/sim ♀	rec sim	dom mel	10 in 79% genome	-
2	Figure 2D	mel Df/Bal ♀ x sim *Lhr* ♂	Df/sim ♂ (down) vs. Bal/sim ♂	rec sim	dom + X-linked rec mel	20 (+ 20 semilethal) in 70% autosome	*Nup96*, *Nup160*
3	Figure 2E	mel Df/Bal ♀ x sim + ♂	Df/sim ♂ (up) vs. Bal/sim ♂	dom mel	dom sim	0 in 89% autosome; multiple minor-effect genes	*Hmr*
4	Figure 2F	mel Df/Bal ♀ x sim + ♂	Df/sim ♀ (up) vs. Bal/sim ♀	dom mel	dom sim	in progress	*Lhr*
5	Figure 2G	mel + ♀ x sim Df/+ ♂	mel/Df ♂ (up) vs. mel/+ ♂	dom sim	dom mel	1 (screening not saturated)	*Lhr*, *gfzf*
6	Figure 3B	mel XXYDp ♀ x sim + ♂	Dp+ ♂ (down) (vs. Dp- ♀)	X-linked dom mel	dom + X-linked rec sim	2 in 72% X chromosome	*Hmr*
mel, *D. melanogaster*; sim, *D. simulans;* Df, deficiency; Dp, duplication; Bal, balancer; +, wildtype; rec, recessive; dom, dominant.							
The dominance of *Lhr* depends on the genetic context.							

Table 1: Genome-wide analyses of hybrid incompatibility genes in the cross between *D. melanogaster* females and *D. simulans* males.

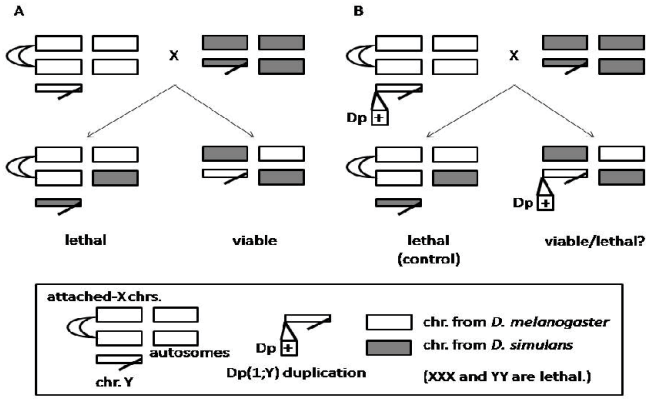

Figure 3: Crosses between XXY *D. melanogaster* females and *D. simulans* males. A, chromosomes are normal other than the attached-X chromosomes in females. B, the *D. melanogaster* Y chromosome carries a duplication (Dp) of genes from the X chromosome; Dp (1;Y). chr., chromosome.

Strategy 6

If *D. melanogaster* has attached-X chromosomes, the cross between XXY *D. melanogaster* females and *D. simulans* males produce only sterile male F1; female F1 is lethal at the late larval stage (Figure 3A) [19]. Matute and Gavin-Smyth [24] used such *D. melanogaster* females who carry a series of X duplications on the Y chromosome (Figure 3B), (and extended the study to *D. mauritiana* and *D. santomea*). The male F1 would be lethal if the duplicated region contains dominant HI genes. Matute and Gavin-Smyth [24] detected two HI gene regions in the 72% X chromosome tested and one seems to be the *Hmr* locus.

Discussion

The genome-wide analyses of HI genes in the cross between *D. melanogaster* females and *D. simulans* males are productive. Number of the HI genes was roughly estimated and some of the HI genes have been molecularly identified. As it can be seen from Table 1, recessive HI genes of *D. simulans* have been well documented; more than 20 such genes exist and two of them (*Nup96* and *Nup160*) have been identified. Dominant HI genes of *D. melanogaster* have also been investigated (e.g., *Hmr*), and more will be discovered by strategy 4. One of dominant HI genes of *D. simulans* is known since classic studies (*Lhr*), and more will be discovered by strategy 5 (e.g., *gfzf*). On the contrary, recessive HI genes of *D. melanogaster* have not been investigated at all. New strategies identifying such genes are awaited. In the near future, more HI genes will be identified not only in this crossing system but also from diverse organisms thanks to the advance of the genomic sequencing technology.

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