

Quantitative genetics of Aedes aegypti vector competence for dengue viruses: towards a new paradigm?

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1 **Quantitative genetics of *Aedes aegypti* vector**
2 **competence for dengue viruses: towards a new**
3 **paradigm?**

4

5

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11

1 **Abstract**

2

3 Like many other host-pathogen interactions, the vector competence of *Aedes aegypti* for
4 dengue viruses appears to be determined by genotype-by-genotype interactions, whereby
5 the outcome of infection depends on the specific combination of mosquito and virus
6 genotypes. This may complicate efforts to dissect the genetic basis of vector competence
7 in nature because it obscures mapping between genotype and phenotype and brings into
8 question the notion of universal mosquito resistance or susceptibility. On the other hand,
9 it offers novel opportunities to better define compatible vector-pathogen associations
10 based on integration of both vector and pathogen genomics, which should eventually
11 improve understanding of pathogen transmission dynamics and the risk of vector-borne
12 disease emergence.

1 **Natural patterns of vector-pathogen specificity**

2

3 Elucidating the genetic determinants underlying patterns of compatibility between insect
4 vectors and the pathogens they transmit is a major goal of vector biology because they
5 largely contribute to vector competence (see Glossary) and thus to the public health threat
6 represented by a given vector-pathogen pair [1]. It is striking, for instance, that parasite
7 species causing human malaria are exclusively transmitted by *Anopheles* mosquitoes [2],
8 whereas the vast majority of vectors of arthropod-borne viruses (arboviruses) belong to
9 the *Culex* and *Aedes* mosquito genera [3]. *An. gambiae*, for example, is the major African
10 vector of the deadliest human malaria parasite, *Plasmodium falciparum*, but is
11 incompetent to most arboviruses, with the notable exception of O'nyong-nyong virus [2].
12 Likewise, *Ae. aegypti* is an efficient vector of yellow fever, dengue, and chikungunya
13 viruses but does not transmit *P. falciparum* [3]. Vector-pathogen specificity is not only
14 observed at the genus level, but also at the species level. For example, *An. freeborni* is a
15 competent vector of the rodent parasite *P. yoelii*, but does not support complete
16 development of the primate parasite *P. knowlesi*. Conversely, *An. dirus* is a competent
17 vector of *P. knowlesi*, but is naturally refractory to *P. yoelii* [4,5]. Genetic specificity of
18 compatibility has also been shown at the intraspecific level between *An. gambiae* and *P.*
19 *falciparum* [6,7]. Until recently, however, genetic specificity of compatibility at the
20 intraspecific level had not been formally demonstrated between arboviruses and
21 mosquitoes.

22

23

1 **G x G interactions between dengue viruses and *Aedes aegypti***

2

3 A recent study [8] provided empirical evidence for genotype-by-genotype (G x G)
4 interactions between dengue viruses and their major vector species worldwide, *Ae.*
5 *aegypti*. In a reciprocal cross-infection design of three field-derived *Ae. aegypti* pedigrees
6 and three low-passage dengue-1 virus isolates, several vector competence indices were
7 dependent on specific combinations of mosquito genotypes and virus isolates (Figure 1).
8 Because critical environmental factors such as maternal effects and viral titer in blood
9 meals were carefully controlled in the experimental design, interactions between
10 mosquito pedigrees and virus isolates could be interpreted as evidence for G x G
11 interactions. This study showed that individual variation in susceptibility to dengue
12 viruses among *Ae. aegypti* mosquitoes derives, in part, from interactions between the
13 mosquito's and the viral genomes. Such genetic interactions between two distinct
14 organisms can be viewed as intergenomic epistasis [9].

15

16 The finding of G x G interactions between dengue viruses and *Ae. aegypti* is no surprise
17 because many natural host-pathogen systems are governed by such specific interactions
18 [7,10–15]. The occurrence of G x G interactions helps to explain the variation previously
19 observed among *Ae. aegypti* populations in their vector competence for different dengue
20 virus strains [16,17]. Although stochastic processes also play a role in dengue virus
21 evolution [18], G x G interactions combined with the fine-scale genetic structure of *Ae.*
22 *aegypti* populations [19–21] could lead to spatial structuring of viral populations through
23 adaptation to their local vector populations [8,22].

1 **Relative nature of *Ae. aegypti* susceptibility to dengue viruses**

2

3 An important implication of G x G interactions between *Ae. aegypti* and dengue viruses is
4 that they bring into question the concept of a resistant or susceptible vector genotype in
5 natural systems. Indeed, no single *Ae. aegypti* pedigree was most resistant or susceptible
6 to all three virus isolates, and reciprocally no single virus isolate was most successful in
7 all mosquito pedigrees (Figure 1). Thus, a resistance allele or genotype against one virus
8 strain may well confer susceptibility against another virus strain. This situation differs
9 from plant-pathogen systems that are governed by typical gene-for-gene interactions. In
10 these systems, one resistance allele in the plant host confers resistance to all pathogens
11 expressing the corresponding ‘avirulence’ factor, whereas a pathogen ‘virulence’ allele
12 confers universal infectivity [23–25]. Under the gene-for-gene model, a cost of infectivity
13 to the pathogen is generally required to maintain genetic polymorphism [26–28]. G x G
14 interactions detected thus far between *Ae. aegypti* and dengue viruses are more consistent
15 with a matching-allele model of infection genetics, whereby successful infection requires
16 an exact genetic match between multiple host and pathogen loci [29,30]. Under the
17 matching-allele model, inspired from self/non-self recognition mechanisms in animals
18 [31], universal infectivity is not possible and genetic polymorphism can be maintained by
19 negative frequency-dependent selection [32,33]. In this context, the resistant or
20 susceptible status of an allele or genotype is frequency-dependent and can only be
21 inferred at the population level [34]. Strict coevolution, however, is unlikely to occur in
22 the case of interactions between dengue viruses and *Ae. aegypti* because of the low

1 encounter rate and small fitness cost of infection that probably limit virus-driven
2 selection of mosquitoes.
3
4 That the resistant or susceptible status of a mosquito depends on pathogen genetic
5 identity will complicate efforts to unravel the genetic basis of *Ae. aegypti* vector
6 competence for dengue viruses. Several quantitative trait loci (QTL) underlying variation
7 in *Ae. aegypti* vector competence for dengue-2 virus have been identified [35–37]. The
8 specific genes and polymorphisms involved are yet to be elucidated. The existence of
9 significant G x G interactions, however, implies that conclusions from a particular
10 combination of mapping mosquito population and virus strain will not necessarily apply
11 in another pair. As was concluded by a meta-analysis of a large set of published QTL
12 studies [38], it is likely that the genetic architecture of *Ae. aegypti* susceptibility to
13 dengue viruses will differ among different combinations of vector and virus genotypes. In
14 other words, sets of QTL and epistatic interactions that explain variation in vector
15 competence will likely change among different combinations of mapping mosquito
16 populations and/or virus strains.

19 **Investigating the genetic basis of vector-virus specificity**

20
21 The pessimistic view that G x G interactions will represent a significant hurdle to
22 elucidate the genetic basis of *Ae. aegypti* vector competence for dengue viruses is
23 counter-balanced by the new perspectives that they offer. G x G interactions mean that

1 phenotypic variation in vector competence is influenced not only by the independent,
2 additive effects of the vector and virus genotypes, but also by a genetic component that is
3 specific to the particular vector-virus combination [9]. It is precisely the dissection of this
4 specific component that represents a promising research avenue because it likely includes
5 the genetic determinants of vector-virus specific compatibility, which is a major
6 unresolved question in vector biology. Understanding the genetic basis of vector-
7 pathogen specificity has important implications for the prevention of vector-borne
8 disease, as illustrated by recent cases of vector-borne disease emergence associated with a
9 change in vector-virus specificity. Examples include Venezuelan equine encephalitis
10 [39], West Nile fever [40], and chikungunya [41,42]. Although one should not forget
11 non-genetic contributions to variation in vector competence [43], including
12 environmental influence on G x G interactions [44], genetic polymorphisms underlying
13 vector-virus specificity may ultimately be used as markers to assess the risk of vector-
14 borne disease emergence and to better understand virus transmission dynamics through
15 time and space.

16

17 Merging vector and pathogen genetics requires a new approach that transcends the
18 traditional disciplines of medical entomology, virology, parasitology, population and
19 quantitative genetics [45]. This methodological shift shares a common goal with what is
20 now called systems biology; i.e., to model and discover emergent properties of complex
21 systems that cannot be predicted from examination of individual system components, but
22 are essential for understanding the system as a whole [46]. The advent of the post-
23 genomic era in vector biology has provided a wealth of genetic tools and resources [47],

1 which, together with theoretical developments in quantitative genetics [48], constitute a
2 solid starting point for dissecting the genetic basis of complex traits associated with
3 vector-pathogen interactions. Following the example of renewed appreciation for intra-
4 genome epistasis to understand the structure and function of genetic pathways [49], there
5 are unprecedented opportunities to study gene interactions between two organisms in a
6 quantitative and comprehensive manner. Challenges ahead include the need to develop
7 experimental and analytical tools that allow the functional effect of genetic
8 polymorphisms in two (sometimes very different) genomes to be examined
9 simultaneously. For instance, *Ae. aegypti* has a diploid DNA genome of an estimated 1.3
10 Gb [50], whereas dengue viruses have a haploid, positive-strand RNA genome of less
11 than 11 kb. Another daunting challenge is to elaborate ways to overcome the
12 overwhelming number of possible genotype combinations. Genetic analysis of pairwise
13 (or even third- or higher-order) gene interactions will need to be based on strong
14 hypotheses generated from functional information. Systems modeling will help to narrow
15 down the list of possible interactions to test empirically those that are predicted to be the
16 most influential. Ultimately, the perspective will expand to include other interacting
17 genomes, such as those of the microbiota and endosymbionts whose influence on vector
18 competence is becoming increasingly apparent [51–54].

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1 **Conclusions**

2

3 Evidence for G x G interactions between dengue viruses and *Ae. aegypti* calls for a more
4 integrated view of the genetics underlying this vector-pathogen association. As for other
5 phenotypes that derive from host-pathogen interactions, variation in vector competence
6 appears to result, in part, from the interplay between two genomes. Thus, focusing on one
7 genome without considering the other will inevitably lead to an incomplete picture of the
8 system. The challenge of future research will be to tackle the shared, comprehensive
9 nature of the genetic basis of vector competence. Development of high-throughput
10 functional genomics and systems approaches to biology offer unprecedented
11 opportunities to accomplish these tasks. This new paradigm in vector biology should
12 eventually improve our ability to define the risk of vector-borne disease emergence and
13 understand pathogen transmission dynamics.

14

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2

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11

12

1 **Glossary**

2

3 **Epistasis:** Complex genetic interactions arising when the effects of alleles at one locus
4 depend on the presence of a specific allele at another locus.

5

6 **Genetic architecture:** Number, effect, location, and interactions of genes underlying
7 phenotypic variation.

8

9 **Genotype-by-genotype (G x G) interaction:** In a host-pathogen system, describes the
10 intrinsic specificity of compatibility among host and pathogen genotypes. It can be
11 measured as the statistical deviation from the additive combination of host and pathogen
12 genotypes in their effects on the infection phenotype.

13

14 **Quantitative trait locus (QTL):** Genomic region that explains part of the phenotypic
15 variation in a continuous trait.

16

17 **Vector competence:** Intrinsic ability of an arthropod to become infected, allow
18 replication, and ultimately transmit a pathogen. It is genetically determined but also
19 influenced by environmental factors.

20

21

1 **Figure Legend**

2

3 **Figure 1.** Genotype-by-genotype interactions between dengue viruses and *Aedes aegypti*.

4 The matrices show experimental measurements of three different vector competence

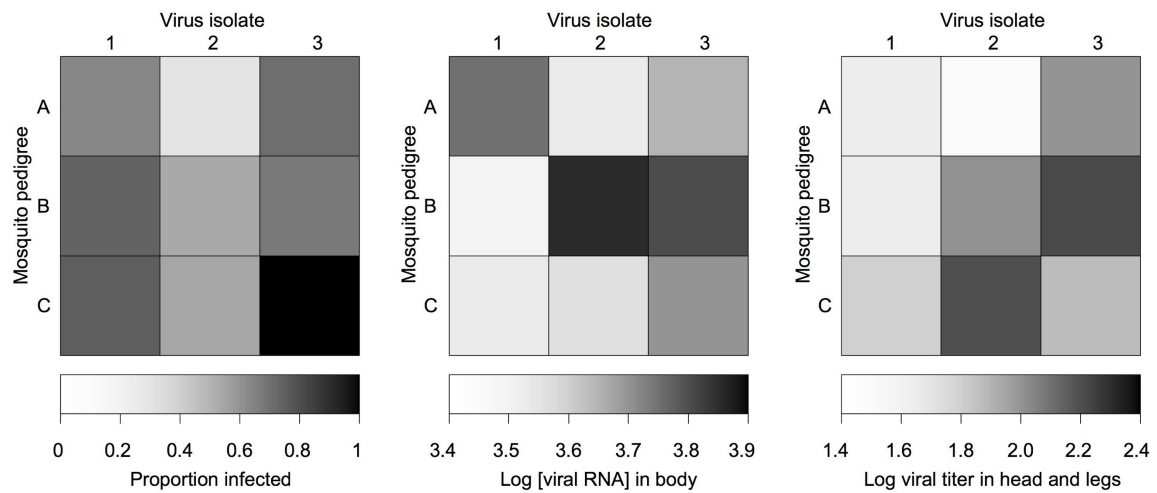
5 indices for all pairwise combinations of three dengue virus isolates and three mosquito

6 pedigrees. Phenotypic values are converted to shades of grey according to the scale bar

7 indicated below. Each vector competence index depends significantly on the specific

8 combination of vector genotype and virus isolate. Modified, with permission, from Ref.

9 [8].



10