Limits to Knowledge in Evolutionary Genetics

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Anticipating Scientific Revolutions in Evolutionary Genetics

JODY HEY

INTRODUCTION

In day-to-day research in evolutionary genetics, it often seems as though our knowledge is bounded. We steadily perceive at least two major limitations on our capacity to understand the mechanisms and history of evolution. First, knowledge seems limited by the nature of history. It is certainly not useful to pursue a historical record that does not exist, as may be the case for many kinds of histories. Not all events, evolutionary or otherwise, leave an imprint in DNA or other media; and of the imprints that are made, none are expected to last indefinitely. Second, for the special case of evolutionary genetic histories, knowledge seems limited by the irreducible nature of DNA sequences. It does an investigator little good to try and glean more information from DNA than is available in the DNA sequence. So far as we know, every "A" base (adenine), for example, is like every other, and the information in a DNA sequence is in quanta (it is digital, base 4). These everyday perceptions of limits to inquiry may seem reasonable, and so they may provide a starting point for accessing what kinds of questions are more feasible than others. Perhaps we cannot reveal all of evolutionary history, but maybe we can understand and assess the limits to our knowledge of this history.

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Is anything wrong with this reasoning? Yes, something is wrong; it is incomplete and there are other issues that bear on research priorities. In this chapter I lay out a case for why a scientific focus on the limits of knowledge is a second-rate kind of science, at least for evolutionary genetics. Despite an accessible and reasonable motivation for a scientific focus on the limits of knowledge, I do not think that questions of that kind are sufficiently motivated for basic researchers to spend much time on them.

QUESTIONS CLEAR AND QUESTIONS NOT

I think that the limit of our knowledge is a worthy subject when our evolutionary questions are strictly posed, such that the words in the question have precise and well-understood meanings. In some sciences, like applied mathematics, where words do have relatively precise and unchanging meanings, questions about the limits of knowledge are frequent. It is common to address a very difficult question not with an answer, which may not be practically attainable, but with a quantitative assessment of how difficult the question is. Even though the specific question may not be answered, some knowledge is gained in explaining why. This kind of meta-knowledge still may carry a fair bit of intellectual satisfaction. However, if the question is important, such that it really mattered that it be resolved, then a concluding statement on the difficulty of the question, no matter how elegant or informative in other contexts, is not useful.

Some of our questions in evolutionary genetics are well posed in this way, and for them the meaning of the question is not a part of the puzzle and the words of the question are clear and invariant. These are often relatively small questions that are pressing for some practical or applied reason. For example, a corn breeder may ask an evolutionary geneticist, "When did maize diverge from its closest teosinte relatives?" The corn breeder needs a number, preferably with some assessment of confidence in that number. In our example, we suppose that the corn breeder does not care about the causes of uncertainty; it is the answer that is paramount. The clarity of the question and the need for the answer are pressing, even if one cause of uncertainty is that, to the evolutionary geneticist, words like "diverge" and "relatives" do not have precise meanings. In an evolutionary context "diverge" usually means to become different, but there are many ways to assess divergence. Also, divergence takes time, and so the question about "when" raises semantic difficulties, as it implies a distinct time point. Similarly, "relatives" in this example is used in reference to the relationship between two closely related species. But the meaning of "species" is one of our most famous and persistent ambiguities.

When the meaning of a question is clear to the person asking the question, and so long as the asker is not going to change those meanings, the question is strictly posed. In this case it is possible to consider the reasons why an answer might be difficult to obtain. Now consider instead that the same question is posed between two evolutionary geneticists. In this case, the question may very well go away or be changed considerably, as the discussion turns to the meanings of the words in the question. The uncertainty of the meanings of the words precludes discussion on the limits of knowledge. In this context the question is not strictly posed.

At any point in time researchers in a basic science are constrained by their concepts and their lexicon of the moment. Within those constraints it is possible to address the limits of knowledge. But a strong focus on the limits of knowledge is only interesting if we presume that our basic concepts and lexicon are fixed. We have seen that they may be fixed for practical reasons. The corn breeder has other things to worry about besides the details of uncertain evolutionary concepts, and so she assumes, for practical reasons, that the terms of her question are fixed. Another way that concepts and lexicon may be fixed is if our science has reached the truth, if no amount of additional evidence could cause our concepts and lexicon to undergo replacement or reduction. If somehow this did happen and we were aware of it, then further research on conceptual knowledge would stop, and probably the only purposeful work that remained for scientists would be to ask questions about the limits of our true knowledge. Of course it is impossible to know when we have the truth, so one might argue that we should never waste time thinking about the limits of knowledge. In practice, scientists necessarily have some level of confidence that their ideas correspond closely to universal truths. The higher the confidence, the more that questions about the limits of knowledge become appropriate, or at least seem to become appropriate.

Are the questions of evolutionary geneticists well posed? Do we have well-understood concepts behind the words we use, and do we have some confidence that those concepts will not be overturned? For many of the most interesting questions of broad scope, I do not think we are even close to these ideals. For example, consider the nature of debates that encircle the following questions: What are species? How did they come into being? How does natural selection shape patterns of variation in natural populations? Why did sex evolve? How did modern humans evolve? These are long-standing questions of broad interest, yet it could be difficult to make the case that they are congealed enough to merit a study of the ways we cannot answer them. For each example, one would have to begin an inquiry

on the limits of knowledge by laying out a precise meaning of the question, and in each case there is little reason for confidence that others would agree with the way the question had been posed.

SCIENTIFIC REVOLUTIONS AND HOW WE DO NOT SEE THEM

Regardless of one's view of the causes of scientific revolutions, they happen to all fields of inquiry. In the case of evolutionary biology, a good case can be made for at least two large turnovers since the time of Darwin's (1859) publication of *The Origin of Species*. The first is the flurry of questions and research that followed the rediscovery of Mendel's work, and the second is the modern synthesis (Provine, 1971). One of the most interesting features of these and other scientific revolutions is how investigators at the time could not anticipate them or even necessarily recognize when they were in the midst of them.

One of the best examples of scientific revolutions and of scientists' inability to anticipate them comes from physics; it hinges on the life and works of James Clerk Maxwell, the brilliant Scottish mathematician and physicist. Maxwell lived from 1813 to 1879 and was arguably the most capable of 19th-century physicists. Though he made many extraordinary contributions, his greatest legacies are the set of differential equations that describe the propagation of electromagnetic waves and the discovery that light and electromagnetic waves are both parts of the same thing. Maxwell's insight was generally far beyond his colleagues, and he was quite capable of simply sitting down and solving some well-posed problem of mathematical physics that had defeated everyone else. In 1871, he said: ". . . that, in a few years, all great physical constants will have been approximately estimated, and that the only occupation which will be left to men of science will be to carry these measurements to another place of decimals" (Harman, 1989, p. 244).

These words, however, were to be undermined by Maxwell's own discoveries. His findings about light and electromagnetism implied that electromagnetic waves propagated at a constant speed regardless of the speed of the observer. This created a conflict, eventually solved by Einstein with his theory of special relativity, that if the speed of light was constant, then velocities could not be additive, which they are under Newtonian mechanics.

Another player in the resolution of the conflict was Albert Michelson, who conducted the famous Michelson–Morley experiment, first in 1888,

which helped to show that the speed of light did not depend on the speed of the observer. Curiously, Michelson made a statement during the dedication of the Ryerson Physics Laboratory at the University of Chicago in 1894 that was very similar to Maxwell's:

> The more important fundamental laws and facts of physical science have all been discovered, and these are now so firmly established that the possibility of their ever being supplanted in consequence of new discoveries is exceedingly remote. . . . Our future discoveries must be looked for in the sixth place of decimals. (Bernard, 1960, p. 123)

These brilliant scientists had no idea what was in store for their field, nor how their most basic concepts on natural laws were fundamentally wrong or at best sorely incomplete. In 1904, Einstein resolved the paradox that Maxwell had started, with the theory of special relativity. However, special relativity in turn generated a contradiction in Newton's theory of gravitation, which until then had been very successful. To resolve this, Einstein developed a new theory of gravity, the theory of general relativity. In this theory, gravity is not an instantaneously propagating force between masses, but rather a manifestation of the curvature of space–time, which in turn is shaped by the distribution of energy and momentum.

Newtonian mechanics and gravitation were wonderfully successful theories that did not quite work. Einstein's view of the universe worked much better—it even predicted the existence of black holes—but it was a very different universe than the one Maxwell and Michelson thought they lived in.

Maxwell's insight and lack of prescience extended even further. His theory of electromagnetism also revealed conflicts between electromagnetic theory and the theory of thermodynamics. The resolution of these conflicts, by Plank, Bohr, Heisenberg, Schrödinger, and de Broglie, took some time, but eventually led to what is now called quantum mechanics. During the problem solving, the view of the electron went from being literally a discrete subatomic particle to being literally a probability cloud.

These theories, special and general relativity and quantum mechanics, hold little resemblance to the physics of the 19th century that they replaced. The "knowledge" held by great scientists like Maxwell and Michelson within a few years was shown to be mostly wrong. The models that came to the fore and that persist were of an almost impossibly strange universe. Ironically, even as these scientists were laying the foundation for the revolution to come, they were boasting of the refined state of their science and elaborating on the limits of the knowledge.

If that kind of transformation can happen to as highly refined a science as physics of the late 19th century, then what transformations of knowledge might still lie in store for physics and other fields? In evolutionary genetics, what kind of revolution would be on a scale comparable to what occurred in physics? We could hope for any number of apparently impossible things. How about finding out that history also leaves an imprint, a better imprint, in some other media besides DNA or rocks. Or suppose time travel became possible for some totally unforeseen reason? Do these things seem any more impossible than the revolutions that occurred in physics? If for some reason we knew a revolution was coming, would we spend time on investigating the limits of knowledge under our current models?

By way of example, this physics history has served two points. The first is that scientific revolutions can happen regardless of our confidence in the anchors of what we presently call knowledge. The second is that we may not see the scientific revolutions coming. Fallible scientists sometimes miss the scientific revolution that is beginning to boil in their midst. Failing this insight, they may even expound on the advanced state of their science or elaborate on the limits of their knowledge.

SCIENTIFIC REVOLUTIONS IN PROGRESS

Not all scientific revolutions are big, and much of the turnover of knowledge and questions that occurs in a field of inquiry does not deserve to be called a "revolution." Yet perhaps we can look at the state of our field and see signs of revolutions (small or big) in progress. The examples from physics suggest this may be difficult, but at the very least we can draw from these historical lessons and try to avoid a strong presumption of the security of our current knowledge. Similarly, there is nothing to prevent us from looking for rumbles of revolutions within our midst, inconsistencies and puzzles that may be the seeds of future turnovers.

Like any quickly moving field, evolutionary genetics is in flux with all manner of minirevolutions happening at any one time. However, there is at least one revolution in progress that seems to portend something larger on the horizon, and so it deserves some telling. This revolution hinges on the recent findings that natural selection plays the major role in shaping patterns of DNA sequence variation within and between taxa. There are two distinct components to these findings. The first are the many rejections of the neutral model that are based on commonly used neutral models and selective alternatives. The second component consists of observations,

coupled with the reawakening of some old theory, that do not fit well into any of the standard neutral–selective paradigms (Hey, 1999).

Rejecting the Neutral Model

In the first category are the numerous reports of rejection of neutral model predictions, all of which fall in the grand tradition of the neutralist–selectionist debate. Repeatedly, we see that the null model (neutrality and sometimes other assumptions) cannot explain a pattern in the data, thus lending statistical support to historical models that include natural selection. There are now dozens of reports of clear rejection of the neutral model. Some date to allozyme days, but the majority have come from applying new tests to comparative DNA sequence data. These observations in turn fall into two major categories. There are those tests that rely on both a specific population model (generally the Fisher–Wright population model) and the neutral infinite sites mutation model. Examples include the tests of Tajima and Fu and Li (Tajima, 1989; Fu and Li, 1993) as well as the famous Hudson Kreitman Aguadé (HKA) test (Hudson *et al.*, 1987). These tests have turned up a number of null model rejections, but they are sensitive to a number of things besides selection. Then there are those tests that do not depend on a specific population model. These include the McDonald–Kreitman test (McDonald and Kreitman, 1991) and a variety of ad hoc tests that have relied on other predicted covariates of selection (Begun and Aquadro, 1992; Kliman and Hey, 1993; Aquadro *et al.*, 1994; Akashi, 1994, 1996).

One of the most interesting and surprising aspects of these findings is that many of the conclusions regarding natural selection do not concern amino acid variation. It is now clear that natural selection plays a large role in determining codon usage in *Drosophila* (Akashi, 1994, 1995; Kliman and Hey, 1993, 1994; Akashi and Schaeffer, 1997). Also, since *Drosophila* introns are less variable and evolve more slowly than synonymous sites, it necessarily follows that intron sites also are under a fair bit of selective constraint.

The Rediscovery of the Hill–Robertson Effect

The second component of what may be a scientific revolution in progress is the reawakening of some 30-year-old theory and the data that have inspired it. In 1966, Hill and Robertson studied the effect of linkage, between two sites each segregating two alleles under selection, on the

probability of fixation of advantageous mutations. They found that under linkage, selection at one locus had a large impact on the probability of fixation at a second locus, and vice versa. In essence, the presence of linkage between two sites, each with alleles that varied in their contribution to fitness, caused the effectiveness of natural selection on both sites to be reduced. It is somewhat incongruous, but the more polymorphic sites that are added in linkage, the more poorly the process of natural selection acts to increase the frequency of the better alleles at each site. The effect is analogous to an acceleration in the rate of random drift: When more polymorphic loci are added in linkage, it is as if there were a reduction of the effective population size experienced by each locus (Hill and Robertson, 1966).

This work did not play a large role in the neutralist–selectionist debate, though it was certainly relevant (Lewontin, 1974), and until recently it has been absent from the molecular evolution literature. It was, however, Felsenstein's major reference in his seminal papers on the evolutionary advantage of sex (Felsenstein, 1974; Felsenstein and Yokoyama, 1976).

The basic idea is that selection at some sites adds an effectively random component to the variance in reproductive success that goes on at linked sites. In the days of population genetics, prior to the advent of large amounts of genotypic data, when allozymes and allele-based models ruled the day, the allozyme loci that were under study typically had large amounts of recombination between them. Rarely did authors find evidence of linkage disequilibrium between loci, and linkage effects were not a large component of our thinking with regard to natural selection. Today, with genotypic data and with more and more data sets emerging that describe lengthy haplotypes, the situation has changed and typically most of the polymorphisms reported in a study are tightly linked.

The observation that has pressed the Hill–Robertson issue is the one by Begun and Aquadro (1992), that polymorphism levels in *Drosophila melanogaster* correlate strongly with per generation recombination rates. This finding falls squarely in the domain of the Hill–Robertson effect: Genomic regions with less recombination experience more of the Hill–Robertson effect, as every polymorphic site is likely to be linked to many selected sites, and have a reduced effective population size and support reduced polymorphism levels. Today, the single most active area of research in *Drosophila*–theoretical population genetics is figuring out what kind of selection best explains this effect (Charlesworth, 1996).

The two main contenders are hitchhiking of selectively favored mutations and background selection against deleterious mutations. Both are models of strong selection and both are a limiting case of the more general Hill–Robertson effect. The hitchhiking model assumes neutrality for

segregating variants and it envisions rare beneficial mutations that effectively run a broom through some portion of the genome, sweeping up all polymorphisms in a swath the width of which is defined by linkage (Maynard Smith and Haigh, 1974). The background selection model also assumes neutrality for segregating variants, at least those detectable in a sample of DNA sequences. In addition, a large proportion of all sequences are linked to deleterious mutations. Though each deleterious mutation is rare, there are many for large genomic regions of low crossing over, and so overall the effective population size can be greatly reduced to just that fraction that is not tightly linked to a deleterious mutation (Charlesworth *et al.*, 1993).

The Seeds of a Revolution

What is sometimes overlooked in discussions of the relative merits of these models is that moderate or weak selection also can generate an appreciable Hill–Robertson effect. A mutation need not be strongly selected in order for selection to perceive it, especially if population sizes are large. Recall the growing heap of evidence that selection, acting within relatively small portions of the genome (e.g., the scope of a typical comparative DNA pop gene study), has played a large role in shaping variation. Recall also the very clear evidence that natural selection has a large impact on synonymous site variation, and that introns are not more variable and do not evolve faster than synonymous sites. In short, there is a large body of evidence that weak selection is acting on many of the polymorphisms that are segregating. It even seems possible that for large populations like *Drosophila*, selection may be able to detect essentially all the variation that is segregating.

The evidence for weak selection (e.g., on synonymous sites and intron sites) necessitates a closer look at the Hill–Robertson effect. In particular, it is worth asking, "How much of the observations that have been made and attributed to the Hill–Robertson effect may be due to weak selection?" The debate over Begun and Aquadro's (1992) observations have concerned the strong selection models, background selection, and selective sweeps (Charlesworth *et al.*, 1995; Hudson and Kaplan, 1995; Hamblin and Aquadro, 1996). Yet it may be that weaker selective effects have made a large contribution to the observation.

By way of example and to consider specifically the effects of weak selection under tight linkage, we can develop a model based upon the *Drosophila* dot chromosome. The euchromatic portion of this chromosome in *D. melanogaster* is probably about one megabase in length (Ajioka *et al.*, 1991). Most importantly, the chromosome experiences no crossing over, and

polymorphism levels on it are sharply reduced relative to most regions of other chromosomes (Berry *et al.*, 1991). Let us ask the question, "What proportion of the observed drop in variation would be found if *all* mutations were weakly selected?" To examine this, assume that the rate of incoming mutations is the same as in the rest of the genome, and assume that all mutations are weakly selected, with a small value for the product of effective population size and selection coefficient (s). We can use estimates of 2 Nu for the rest of the genome as a starting point for the population mutation rate experienced by the fourth chromosome (N is the effective population size and u is the mutation rate per generation). From a variety of genes, estimates for 4 Nu, tend to be around 0.005 per base pair for *D. melanogaster* (Moriyama and Powell, 1996). Assuming conservatively that this is twice the *total* (i.e., not just neutral) input of mutations every generation (i.e., $2 \times 2\ Nu$), then we can use the value of 0.0025 as the mutation rate per generation per base pair for the entire population. Then, for the entire megabase of the fourth chromosome we would expect there to be about $10^6 \times 0.0025 = 2500$ new mutations each generation.

A computer program was written that simulates a population of chromosomes that is receiving new mutations and from which samples are periodically assayed for polymorphism levels. Figure 1 shows results for the case of 2 $N = 50$, over a range of 2 Ns values and 2 Nu values. The highest value of 2 Nu (2500) mimic the case described for the *Drosophila* fourth chromosome. Figure 2 shows the results for 2 $N = 500$. In both figures, it is clear that very weak selection ($2\ Ns \leq 1$) can have a large effect on polymorphism levels. The effect is slightly less for 2 $N = 500$ than for 2 $N = 50$, suggesting that N is an important parameter in these considerations. Thus it is not clear from these results what proportion of the observed fourth chromosome effect (which arises from very large values of N in natural populations) could be due to very weakly selected mutations. However, these results clearly show that weak selection and tight linkage can lead to a strong reduction in polymorphism levels. In practice, we have little insight on the strength of selection on synonymous sites and intron sites [but see Akashi and Schaeffer (1997)]. However, if they are under selection, they will contribute to a Hill–Robertson effect, and this effect may be considerable under high mutation rates and tight linkage. Also, all these simulations generated slightly to moderately negative values of Tajima's D (Tajima, 1989), typically on the order of –0.5 (results not shown).

If indeed most segregating variants have some phenotypic effect and are under selection, and if they make an appreciable contribution to a Hill–Robertson effect, then there are several ideas held dear by evolutionary geneticists that may get overturned. There seem to be at least three noteworthy components of the scientific revolution in progress, and it remains to be seen how large they will grow:

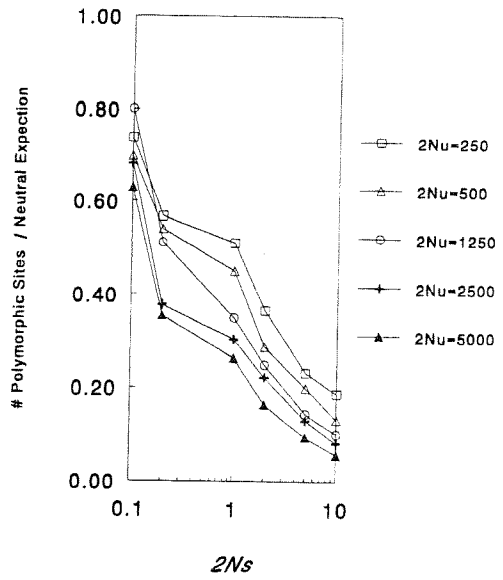

FIG. 1. The number of polymorphic sites, relative to that expected under neutrality, as a function of the strength of selection, 2 Ns, and the mutation rate, 2 Nu. Each point represents the mean of 100 measurements of the number of polymorphic sites in a random sample of 8 sequences. This mean value was divided by the expected number of polymorphic sites assuming neutrality of all mutations:

$$4\ Nu \sum_{i=1}^{n-1} \frac{1}{i}$$

for $n = 8$ (Watterson, 1975). Simulations were carried out using a constant population size of 50 chromosomes ($N = 25$), with no recombination. Mutations were added following an infinite sites model, each new mutation assigned to an unused segment of the genome (Kimura, 1969). Half of all mutations had a beneficial selection coefficient of s and half had a deleterious effect of s. Fitness was multiplicative across loci, with no dominance. In each generation following the addition of new mutations, individuals are grouped by fitnesses, and the numbers in each class in the next generation were generated by randomly sampling from a multinomial distribution having parameters that were the expected number of individuals in each fitness class following selection. The next generation was formed by randomly drawing (with replacement) the appropriate multinomial random number from each fitness class.

1. The ongoing debate over selective sweeps versus background selection may be too simplistic. At present, discerning the two models is very difficult, and the problem may become more difficult as we realize that other models also account for the data.
2. Our current search for estimates of the population neutral mutation parameter, 4 Nu, may be misguided. If all polymorphisms are under selection, then neutral model predictions are less interesting.

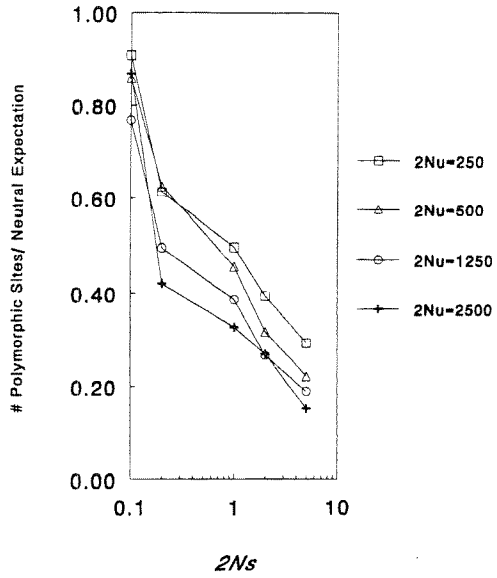

FIG. 2. Simulations results for a population size of 500 chromosomes ($N = 250$). See Fig. 1 legend for details.

Furthermore, if segregating polymorphisms are causing a Hill–Robertson effect, then they are reducing the effective population size for that portion of the genome in which they segregate. Thus even the highest current estimates of 4 *Nu* may be a good bit lower than would be found with only neutral mutations and no Hill–Robertson effect.

3. What do we mean by "natural selection" when we think of it acting on DNA sequence variation? If most polymorphisms are under selection, and the Hill–Robertson effect is pervasive, then the conventional distinction between genetic drift and natural selection becomes completely entangled with itself. Consider this circle: (1) if there are multiple sites under selection and linkage, then the Hill–Robertson effect comes into play and there is more genetic drift; but (2) the faster genetic drift goes, then the fewer sites are perceived by natural selection and the more weakly selected sites become effectively neutral. The idea seems constitutively antithetical, as if "natural selection equals genetic drift." Actually it is close to this, but there is an important distinction to be made. It is not natural selection that causes more drift, but rather segregating functional variants. In short, when there are more of these under linkage, then natural selection works more poorly, necessarily, as there is a concomitant acceleration in the rate of genetic drift.

This last point may be the most significant in the context of scientific revolutions. In the time since Kimura taught us the neutral model, evolutionary geneticists have had two poles of evolutionary forces between which lay virtually all their thinking about the way that evolution worked. Natural selection has been the deterministic force, whereas genetic drift is the random force. There is a possibility that this paradigm will have to give way, as we find that the two are interlinked in ways we are only poorly prepared to think about.

CONCLUSIONS

While it may be appropriate for scientists in some mature fields to look inward and develop a research program on the limits of their science, I do not think evolutionary genetic research of this type is worthwhile. In this chapter I have outlined three main reasons for this view.

In the first place, the large questions of evolutionary genetics are not very well posed, and this is for the simple reason that there is considerable disagreement among scientists on the meanings of a large portion of our lexicon. Any attempt to focus on the limits in pursuing a specific question would have to occur within a relatively small community who understood with unanimity the meaning of that question. In general, questions of this type will be small and so the value of insights to the limits of knowledge may not be very interesting.

But suppose we were to consider just those questions that are not subject to very much uncertainty and that seem to be clear in the same way (and for the same reasons) to an entire community of scientists. Certainly we perceive limitations on our capacity to answer questions of this sort, so why not explore these limitations? In this situation scientists can and often do focus on the limits of knowledge. However, even these efforts may prove pointless. The reason, and this is the second reason against dwelling on the limits of knowledge, is that scientific revolutions do occur. They can arrive suddenly, without foreshadowing, and when they do, the old knowledge goes into the history books. Imagine being a researcher focused tightly on the limits of knowledge in your field, when suddenly your firmament is overturned. Your work may not even make the history books. Imagine instead, spending one's energy bringing on the revolution; how much more potential for discovery, and fun, lie in the path of a research program that is focused on resolving the large primary questions in a science.

The third and final point is that evolutionary genetics is currently undergoing scientific revolutions, though most are probably small. Ongoing

revolutions can be difficult to recognize, as they may not be quick, and it may be difficult to foresee the future impact of day-to-day discoveries. But I think a good case can be made that we may be in the midst of a fairly large scientific revolution. There is a chance that our current ways of thinking about natural selection and our usual distinctions between genetic drift and natural selection may be about to undergo a fairly large change. At least, it does not seem to be a good time to dwell on the limits of our current knowledge when there is the chance to find out that much of what we think we know is wrong.

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