Genetics of host–parasite interactions

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The evolution of host susceptibility or resistance to parasitoids has important consequences for the evolution of parasite virulence, host sexual selection, population dynamics of both host and parasite populations, and programs of biological control. The general observation of a fraction of individuals within a population that is not parasitized, and/or the variability in parasite intensity among hosts, may reflect several phenomena acting at different levels of ecological organization. Yet, host–parasite coevolution requires host susceptibility and parasite virulence to be genetically variable. In spite of evolutionary and epidemiological implications of genetic heterogeneities in host–parasite systems, evidence concerning natural populations is still scarce. Here, we wish to emphasize why we need a better knowledge of the genetics of host–parasite interaction in natural populations and to review the evidence concerning the inheritability of host susceptibility or resistance to parasites in natural populations of animals.

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Models of host–parasite coevolution usually assume that variation in host resistance to parasite infection is, at least partially, genetically determined. However, despite evolutionary (e.g., the evolution of parasite pathogenicity, genetic adaptation to local environment) and epidemiological (e.g., population dynamics of both hosts and parasites) consequences of genetic variation for parasite resistance, the presence of genetic heterogeneity in host populations with respect to probability of infection has been neglected, at least in natural populations of animals.

Most experimental evidence concerning genetic variability in susceptibility to parasites in animals comes from studies dealing with variation in disease resistance in domesticated and laboratory populations. The emphasis of these studies is understandable given the potential implication arising from the importance of the evolution of mechanisms of pathogen resistance for pest control and veterinary medicine. However, we have several reasons to expect a discrepancy between patterns observed from laboratory studies and natural situations.

Before addressing this particular issue, we review the evolutionary, ecological and epidemiological implications of genetic variation of susceptibility to parasite infections.

Host–parasite genetics and the evolution of virulence

In the past decade, a burst of work dealing with host–parasite interactions has provided a theoretical framework that has improved our understanding of the evolution of parasite virulence. The underlying idea is that parasite reproduction is traded against the negative effects of parasite proliferation on host fitness. In other words, the parasite faces a dilemma: should it speed up its own reproduction, with the potential damage to host survival, or manage host survival to increase its transmission? When the opportunity for transmission to a new host is high, the optimum value of this trade-off tends toward an increase in parasite virulence, whereas when the opportunity of transmission is low, the optimum tends toward a decrease in virulence. Linked to the effect of the opportunity of transmission for the evolution of virulence is the mode of transmission from one host to another. Vertical transmission, that is, transmission between closely related hosts (usually between mother and offspring) should select for benign parasites, whereas horizontal transmission (between unrelated hosts) should select for virulent parasites. Experimental and comparative evidence in agreement with this theoretical prediction is now accumulating.
How do host and parasite genomes interact to determine parasite virulence? In an elegant artificial selection experiment Bull et al. 11 addressed the question of the evolution of parasite virulence as a function of transmission mode, using bacteria and bacteriophages. They selected two lines of bacteria for ‘high partner fidelity’ (HPF; i.e. vertical transmission) and ‘low partner fidelity’ (LPF; i.e. horizontal transmission). The findings indicated a general decrease in virulence associated with phages selected in the HPF line as compared with those selected in the LPF line. Interestingly, the evolution of benevolence in the vertically transmitted phages was associated with genetic changes in both hosts and parasites. The descendant phages in the HPF line were considerably smaller than the ancestor, whereas the descendant phages in the LPF were identical to the ancestor phage. Similarly, comparisons of the HPF and LPF hosts with original bacteria showed that HPF and LPF had higher and lower growth rates, respectively, than the original hosts. Finally, HPF hosts evolved resistance to infection by another phage (T386), whereas the original bacteria were sensitive to it. These results indicate that both hosts and parasites experienced genetic changes during the evolution of the HPF line.

Host-parasite coevolution

Host-parasite coevolution is driven by the reciprocal evolution of host resistance and parasite infectivity. The mechanisms of host resistance and parasite infectivity may involve a single gene in each member of the association, as well as a complex of genes. On the basis of a ‘gene-for-gene’ interaction 12,13,14, only two possible outcomes for any host-parasite interaction are expected: susceptibility, which combines high disease severity with high parasite success, and resistance, which implies parasite failure to establish in the host. In another coevolutionary model—the matching allele model—each host allele confers resistance to one parasite allele. Parasites may thus successfully infect a host when there is no match between host and parasite alleles 15. The knowledge of the genetic model underlying susceptibility to parasite infection has important repercussions for our understanding of the mechanisms of host-parasite coevolution. Plant–pathogen systems offer many examples of ‘gene-for-gene’ interactions 13,14 (see Box 1; although it is not clear to what extent available data actually allow us to discriminate between the two models 15,16,17), but what about host-parasite coevolution in animals? Ogunremi and Tabel 18 conducted a breeding experiment with two mouse strains: one highly susceptible to Trypanosoma congolense, the other relatively resistant to the parasite. They crossed these two strains to produce reciprocal F1 and F2 offspring. The original susceptible and resistant strains differed in terms of parasite persistence and host survival, which was on average 12 days for susceptible mice and 163 days for resistant ones. The F1 had an intermediate phenotype between susceptible and resistant strains in terms of parasite clearance and host survival, with a survival period of 69.5 days. Resistance in F2 mice was inherited as a polygenic trait. Similar crosses conducted in laboratory animals provided estimates of heritability of susceptibility to parasites, confirming that in most cases resistance relies on a multigene system. Young et al. 19 estimated the heritability of susceptibility to infection using the protozoan Theileria parva in the tick Rhipicephalus appendiculatus. Using full-sib families, they found that heritability of susceptibility to infection ranged from 0.24 to 0.26 depending on the tick stocks used.

The evolution of genetic resistance to parasite infection is often assumed to be traded against other fitness components such as fecundity and growth 20. The rationale for this assumption is that an uncoupling resistance would spread very rapidly in the host population and the underlying genes should go to fixation within a few generations, leading to a population of resistant individuals. Costs of resistance can, however, include other types of indirect fitness reduction, such as increased susceptibility to other pathogens 21. Bell et al. 22,23 studied responses of mouse strains infected concurrently with Trichinella spiralis and Trypanosoma musculi, a haemosiagellate protozoan. They found that levels of Trypanosoma musculi in the blood were generally positively correlated with levels of Trichinella spiralis in the gut or muscles. In contrast, the effect of Trypanosoma musculi on levels of infection of Trichinella spiralis was dependent on the mouse strain and on the timing of infection with

### Box 1. Gene-for-gene systems in plant–pathogen associations

Extensive genetic polymorphism for both host resistance and parasite virulence has been reported in a number of plant–pathogen associations 13,14,43,44. The determinism of genetic resistance in plant–pathogen systems often involves a single gene: hosts are resistant when the dominant resistance allele (R) matches a corresponding avirulent (V) allele in the pathogen, and they are susceptible either when the pathogen are homoxogenous for virulence (vv) or when they are homozygous for susceptibility (rr). More than one locus can be involved in this gene-for-gene interaction 13. Gene-for-gene interactions have been demonstrated or suspected for a large number of plant–pathogen associations, including a wide variety of pathogens and host taxa 14,45. The table below shows the outcome of infection in a single locus gene-for-gene interaction:

<table>
<thead>
<tr>
<th>Pathogen genotype</th>
<th>Host genotype*</th>
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<tbody>
<tr>
<td></td>
<td>RR</td>
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<tr>
<td>vv</td>
<td>–</td>
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<tr>
<td>Vv</td>
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<td>vv</td>
<td>+</td>
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* R and r are rare resistance and susceptibility alleles, respectively; V and v are pathogen avirulence and virulence alleles, respectively; + and – indicate the outcome of pathogen infection: failure or success.

### Box 2. Genetic resistance in domesticated animals

Recent advances in molecular genetic techniques have led to an explosion of information on gene and genome structure and function, and this knowledge has been successfully applied to the understanding of the molecular basis of genetic resistance in several species of economically important domesticated animal species. Avian leukosis viruses

Avian leukosis viruses (ALV) are typical retroviruses that infect most chickens. The virus is responsible for the appearance of bursal lymphomas, so-called lymphoid leukosis, in adults 47. The ALV belongs to a group of avian retroviruses, the leukosis/sarcoma group. Three loci have been identified as controlling host resistance to these avian retroviruses. Susceptibility is dominant and the dominant allele at each locus apparently codes for a cell membrane receptor for ALV penetration. A survey of commercial White Leghorn (Gallus domesticus) breeding stock, and trials by primary White Leghorn breeders, showed that the frequency of the recessive resistance allele was very low. After an artificial selection experiment for resistance and susceptibility in three strains of White Leghorn, it was possible to obtain 100% resistance and 100% susceptibility in the two selection lines 47.

Major histocompatibility complex

The major histocompatibility complex (MHC) is a group of genes, present in all vertebrates, that codes for proteins located on cell surfaces. These proteins allow recognition of self and exapt genetic influence over a variety of biological functions, including immune response and disease resistance 48. Various examples of association between the MHC and parasite and disease resistance exist. In chickens, for instance, it has been shown that the B–G region of the MHC is involved in resistance to fowl cholera, a bacterial disease 49.
**Trypanosoma musculi** relative to that of *Trichinella spiralis*.

These examples clearly show that without a detailed knowledge of the genetics of both the host and the parasite, the outcome of the host–parasite interaction in natural populations, either in terms of coevolutionary interactions, or in terms of population dynamics may be difficult to predict. Although laboratory studies of parasite infections in various host populations may provide estimates of the range of responses expected to occur in an outbred population, such data must be interpreted cautiously. Results obtained from studies of a single host strain may not apply to others, and extrapolation to different host species may be particularly difficult.

**Genetic variability of susceptibility to parasites in natural populations of animals**

What is the evidence for genetic variation of susceptibility and infectivity in natural host populations? Unfortunately, very few studies have attempted to investigate the genetics of host–parasite interactions in natural populations; some of these are briefly reviewed below. The lack of data concerning natural populations is even more striking when compared with the relatively good knowledge of the molecular basis of those interactions in domesticated animals (Box 2).

Grosholtz24 presented evidence of significant levels of additive genetic variance in parasite resistance in the association between the mollusc bivalve *Transversella tantilla* and the trematode *Paravairreba borealis*. He used field enclosures to estimate the heritability of parasite resistance in natural conditions. The adult female molluscs were collected in the field and the offspring of these females were outplanted in the field enclosure where natural parasitism occurred. About two months later the clams were collected and the parasite load scored. The intensity of parasitism was significantly different among the clam families, with a moderate but significant heritability of 0.358. Similar results have been found for another invertebrate host, the aphid *Acrithosiphon pismum*, parasitized by the parasitoid wasp, *Aphidius ervi*. Henter and Via25 found significant variation in susceptibility to the wasp among aphid clones with levels of parasitism ranging from 2% to 77%, from 0% to 90% and from 0% to 85% in the three aphid groups they tested.

Bird nestlings are usually exposed to a large number of ectoparasites, which can induce considerable fitness losses to their hosts.26,27 Two studies have provided evidence of genetic variation in susceptibility to ectoparasites in birds. By using a partial cross-fostering method, Möller28 showed that siblings of the barn swallow (*Hirundo rustica*) reared by different adults in different nests had similar mite load of their natural parents (Fig. 1). In the kittiwake (*Rissa tridactyla*), a long-lived seabird, Boulinier et al.29 found a significant parent–offspring regression in tick (*Ixodes uriae*) load. The long-term population dynamic study conducted on this association allowed Boulinier et al. to compare tick load in parents and offspring at the same age, and to control for the principal environmental factors (spatial and temporal variability in parasite load), which could lead to a resemblance between parents and offspring.

**Conclusions and future prospects**

The findings of genetic variability of susceptibility to parasites in homogeneous environments (such as those created in the lab) does not necessarily imply that the same amount of genetic variation is actually expressed in variable environments. There is now convincing evidence showing that heritability estimates (of morphological traits, for instance) are higher when measured in the laboratory as compared with estimates from the field.30,31 The discrepancy between laboratory and field estimates of genetic variation has important evolutionary implications, since the response to selection depends on phenotypic variation, genetic correlations and genetic variances.32 It is likely that the same pattern of higher laboratory estimates of heritability holds for susceptibility to parasites; this would imply that parasites may add to the evolutionary advantage of a shorter generation time, a reduced amount of genetic variation being expressed for parasite resistance. The possibility of lower heritabilities of parasite resistance highlights the role of environmental (ecological) factors in determining phenotypic variation in natural populations.

On the other hand, the expression of genetic variation is likely to depend also on the quality of the environment.33 Heritability can be higher in poor environments if we consider parasites as an environmental factor, it is then possible to conceive that the expression of genetic variance is higher in those populations facing high levels of parasitic infections. Unfortunately,
no empirical evidence exists to support these hypotheses.

A better knowledge of the heritability of host resistance in natural populations would provide useful insight into several evolutionary and ecological issues related to host–parasite associations\(^4\). In other words, heritability estimates could be used to test existing theories or to predict how the host–parasite systems could behave. As an example, recent work has emphasized that parasites may be locally adapted to their hosts as a result of a coevolutionary process\(^29,35\). The likelihood that the parasite and the host are locally adapted to each other has theoretically been shown to depend on the relative importance of parasite and host migration and on the potential for evolution\(^36,37\). Empirical studies have provided qualitative support to this view showing that parasites may be better able to infect and develop in sympatric rather than in allopatric host populations\(^34,35\). However, counter-examples also exist where no local adaptation has been found\(^38\). Further studies should attempt to estimate migration rate of both parasites and hosts and genetic variability of host resistance and parasite virulence to know to what extent ecological and evolutionary factors may actually be responsible for local adaptation.

Heritability estimates from natural populations cannot be obtained easily. There is a large body of literature dealing with the potential bias of investigating genetic variation in the field\(^22\). Here, we sketch some potential protocols that could be used to obtain relatively 'unbiased' heritability estimates for natural populations of animals.

Cross-fostering experiments have provided useful insights into the genetic variation of morphological and life history traits in natural populations of birds\(^39,40\). Swapping eggs or nestlings from one nest with eggs or nestlings from another nest provides a possibility for control of post-hatching common environments, such as nest site and parental effort. The potential bias of this method involves non-genetic maternal effects acting during egg production. There is, for instance, some evidence that maternal antibodies can be transferred directly to eggs\(^41\), and this may result in related individuals having similar parasite loads even when raised by different parents in different environments. Since the production of maternal antibodies is likely to be largely influenced by environmental factors, such as body condition\(^42,43\), this can result in an overestimate of the genetic variation of susceptibility to parasites.

Long-term studies of population dynamics can also be used for estimates of 'broad-sense' heritability of susceptibility to parasites provided that sources of environmental variation can be statistically controlled\(^23,44\). Parent–offspring regression and full-sib analysis are probably the easiest way to estimate heritability for most vertebrate species, but they only allow partitioning of the phenotypic variance in overall genetic and environmental sources, whereas the heritability represents only the additive genetic variance\(^32\). Moreover, it is extremely difficult to obtain complete knowledge of the environmental factors that may account for resemblance among sibs or between parents and offspring, and therefore such heritabilities may be inflated because of environmental sources of variation.

A third method, which has been used in recent years, involves the use of semi-natural enclosures, where only some of the environmental factors are allowed to vary\(^34\). In this semi-natural situation we should expect to find heritability values of intermediate magnitude, since the environmental heterogeneity lies between those of homogeneous laboratory conditions and natural conditions.

In conclusion, while advances in molecular biology undoubtedly have provided fruitful insight into the mechanisms of parasite resistance, substantial effort is still required if we are to improve our knowledge of how these mechanisms are expressed in natural populations.

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References


I argue that there is a very good reason why the students of life's history are unknown today. They were second-rate scientists who inadequately (if at all) absorbed the message of Darwin's Origin, who indulged in intellectual navel gazing of a kind that makes contemporary French philosophy look good, who resolutely turned their back on the standards of good science, whose main motivation was not truly scientific but rather social (primarily, pushing messages about progress), who made their courses so dull that students would turn to Ancient Greek with relief, and who were rightly rewarded by being booted out of the universities and into less-demanding institutions, chiefly museums. In short, they retarded the advance of evolutionary studies by over half a century—in this at a time when Einstein was discovering relativity and the Curies were radioactive. Far from being significant factors for anything, from the point of view of evolution, they were an unmitigated disaster.

How can two historians of the same subject draw such completely different conclusions? I am sure we could both line up people to endorse our respective positions. I would start with John Maynard Smith who told me that he threw out all of the morphology when he started his vibrant school at Sussex. But it would be best if you read both of our books and made your own judgement. I will say that I think that Bowman limits himself by rarely working outside the printed text. This book shows that he has a brilliant ability to rummage through the libraries, bringing to light works that the rest of us miss, and he has an equally brilliant ability to read these texts. But if you work only through the printed word, you miss a vital part of the scientific enterprise. You start to take people too seriously at their public face value, you miss the social side to science (organizations, journals, grants, posts, and the like), and you fail to grasp the real status of the work you are considering.

In short, I argue that Life's Splendid Drama is an important but flawed book. Now what, I wonder, will Peter Bowler say about mine?

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