

1 **Genetics of host-parasite interactions: towards a more comprehensive dissection of *Drosophila***
2 **resistance to viral infection**

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11 **One of the major challenges in Evolutionary Biology is to unravel the genetic basis of adaptation.**
12 **This issue has been gaining momentum in recent years with the accelerated development of novel**
13 **genetic and genomic techniques and resources. In this issue of *Molecular Ecology*, Cogni et al.**
14 **(2016) address the genetic basis of resistance to two viruses in *Drosophila melanogaster* using a**
15 **panel of recombinant inbred lines with unprecedented resolution allowing detection of rare alleles**
16 **and/or alleles of small effect. The study confirms the role of previously-identified genes of major**
17 **effect, and adds novel regions with minor effect to the genetic basis of *Drosophila* resistance to**
18 **the *Drosophila C virus* (DCV) or the Sigma virus. Additional analyses reveal the absence of cross-**
19 **resistance and of epistasis between the various genomic regions. This detailed information on the**
20 **genetic architecture of host resistance constitutes a crucial step towards the understanding of**
21 **both the physiology of anti-viral immunity and the evolution of host-parasite interactions.**

22 It has been argued that identifying the genetic basis of adaptation may add little to the
23 understanding of some evolutionary phenomena (Rausher & Delph 2015). Indeed, even in research
24 areas where the genetic architecture of adaptation is relevant, the identification of the particular
25 genes involved may not be essential. For example, the genetics of host-parasite interactions may be

26 captured by a matching-allele model, in which specific parasite and host genotypes can only infect
27 and resist, respectively, antagonists with a particular (matching) allele. Alternatively, it may follow a
28 gene-for-gene model, where some parasites infect a subset of hosts whilst others infect the whole
29 range of host genotypes. Distinguishing between these alternatives is important because only under
30 the matching allele model is selection for increased recombination expected (Agrawal & Lively
31 2002). Importantly, it was recently found that the interaction between *Daphnia magna* hosts
32 infected by *Pasteuria ramosa* is consistent with a matching allele model (Luijckx *et al.* 2013).
33 However, the identification of the specific alleles involved in the interaction was not necessary for
34 this compelling result.

35 Still, some features of the genetics of host-parasite interactions are highly relevant to understand
36 their evolution. For example, the number of genes coding for host resistance impacts on the degree
37 of maladaptation of parasites in a heterogeneous landscape (Ridenhour & Nuismer 2007). One of
38 the systems with more information concerning the genetics of host resistance is that of *Drosophila*
39 and its parasites. Indeed, several studies have identified genes or genome regions responsible for
40 variation in survival upon bacterial (e.g., (Sleiman *et al.* 2015) and viral infections (e.g., (Magwire *et*
41 *al.* 2012; Martins *et al.* 2014). In the latter case, alleles of major effect have been recurrently
42 identified to confer resistance to DCV (*Pastrel*; (Magwire *et al.* 2012; Martins *et al.* 2014) and to the
43 Sigma virus (*ref(2)P* and *CHKov1*; (Bangham *et al.* 2007; Magwire *et al.* 2011). However, candidate
44 alleles of minor effect (*CG16998*, *UbcE2H*; (Martins *et al.* 2014) and rare alleles of large effect (*Ge-1*;
45 (Cao *et al.* 2016) have been identified in some studies, but not in others. These different outcomes
46 may arise because standing genetic variation in these loci is absent from some of the initial
47 populations, different approaches have intrinsically distinct outcomes (association studies vs
48 experimental evolution), or studies differ in their degree of resolution.

49 In this issue of Molecular Ecology, Cogni *et al.* (2016) add significantly to the understanding of the
50 genetic basis of resistance to viruses in *Drosophila*. The authors use the *Drosophila* Synthetic

51 Population Resource (DSPR) panel (<http://wfitc.bio.uci.edu/~dspr/>; (Long *et al.* 2014)) to identify
52 the genes involved in *Drosophila* differential survival to DCV and Sigma virus. This resource is
53 composed of 1700 recombinant inbred lines that are formed from the interbreeding of two sets of 8
54 fully-sequenced inbred founder lines from distinct geographic locations (one of the lines being
55 repeated in the two panels). This resource allows a much finer mapping resolution of quantitative
56 trait loci (QTL), enabling detection of rare alleles present in the original set and of alleles of small
57 effect (Long *et al.* 2014). Using this panel, the authors confirm the role of *Pastrel* and *ref(2)P* in
58 conferring resistance to DCV and to Sigma virus, respectively. These genes had already been
59 identified using the DGRP panel (Bangham *et al.* 2007; Magwire *et al.* 2012) and an evolve-and-
60 resequence methodology (Martins *et al.* 2014). Importantly, they also find additional regions
61 contributing to these responses, namely one new locus involved in resistance to DCV and five extra
62 QTLs involved in fighting Sigma virus. This more complete and complex landscape provides a basis
63 for 90% of the response against DCV and 43% for Sigma virus. Interestingly, previously-found rare
64 and small-effect alleles were not detected. Given the level of resolution now achieved, it is likely that
65 the lines from which this panel was generated did not contain the relevant allelic variation at those
66 loci. Be it as it may, the finer grain analysis here provided, certainly brings to light novel candidates
67 involved in the physiological response deployed against viral infections. Future validation of these
68 candidates will certainly add important new elements to the mechanistic understanding of anti-viral
69 immune responses.

70 Another important conclusion of this study is the absence of cross-resistance and of epistasis
71 among QTLs involved in the response to the same virus, which is an important component of
72 theoretical predictions concerning the evolutionary outcome of host-parasite interactions (*e.g.*,
73 (Fenton & Brockhurst 2007). Additional analyses, however, point to the existence of yet another QTL
74 that is not directly involved in conferring resistance but that modifies the effect of one of the QTLs
75 affecting resistance to the sigma virus. Further studies will help understanding whether this mild

76 epistasis is a general feature of the host-parasite interaction described here or a result that is
77 specific to the panel of inbred lines used.

78 We still do not know whether alleles from genes identified through these association studies
79 are those that will increase in frequency during the adaptation process. Indeed, the genetic
80 variance–covariance matrix (the G-matrix) is likely to evolve even within short time frames,
81 especially given that, as shown by this study, more genes are involved in host resistance than
82 previously thought, and this will affect the evolutionary trajectory of hosts and parasites (Gilman *et*
83 *al.* 2012). Moreover, the genetic architecture of host resistance will interact with that of parasite
84 virulence, and generate evolutionary dynamics that cannot be captured by the analysis of one of the
85 players alone. Therefore, the genetic diversity for parasite resistance identified in the host
86 population at a given time may or may not contribute to the evolutionary process. Given the
87 potential importance of the findings presented by Cogni *et al.* (2016) for the evolution of host-
88 parasite interactions, further research on this topic can directly test if the genes identified
89 participate in the adaptation process, for example via experimental (co)evolution studies, coupled
90 with functional validations.

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92 **Reference list**

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125 Figure 1

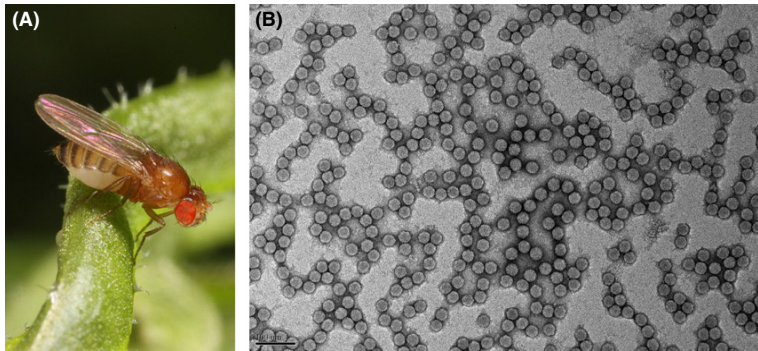


Fig. 1 *Drosophila melanogaster* (A; photograph credit: Darren Obbard) and an electron microscopy image of purified Drosophila C virus (DCV) (B; photograph credit: Estelle Santiago and Jean-Luc Imler).

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