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Parallel genotypic adaptation: when evolution repeats itself

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Abstract

Until recently, parallel genotypic adaptation was considered unlikely because phenotypic differences were thought to be controlled by many genes. There is increasing evidence, however, that phenotypic variation sometimes has a simple genetic basis and that parallel adaptation at the genotypic level may be more frequent than previously believed. Here, we review evidence for parallel genotypic adaptation derived from a survey of the experimental evolution, phylogenetic, and quantitative genetic literature. The most convincing evidence of parallel genotypic adaptation comes from artificial selection experiments involving microbial populations. In some experiments, up to half of the nucleotide substitutions found in independent lineages under uniform selection are the same. Phylogenetic studies provide a means for studying parallel genotypic adaptation in non-experimental systems, but conclusive evidence may be difficult to obtain because homoplasy can arise for other reasons. Nonetheless, phylogenetic approaches have provided evidence of parallel genotypic adaptation across all taxonomic levels, not just microbes. Quantitative genetic approaches also suggest parallel genotypic evolution across both closely and distantly related taxa, but it is important to note that this approach cannot distinguish between parallel changes at homologous loci versus convergent changes at closely linked non-homologous loci. The finding that parallel genotypic adaptation appears to be frequent and occurs at all taxonomic levels has important implications for phylogenetic and evolutionary studies. With respect to phylogenetic analyses, parallel genotypic changes, if common, may result in faulty estimates of phylogenetic relationships. From an evolutionary perspective, the occurrence of parallel genotypic adaptation provides increasing support for determinism in evolution and may provide a partial explanation for how species with low levels of gene flow are held together.

Keywords

adaptation; artificial selection; convergent evolution; experimental evolution; homoplasy; natural selection; parallel evolution

Introduction

Homoplasy, or the recurrence of similarity in distinct evolutionary lineages, occurs frequently in nature. Such similarities have been documented at practically every level of biological organization, from nucleotide/amino acid sequences (Stewart, Schilling & Wilson 1987) to large scale deletions (Downie & Palmer, 1992), whole genome duplications (Soltis & Soltis, 1991), and the acquisition of complex phenotypic characters such as succulent, spiny stems in the Euphorbiaceae and Cactaceae. There is even evidence of the repeated origin of animal and plant species (Soltis & Soltis, 1991; Rundle et al., 2000; reviewed in Levin, 2001). This list includes examples of both molecular and morphological homoplasy, which are generally

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thought to be the result of distinct evolutionary processes. Because it is unlikely that complex phenotypes would arise repeatedly via a stochastic process, morphological homoplasy is widely regarded to be the result of selection. In contrast, nucleotide sequences are limited in the number of ways that they can evolve, thus most instances of molecular homoplasy have been interpreted as the chance fixation of independently arising variants in diverging lineages (Doolittle, 1994; Wells, 1996).

Although morphological homoplasy is generally viewed as being driven by natural selection, many evolutionary biologists assume that the phenotypes of interest result from unique genetic changes. In some cases, they are clearly right: The evolution of spines in euphorbs and cacti results from the modification of non-homologous structures. In cases where homology is plausible, this view is perhaps best explained by the traditional acceptance of Fisher's infinitesimal model, in which quantitative traits are assumed to be controlled by an effectively infinite number of genes, each of very small effect (Fisher, 1930). Under this view, there should be numerous paths from any one phenotype to another. Thus, the likelihood that two lineages would independently accumulate changes at the same subset of underlying loci would be low. It has become increasingly clear, however, that continuous patterns of variation may sometimes be explained by the existence of a few major quantitative trait loci (QTLs) (Tanksley, 1993). Under this so-called oligogenic model of inheritance, the number of pathways from one phenotype to another is considerably more limited, increasing the likelihood that parallel phenotypic changes have a common genetic basis.

In organisms where connections between genotype and phenotype have been made, there is emerging evidence that molecular homoplasy is sometimes driven by natural selection. Unfortunately, our understanding of the genetic basis of all but the simplest traits in the simplest organisms is woefully incomplete. Thus, it is difficult to say with any certainty whether or not some of the more complex instances of morphological homoplasy have a common genetic basis. Here, we review the best examples of selection driving different lineages to the same phenotype through the fixation of independent changes at homologous loci. This pattern of evolution has several important implications. With respect to phylogeny reconstruction, it is widely recognized that homoplasy, regardless of the cause, can lead to inaccurate conclusions regarding the evolutionary history of taxa. Parallel selection responses at the genotypic level also suggest that adaptation may be a more deterministic process than previously believed, with genetic background effects and historical contingency playing a lesser role. If parallel changes prove to be common, they may provide a mechanism by which populations of a species can evolve collectively. Furthermore, such changes may increase the likelihood of the recurrent origin of taxa by allowing geographically isolated populations of the same species to independently invade a novel, unoccupied habitat.

Definitions

Historically, taxonomists have divided phenotypic homoplasy into two categories, parallelism and convergence. Parallel evolution is defined as 'the independent occurrence of similar changes in groups with a common ancestry and *because* they had a common ancestry' (Simpson, 1961, p. 103). In contrast, 'convergence is the development of similar characteristics separately in two or more lineages without a common ancestry pertinent to the similarity but involving adaptation to similar ecological status' (Simpson, 1961, pp. 78–79). As noted above, selection is believed to be the primary evolutionary force causing the recurrence in both situations.

The advent of DNA and protein sequencing necessitated a more precise definition of these terms. Molecular evolutionary biologists use parallelism and convergence in an analogous yet distinct manner. Nucleotide or protein sequence changes from the same ancestral state to the

same derived state are called parallel changes, whereas changes from different ancestral states to a common derived state are considered convergent changes (Zhang & Kumar, 1997; Figure 1). Because our goal is to make an explicit connection between evolution at the phenotypic and genotypic levels, we need an operational definition that bridges the phenotypic and molecular views. Thus, we define parallel genotypic adaptation as the independent evolution of homologous loci to fulfill the same function in two or more lineages. Note that these changes need not be identical, just functionally equivalent. Under this definition, changes at non-homologous loci resulting in the same phenotype would be considered convergent (e.g., Chen Devries & Cheng, 1997), and fall outside the scope of this review.

Another possibility involves the independent duplication of a homologous, ancestral locus (A) to yield two descendant loci (B) (Figure 2). In this case, the two independently derived loci are not technically homologous. However, because the two loci are direct descendants of true homologues, we consider cases in which such loci evolve to fulfill a common function to be examples of parallel genotypic evolution. The growing body of genomic data suggests that gene duplication is a common phenomenon (Lynch & Conery, 2000), and its importance in generating the raw material for adaptive evolution has been widely recognized (e.g., Haldane, 1932;Ohno, 1970). Thus, future analyses may reveal this process to be a common mode of parallel evolution.

Empirical evidence

Experimental evolution studies

The clearest evidence of parallel genotypic adaptation comes from artificial selection experiments in the lab or greenhouse (Table 1, Section A). The strength of this approach lies in the fact that researchers control both the relevant selective pressures acting upon and the evolutionary histories of the populations under study. The short generation time and relative ease of characterizing genetic variation in certain microbes makes them ideal organisms in which to study the genotypic response to uniform selective pressures. In general, these studies have revealed that selection pressures such as temperature or host shifts commonly lead to parallel genotypic adaptation (Table 1). Moreover, there is evidence that these phenotypic shifts often result from minor sequence changes; in some cases, one or a few nucleotide substitutions at a single locus accounted for the entire response to selection (Liao, Mckenzie & Hageman, 1986;Cunningham et al., 1997;Crill, Wichman & Bull, 2000). While these studies are intriguing, they have an obvious shortcoming – the dynamics of selection in these simple organisms might not be representative of adaptation in more complex organisms. In taxa with larger and more complex genomes, selective constraints due to genetic background effects or antagonistic pleiotropy may play a more important role.

Although our understanding of the molecular basis of selection response in higher organisms is incomplete, several studies in Table 1 document parallel evolution in eukaryotes. The best experimental evidence comes from a comparison of resistance to acetolactate synthase inhibitors in naturally occurring cocklebur and two mutagenized maize lines (Bernasconi et al., 1995). Given that resistance in this case is based on a single enzyme, this result may not be predictive of the types of changes that underlie parallel phenotypic evolution in more complex traits. While there are very few studies that bear on this issue, Ungerer (2000) found that the frequency of QTL alleles governing life history traits responded uniformly to viability selection in replicate *Arabidopsis* populations, even when genetic background was varied. Similarly, working in sunflower, Rieseberg et al. (1996) showed that experimental hybrid lineages subjected to strong fertility selection converged on a common genomic composition. Because this fertility selection was primarily the result of selection for the recovery of viable gametes in interspecific hybrids, the underlying adaptive process is mechanistically distinct from classical examples of adaptation involving allelic substitution at a targeted locus.

However, this study clearly demonstrates that parallel selection among lineages can yield remarkably similar genotypic responses. One weakness of conclusions drawn from these two studies is that they did not provide the necessary resolution to conclude that selection is acting on variation at homologous loci across populations. In addition, both of these studies relied on variation generated in crosses between different lineages, rather than on novel variation. They do, however, show that selection response at the genotypic level is repeatable across populations. Thus, given the appropriate genetic variation, we might expect the evolution of complex traits to mirror the findings from genetically simpler traits.

Phylogenetic studies

While experimental studies allow researchers to control the branching pattern of lineages and monitor their response to selection, parallel genotypic adaptation can be assessed in non-experimental systems as well. One approach is to use phylogenetic methods to infer the evolutionary history of the organisms of interest. This phylogeny can then be used to reconstruct the historical sequence of mutational changes in a nucleotide or protein sequence with known function. The advantage of this approach is that it can be applied to virtually any organism; thus, parallel evolution can be studied across vast taxonomic distances and in organisms that are not amenable to experimental manipulation. The main difficulty is that, in order to show that homoplasy is adaptive in origin rather than the result of chance fixation, the functional effects of a sequence change must be known, or at least inferred (Doolittle, 1994).

Once a relationship between genotype and phenotype has been established, the basic challenge is to demonstrate that shared sequence similarities are not simply the result of common ancestry. Because sequences that have evolved in parallel will show phylogenetic affinity, the detection of parallel genotypic adaptation can be problematic. Of course, if the adaptive change results from relatively few nucleotide substitutions, homoplasy may have only minor effects on phylogenetic inference. In other cases, where the ratio of informative sites to selectively advantageous substitutions is relatively low, the framework for these analyses should be based on independent phylogenetic data. Assuming that the structure of the resulting tree represents the true evolutionary history of the organisms, detecting homoplasy is as simple as mapping character states onto this tree (Figure 1). The phylogenetic approach can also be used within taxa to examine the pattern of evolution of a gene in a geographic context. For example, Andreev et al. (1999) used a phylogeny of alleles of *Resistance to dieldrin* to demonstrate that the same point mutation arose on multiple occasions in different populations of the red flour beetle, *Tribolium castaneum*

The middle panel of Table 1 lists examples of parallel genotypic adaptation documented with phylogenetic methods. Although this set of studies includes examples from microorganisms, the taxonomic diversity represented clearly demonstrates that parallel genotypic adaptation occurs at all taxonomic levels. Once again, many of these examples involve minor sequence changes. In fact, parallel adaptation in four of these studies was based on a single amino acid substitution (Morris, Bowmaker & Hunt, 1993;Elard, Comes & Humbert, 1996;ffrench-Constant, 1996;Andreev et al., 1999).

While many of the traits listed would generally be viewed as complex, what the studies in Table 1 say about parallel evolution in simple versus complex traits is unclear. Part of the problem here stems from the definition of traits. For example, the spectral properties of visual pigments represent one aspect of color vision, which is clearly a complex trait (Yokoyama & Yokoyama, 1990;Morris, Bowmaker & Hunt, 1993;Shyue et al., 1995). Thus, parallel evolution of the genes encoding these pigments could be viewed as the parallel evolution of a highly complex trait. If, on the other hand, the trait is defined to be spectral tuning, then the trait of interest is Mendelian, no different from herbicide resistance in cocklebur and maize. The difficulty here lies in the fact that, from an evolutionary perspective, traits should be defined by what selection

sees, not what the researcher sees. For example, if selection acts to increase the height of a hypothetical organism, parallel genotypic responses may be less likely than if selection acts on a specific component of height, such as cell number or cell size.

A number of the studies included in this section demonstrate sequence homoplasy for loci that have a known adaptive function, but the parallel changes themselves have not been demonstrated to be under selection. Thus, although an adaptive role for these changes is plausible, their functional significance has not been directly assessed (e.g., Romero-Herrera et al., 1978; Jouvin-Marche et al., 1988). Moreover, only two of the examples in this section (Stewart, Schilling & Wilson, 1987; Zhang & Kumar, 1997; Kriener, 2000) have been evaluated statistically. Unfortunately, the statistical model used to evaluate the role of selection in parallel sequence changes (Zhang & Kumar, 1997) is, out of necessity, naive to protein function. Because it uses a general evolutionary model to ascribe probabilities to changes between sequence states, this approach can lead to false positives. For example, if a given amino acid site is constrained on the basis of charge, it is free to evolve, but in a more limited number of ways. Therefore, the number of possible states can be far fewer than the model allows. In such cases, the test will be biased toward detecting significant parallelisms even though the changes may have occurred by chance. Ultimately, sequence changes need to be linked to a change in function to demonstrate unequivocally parallel genotypic adaptation.

Quantitative genetic studies

Another approach to detecting parallel genotypic adaptation in non-experimental systems involves quantitative genetic analysis. The most direct method is a complementation test, in which two lineages are crossed and the segregation patterns of their hybrid offspring are analyzed. If a shared, yet independently derived character state has a common genotypic basis, it will not segregate in the second (or later) generation(s). In contrast, if the character is determined by non-homologous loci, the hybrid progeny should exhibit significant phenotypic variation. An example of this approach is the work of Schat, Voour & Kuiper, (1996; Table 1), who demonstrated that metal tolerance in genetically isolated populations of *Silene* results from changes at homologous loci.

Comparative QTL mapping can also yield evidence for parallel genotypic responses. In this case, molecular markers are used to identify chromsomal regions underlying the trait(s) of interest in a segregating population (see Mauricio, 2001 for a review). In cases where homologous markers are shared across mapping populations, QTL positions can be compared between taxa. When QTLs map to the same marker intervals, the results are consistent with parallel genotypic adaptation. Although QTL methods have been applied to a wide variety of study organisms, there are only three good examples of parallel adaptation identified through this approach (Fatokun et al., 1992; Paterson et al., 1995; Hu et al., 2003; Table 1).

In all three of these cases, it is important to note that the effects of closely linked, but non-homologous loci cannot be discounted. Thus, like the map-based studies of Ungerer (2000) and Rieseberg et al. (1996) detailed above, conclusions regarding homology of the changes are premature. In addition, all three of the studies focus on domestication traits. Like the examples listed under experimental evolution above, these traits have evolved in response to strong artificial selection. Because artificially selected lineages are generally maintained in a controlled environment (e.g., lab, greenhouse, or agricultural setting), they are not necessarily subject to the same pleiotropic constraints as naturally evolving populations. Therefore, the relevance of these studies to the evolution of traits in the wild is tenuous (Coyne & Lande, 1985).

Evolutionary implications

Each of the studies reviewed here provides at least circumstantial evidence that parallel genotypic adaptation occurs at all taxonomic levels. This finding stands in stark contrast to the traditional view that parallel phenotypic evolution results from unique genetic changes. Given that a number of the traits listed above are simple (i.e., Mendelian), this result should not be surprising. After all, if a trait is controlled by a single gene, phenotypic evolution can involve changes in only that gene. As the complexity of an adaptation increases, the likelihood of its parallel recurrence should decrease. In other words, if there are numerous pathways connecting two phenotypic states, it is relatively unlikely that evolution will follow the same path twice. As stated above, however, there is a growing body of evidence that many quantitative traits are controlled oligogenically (Tanksley, 1993). In addition, apparently complex traits can often be decomposed into their component parts (e.g., color vision versus visual pigments; Morris, Bowmaker & Hunt, 1993; Shyue et al., 1995; Yokoyama & Yokoyama, 1990). If selection acts on these parts, rather than on their sum, the number of potential pathways will be fewer, which makes parallel genotypic adaptation even more likely. Finally, if the genetic variance–covariance matrices are similar across populations or taxa, then populations may be predisposed to adaptation along the path of least resistance, thereby leading to parallel genotypic adaptation (Endler, 1986; Schluter, 1996).

From a practical standpoint, perhaps one of the greatest concerns regarding homoplasy is the confounding effect it can have on phylogeny reconstruction. Because phylogenetic algorithms are designed to minimize homoplasy, shared character states that truly arose multiple times may be grouped together erroneously (Forey et al., 1992). However, a number of the studies reviewed here suggest that selection often targets only one or a few sites in a sequence (e.g., Andreev et al., 1999). Thus, even if a gene responds identically to selective pressures in evolutionarily distinct lineages, the majority of the sequence will track the branching patterns of the taxa. That is, if the selectively important changes are rare relative to the number of phylogenetically informative sites, the gene tree may still track the species tree. On the other hand, if the sequence changes represent a larger proportion of the informative sites, the resulting tree may be incongruent with the true phylogeny. For example, Kriener et al. (2000) examined sequence variation in certain alleles of the *DRB* gene family in monkeys and humans. Similarities among coding sequences were strong enough to cause a conflict between the exon-based tree and true organismal relationships. Because systematists are increasingly using multiple gene sequences to reconstruct phylogenies, these sorts of conflicts are less likely to lead to incorrect phylogenetic inferences.

From an evolutionary perspective, the occurrence of parallel genotypic adaptation suggests that adaptive evolution may be a more deterministic process than previously believed. Although some authors have argued that the most likely outcome of parallel selection in isolated populations is divergence (e.g., Wade & Goodnight, 1998; Goodnight, 2000; Levin, 2000), two studies in particular suggest that selection response at the genotypic level is repeatable across populations (Rieseberg et al., 1996; Ungerer, 2000). These studies, therefore, suggest that the effects of genetic background on selection response may have been overemphasized. If this turns out to be generally true, then parallel genotypic adaptation might provide a mechanism for both the collective evolution of populations within a species (Lande, 1983; Templeton, 1989) and the recurrent origin of taxa (reviewed in Levin, 2001).

Classical studies of gene flow have suggested that migration rates are too low to account for the apparent integration of species across their ranges (e.g., Ehrlich & Raven, 1969; Grant, 1980). If this were true, species would not be different from higher taxa, mere aggregates of the actual units of evolution (local populations or metapopulations). Recent work has revealed that the joint effects of selection and migration are, in general, sufficient to account for the

integration of populations across a species range (Rieseberg & Burke, 2000). The studies reviewed above take this idea further, suggesting that local populations of a species subjected to similar selective pressures may arrive at the same genetical solutions. Another type of evidence supporting this idea comes from experimental selection studies in which populations subjected to parallel selection maintained reproductive compatibility, whereas those subjected to divergent selection often evolved incompatibilities (Rice & Hostert, 1993). The importance of parallel genotypic adaptation in species cohesion will vary with the relative rates of mutation and migration; in cases where gene flow is limiting, parallel genotypic adaptation would be expected to play a more central role. In this context, it is interesting to note that many of the characters used to differentiate plant species are governed by one or two genes (Gottlieb, 1984; Hilu, 1983). Thus, traits used in species identification may be especially likely to evolve in parallel.

Just as parallel genotypic adaptation can help maintain species cohesion, the potential for recurrent evolution of key adaptations makes the repeated origin of taxa plausible. In general terms, this evolutionary process could allow local populations to independently invade a similar habitat. Because these lineages would share a common solution to a unique ecological challenge, they would be demographically exchangeable (sensu Templeton, 1989) for the same genetic reasons. Indeed, more and more evolutionary biologists are recognizing the importance of ecology in speciation (Schluter, 2001). Because different habitat types are often interspersed across the range of a species, the requisite ecological opportunities may occur frequently. An example of this process, albeit at the infraspecific level, would be metal tolerance in *Silene* (Schat, Voour & Kuiper 1996; Table 1). Given enough time, these independently derived populations may ascend to species status. Though not yet characterized genetically, threespine stickleback fishes are another possible example of recurrent divergence due to parallel genotypic adaptation (Rundle et al., 2000).

Taken together, the studies reviewed here provide evidence that parallel genotypic adaptation can occur in organisms ranging from microbes to plants to primates. Although the relevance of studies in microorganisms to adaptation in general has been questioned, this body of data suggests that Jacques Monod may have been right when he suggested that ‘What is true for *E. coli* is true for elephants, only more so.’ In some cases, the parallelisms spanned remarkably wide taxonomic distances – e.g., the independent evolution of ethanol-active ADH in pea plants and humans (Shafqat et al., 1996). Given that the genetic basis of most adaptations is still unknown, our understanding of the prevalence of parallel genotypic adaptation is still in its infancy. The advent of functional genomics should lead to a wealth of data connecting genotype to phenotype, allowing researchers to identify and compare the genetic mechanisms underlying adaptive traits in a variety of organisms.

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Appendix 1

Brief summaries of studies

A. Experimental Evolution Studies

1. Barlow and Hall (2002, 2003), Mutations in genes in the TEM family of β-lactamases are known to confer resistance to the β-lactam antibiotics. The authors compared analyses of *in vitro* selection experiments targeting the TEM-1 gene to naturally occurring, resistant TEM-alleles. Nine substitutions have evolved multiple times in natural bacterial populations, and seven of these were recovered in the *in vitro* experiments. The authors (2003) also showed that mutagenized TEM-1 alleles conferred resistance to the relatively new antibiotic, cefepime. Resistant alleles contained two to six substitutions each, and many of these substitutions were shared across allelic variants. Thus, adaptation at this locus in response to antibiotic challenge is highly predictable.

2. Bernasconi et al. (1995), Bernasconi and colleagues examined the molecular basis of resistance to acetolactate synthase (ALS) inhibitors, which are commonly used as herbicides. The molecular basis of resistance was characterized in two field isolates of cocklebur and compared to experimentally mutagenized maize lines that also show resistance. Two different amino acid substitutions were responsible for resistance in the two cocklebur isolates. These mutations were identical to those conferring resistance in two mutagenized maize lines.

3. Brown et al. (2001), A clinical, mouse-naive isolate of human influenza A virus, A/HK/1/168, was selected for virulence in mice. This process resulted in three mutations identical to those characteristic of the virulent human H5N1 isolate A/HK/156/97, the strain that infected humans directly from birds in Hong Kong.

4. Bull et al. (1997), In this explicit test of parallel evolution, genomic sequence analysis of different lineages of bacteriophage ΦX174 challenged with high temperature revealed that over half of the substitutions were identical with substitutions in other lineages. The

phages were grown on two different hosts, *Escherichia coli* C and *Salmonella typhimurium*, and some of the parallel changes were host-specific.

5. Crill, Wichman and Bull (2001), Bacteriophage ΦX174 was grown alternately on its typical laboratory host, *Escherichia coli* C and a novel host, *Salmonella enterica*. Experimental adaptation to this novel host inhibited the phage's ability to grow on *E. coli* C. Two to three non-synonymous substitutions in the major capsid gene accounted for this inhibition, and when phages adapted to *S. enterica* were grown on *E. coli*, fitness recovery was based on reversions at these same sites.

6. Cunningham et al. (1997), Six bifurcating lineages of bacteriophage T7 were grown in the presence of the mutagen nitrosoguanidine. Every lineage evolved a ~1.5-kb deletion that fused the 0.3 and 0.7 genes, and this loss was associated with a gain in fitness. In addition, three different sets of parallel nonsense mutations, which produced identical ORFs in independent lineages and were under positive selection, resulted in truncation of the 0.7 gene product.

7. Levin, Perrot and Walker (2000), In the absence of an antibiotic challenge, antibiotic resistance often engenders a cost in the fitness of bacteria. In this study, two candidate genes (*rpsD* and *rpsE*) were sequenced from 24 independently derived, streptomycin resistant (*rpsL*) *Escherichia coli* strains known to be carrying compensatory mutations. For *rpsD*, there were three different single amino acid replacements and two instances of tandem duplications leading to the insertion of three or five amino acids. At *rpsE*, there were five different single base changes leading to four amino acid replacements. One of the non-synonymous changes occurred in five different strains. In no cases were there compensatory changes in both *rpsD* and *rpsE*.

8. Liao, McKenzie and Hageman (1986), In order to produce a thermostable enzyme, the authors transformed the thermophilic *Bacillus stearothermophilus* with a plasmid containing kanamycin nucleotidyltransferase (KNTase) from the mesophilic *B. subtilis* and subjected it to selection at 63°C. KNTases purified from variants that retained kanamycin resistance at 63°C shared a single amino acid replacement, Asp 80 to Tyr. Further selection at 70°C yielded another shared substitution, Thr 130 to Lys.

9. Riehle, Bennett and Long (2001), Six lines of *Escherichia coli* were adapted to 41.5°C and examined for duplications and deletions across their genomes. The authors detected five duplication/deletion events in three lines (no events were detected in the other three lines). Three of the events involved duplications at the same location in the genome, a region harboring four genes previously identified to be important in stress and starvation survival. In both instances examined, the duplications were coincident with increases in fitness.

10. Rieseberg et al. (1996), Rieseberg and colleagues analyzed the genomic composition of three experimental hybrid lineages derived from a cross between *Helianthus annuus* and *H. petiolaris*. As a result of fertility selection in the early generations, all three lineages converged on a common genomic composition. Moreover, this genomic structure was in accord with the recombinant genome of a natural hybrid species (*H. anomalus*) derived from the same two parental taxa. These findings suggest that selection plays a central role in the formation of hybrid species.

11. Ungerer (2000), Populations derived from a cross between the Niederzenz and Landsberg ecotypes of *Arabidopsis thaliana* were subjected to three generations of selection for increased viability. For QTL alleles governing life history traits, as well as other genomic regions, selection response was almost always uniform. The results of this work were consistent across different genetic backgrounds, suggesting that the selective value of an allele is not strongly influenced by variation in genetic background.

12. Wichman (1999), Replicates of two lines of bacteriophage ΦX174 were adapted to high temperature and a novel host and resultant populations were surveyed for genome-wide changes. Each replicate displayed over a dozen nucleotide changes that reached high frequency, and half the substitutions in one line also arose in the second line. In total, six nucleotide changes and one 27–bp deletion arose in parallel. All of these changes were determined to be adaptive, and the order of occurrence of these changes varied between the lineages. This result suggests that their selective value is independent of genetic background. An important antithetical point is that the parallel changes were not those with the largest beneficial effect.

B. Phylogenetic Studies

13. Andreev et al. (1999), In the flour beetle, *Tribolium castaneum*, point mutations in the gene *Resistance to dieldrin (Rdl)* confer resistance to cyclodiene pesticides. Resistance results from a point mutations resulting in replacement of Ala 302 by Ser. Of 141 strains examined, 24 contained resistant individuals. A phylogeny of resistant alleles inferred from a 694–bp stretch of *Rdl* that contains the codon for Ala 302, resolved six distinct clades. The pattern of nucleotide variation in this region is better explained by multiple (parallel) independent origins of the resistant genotype.

14. Elard, Comes and Humbert (1996), The authors demonstrate that resistance to benzimidazole (BZ) antihelmentics is conferred by a substitution at residue 200 (Phe to Tyr) in beta-tubulin (a precursor to the structural microtubules) in the nematode *Teladorsagia circumcincta*. A review of the literature shows that this same substitution is associated with BZ resistance in two other nematode species and two of four fungi examined.

15. ffrench-Constant (1994), A survey of *Rdl* sequences (see #11) from a wide range of insects (Coleopterans, Dipterans and Dictyopterans) resistant to cyclodiene revealed that all these lineages share the same point muation, the replacement of Ala 302 by Ser.

16. Johanson et al. (2001), The *FRIGIDA* locus (*FRI*) has been shown to be a major determinant of flowering time in *Arabidopsis*. A majority of *Arabidopsis* early-flowering ecotypes (i.e., those that do not require vernalization to flower early) contain one of two deletions that cause a frame shift in the ORF of *FRI*, suggesting that this phenotype has arisen at least twice.

17. Jouvin-Marche et al. (1988), Sequence analysis of the immunoglobulin kappa light-chain constant region gene (Ck) sampled from five wild mouse species suggests that parallel evolution of sequences is common at this single-copy locus. Of 47 codons with at least one substitution, 21 of these changes are most likely the result of parallel evolution. Thirteen of these 21 changes result in amino acid substitution. In two cases, parallelism is exhibited at the amino acid level only.

18. Kermarrec et al. (1999), Human and non-human primates share the ABO histoblood group system. This system is based on a single locus encoding a galactosyltransferase, which modifies the O antigen and whose specificity determines the blood group. *O* alleles are null-recessives resulting from a deletion, and their non-functional products do not affect the O antigen. Molecular phylogenetic analysis of human and non-human primate *O* alleles established that these alleles are the result of four independent silencing mutations. The large coalescence times of these alleles at intermediate frequencies suggests that balancing selection (Saitou & Yamamoto, 1997) governs the dynamics of this locus, but the selective value of the silent *O* alleles is unknown.

19. Kriener (2000), Some alleles in the *DRB* gene family in Old and New World monkeys resemble human *DRB1*03* and *DRB3* sequences in their second exon. Phylogenetic analyses based on the flanking intron sequences grouped genes in a taxon-specific fashion

(i.e., gene and species trees were congruent). In contrast, the exon-based tree conflicts with taxonomic groupings (i.e., gene and species trees were incongruent). In other words, exon sequences with similar motifs grouped together, even though the flanking intron sequences suggest that the sequences had separate evolutionary histories. The authors found statistical support for the hypothesis that the sequence similarities among these diverse lineages were selected independently, allowing them to reject the hypothesis of common ancestry.

20. Low et al. (2001), Low and colleagues isolated multiple, independently derived strains of *β*-lactam resistant *Escherichia coli* from the infected kidney cysts of a single patient. Resistance resulted from one to three nucleotide substitutions in the promoter region of the *ampC* locus (four variable sites total), which led to an increase in expression of the AmpC enzyme. Two of the resistant strains carried the same set of three substitutions. Because the strains carried the same basic *ompC* sequence, which is often highly variable among strains, their results are consistent with an initial infection by a single *E. coli* strain, followed by the acquisition of resistance with different cysts.

21. Malcuit et al. (2000), Potato (*Solanum tuberosum*) has evolved two distinct modes of resistance to potato virus X (PVX): one controlled by the N genes (Nx and Nb), and one governed by the Rx genes (Rx1 and Rx2). For each of these host genes, PVX has a single determinant that specifies virulence (i.e., breaks resistance) or avirulence. While this study does not pinpoint the substitutions responsible for these determinants, a genomic phylogeny of strains variable for these determinants revealed that the Nb-resistance breaking factor (located in ORF2 of the viral genome) has evolved on five separate occasions. Alternatively, the topology could be the result of seven independent losses.

22. Molla et al. (1996), The evolution of resistance at the HIV protease gene was monitored in 48 patients treated with the protease inhibitor, ritonavir. While there was variation among sequences in resistant lineage, the authors pinpointed nine amino acid changes that resulted from drug selection. For example, mutation at site 82 (V to A or F) was always associated with the evolution of resistance and associated mutations at four other sites occurred in more than one half of the sequences analyzed. Moreover, multiple mutations consistently accumulated in an ordered fashion.

23. Morris et al. (1993), The absorbance maxima (max) of the rhodopsin visual pigments of squid species have been shown to be correlated with their maximum depth distribution – species that inhabit deeper waters have lower maxima. In this study, the authors show that the 5 nm spectral shift in rhopdopsin maxima between *Alloteuthis subulata* (max depth of 200 m) and *Loligo forbesi* (360 m) is associated with a substitution of phenylalanine by serine at residue 270. This residue is homologous to site 277 in primate cone visual pigments, a site that is important in spectral tuning in primates (Neitz et al., 1991 and Williams et al., 1992).

24. O'hUigin, Sato and Klein (1997) Sequences of introns 5 and 6 of the *ABO* gene were analyzed to distinguish between parallel evolution and trans-species inheritance of polymorphism at this locus. Four substitutions and one indel separate human *A*, *B*, and *O* variants from chimpanzee *A* and gorilla *B* alleles. There is no phylogenetic support for trans-species inheritance, thus the authors conclude that the chimpanzee *A* and gorilla *B* alleles evolved in parallel with the human *A* and *B* alleles, respectively. Note that cloning and homology assessment demonstrated that the *A* and *B* alleles are distinguished by the same four amino acid residues (sites 176, 234, 265 and 267) within humans and between the chimpanzee *A* and gorilla *B* alleles. In a similar study, Saitou and Yamamoto (1997) hypothesize that *B* alleles have evolved at least three times from an ancestral *A* form.

25. Palacios et al. (1998), The transmembrane receptor, CCR5, serves as a cellular gateway for the entry of HIV-1 and all strains of SIV. Humans homozygous for a null allele of *CCR5*, which has a 32-bp deletion, are highly resistant to HIV-1. A novel 24-bp deletion allele of *CCR5* was discovered in sooty mangabeys (*Cercocebus torquatus atys*), a host of SIV, at an appreciable frequency. This allele is expressed, but its encoded protein is not transported to the cell surface, and thus monkeys homozygous for this allele are expected to be resistant to SIV infection.

26. Reid et al. (2000), The authors constructed a phylogeny of enteropathogenic *Escherichia coli* strains based on six housekeeping genes. The phylogenetic distribution of mobile elements that confer virulence suggests that the high virulence of certain lineages is a derived (not ancestral) state. More importantly, the phylogeny supports the parallel gain and loss of specific mobile virulence elements. For example, the chromosomal acquisition of the LEE pathogenicity island, a critical first step in the evolution of pathogenicity, occurred at least twice. In addition, a plasmid-borne haemolysin and phage-encoded Shiga toxins were acquired in parallel in distinct lineages.

27. Romero-Herrera et al. (1978), Phylogeny reconstruction of vertebrate myoglobin sequences revealed that 139 of 278 mutations, corresponding to 39 of 83 variable sites, occurred in parallel. Although the adaptive significance of these changes is unclear, myoglobin function is likely to be under strong selection in diving mammals. Certain changes that arose independently in cetaceans and pinnipeds are also intriguing: 54 Asp and 122 Glu in both harbour seal and dolphin, 83 Asp in sea lion and dolphin, 121 Ala and 152 His in harbour seal, dolphin and porpoise.

28. Shafqat et al. (1996), Shafqat and colleagues examined the interrelationships of formaldehyde-active and ethanol-active alcohol dehydrogenase (*ADH*) in plants and animals. Their results indicate that the plant and animal forms of formaldehyde-active (class III) *ADH* share a common ancestor. In contrast, the ethanol-active (classes P and I) forms are derived from independent duplications of the class III enzyme-encoding loci within each lineage, followed by functional convergence. These forms are characterized by parallel changes at four of the thirteen substrate binding amino acid residues. See also Fliegmann and Sandermann (1997).

29. Shyue et al. (1995), Color vision is governed by two genes in the New World marmosets and squirrel monkeys, one of which is X-linked. Both marmosets and squirrel monkeys have evolved multiple alleles at the X-linked locus, each encoding photopigments with distinct spectral sensitivities. Consequently, heterozygous females are trichromatic. Phylogenetic analysis supports the independent evolution of these multi-allelic systems. In addition, a comparison of the amino acid sequences of the X-linked loci in New World monkeys and humans (which have two such loci) reveals parallel changes at three sites that are believed to be critical for spectral tuning.

30. Stewart, Schilling and Wilson (1987), Zhang and Kumar (1997), The digestive system of colobine monkeys, ruminants, and the avian hoatzin all involve the recruitment of lysozyme expression (lysozyme *c*) in the stomach, where it serves as a bacteriolytic enzyme. Phylogenetic analysis revealed that two amino acid sites evolved in parallel across taxa, supporting the hypothesis that these substitutions were the result of positive selection.

31. Yokoyama and Yokoyama (1990), Red- and green-like visual pigment genes of the blind cave fish, *Astyanax fasciatus*, were compared to their homologous counterparts in humans. Like humans, this species of fish has one red-like pigment gene and multiple green-like pigment genes. A phylogeny of these genes allowed the authors to infer the direction of evolution of amino acid sequences. The results of this analysis point to independent origins of the red pigments, from a green ancestor, in human and fish by identical amino acid substitutions at two, or possibly three, critical positions.

C. Quantitative Genetic Studies

32. Fatokun et al. (1992), The most important yield trait in both cowpea (*Vigna unguiculata*) and mung bean (*V. radiata*) is seed weight, thus this trait has been the target of selection during the independent domestication of both of these species. Fatokun and colleagues identified QTLs with major effects on seed weight in both species. Furthermore, they used orthologous RFLP markers to demonstrate that the QTL with the greatest magnitude maps to the same marker interval in both species.

33. Hu et al. (2003), Rhizomatousness was mapped in an F2 population derived from a cross between *Oryza sativa* and *O. longistaminata*. Two key loci were identified, each having strong affects on several rhizome traits. Each of these QTLs is coincident in map position to a major QTL affecting rhizome growth in *Sorghum propinquum*, a wild congener of domesticated sorghum.

34. Paterson et al. (1995), Paterson and coworkers mapped agronomically important traits in rice, maize and sorghum, which diverged up to 65 million years ago. A significant portion of QTLs underlying seed mass and seed dispersal (i.e., shattering versus non-shattering) show correspondence among rice, maize and sorghum. QTLs for daylength-insensitive flowering also map to corresponding regions in rice, maize, sorghum, wheat and barley, suggesting that artificial selection resulted in parallel changes at a single ancestral locus.

35. Schat, Voous and Kuiper (1996), Schat and colleagues crossed individuals from four geographically isolated, zinc tolerant *Silene vulgaris* populations *inter se* and to a non-tolerant line. One of the tolerant lines exhibited an intermediate level of tolerance. The segregation patterns in F2 and F3 families fit a major genes model of inheritance, and the authors concluded that tolerance was governed by two additive genes. All three highly tolerant populations appear to be homozygous tolerant at both loci, while the intermediate population possesses only one tolerant allele. Because the tolerant populations are geographically isolated, it is unlikely that tolerance in these populations resulted from common descent. In addition, copper and cadmium tolerance are controlled by two loci that correspond among all tolerant populations examined.

36. Sucena et al. (2003), In the *Drosophila virilis* species group, the loss of thin trichomes on the dorsal cuticle of first-instar larvae has evolved in parallel in three distinct lineages. Sucena et al. examine controlled crosses and gene expression patterns to demonstrate that all three instances of trichome loss are the result of regulatory changes affecting the *shavenbaby/ovo* gene.

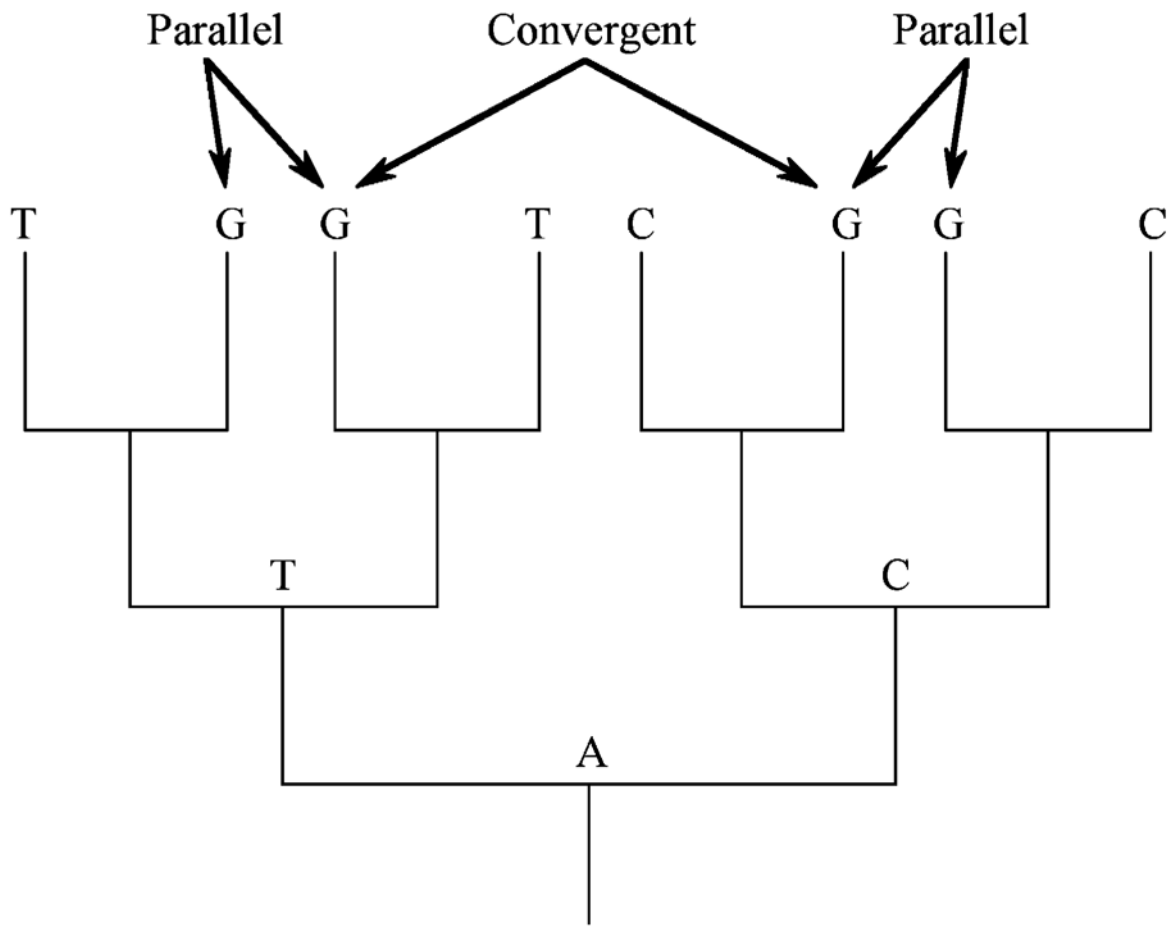

Figure 1.
Parallelism versus convergence in molecular evolution. Character states at a single, homoplastic nucleotide site are mapped onto a gene tree. Parallelism refers to the independent evolution of the same derived state from a common ancestral state (the two Gs from T, or the two Gs from C). In contrast, convergence involves the evolution of the same derived state from different ancestral states (G derived independently from T and C). (After Zhang & Kumar, 1997)

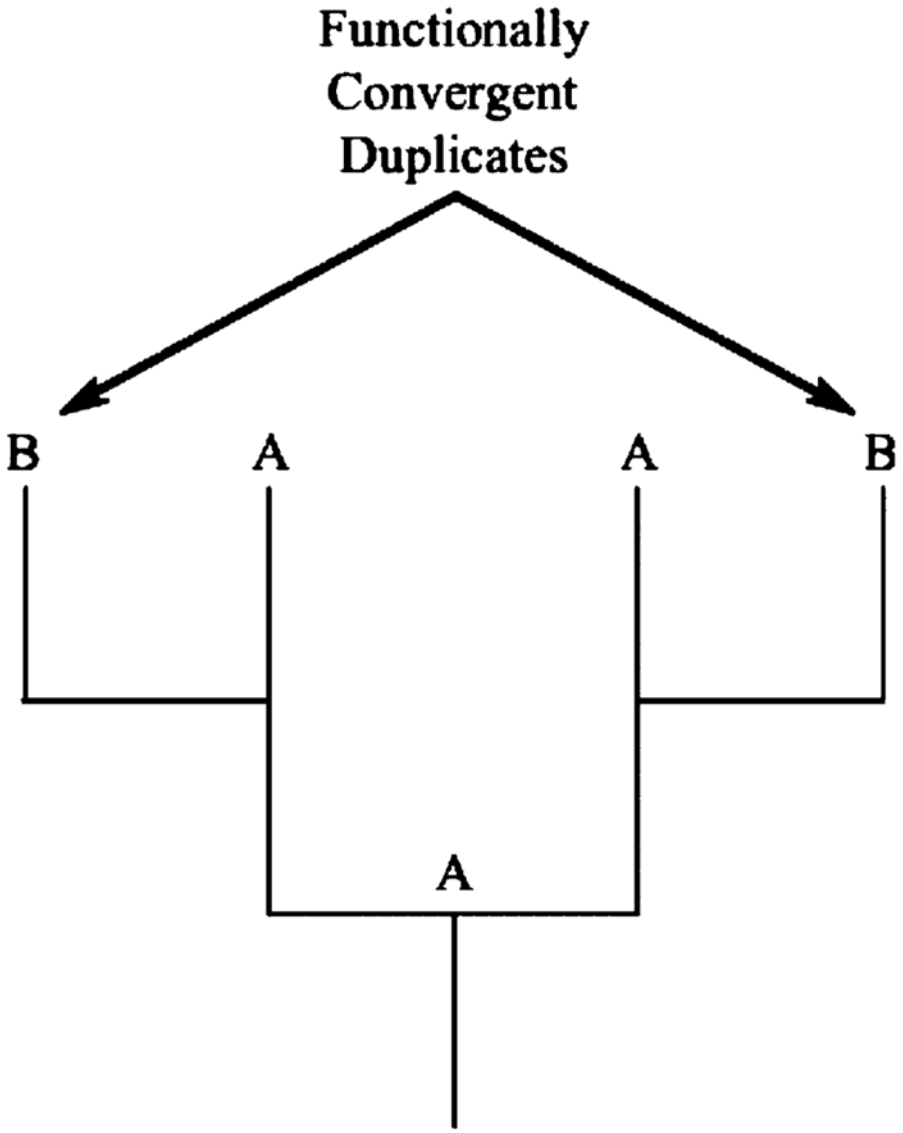

Figure 2.
Convergent evolution of gene duplicates. The lateral branches leading to functional state B represent independent duplications of a homologous gene that fulfills function A. Functional state B evolved independently from changes in the duplicate copies. See text for details.

Table 1

List of studies documenting parallel genotypic adaptation. The upper, middle, and lower panels include laboratory or greenhouse selection experiments, phylogeny-based studies, and genetic analyses of controlled crosses, respectively. See Appendix 1 for a summary of each study

Taxonomic Group(s)	Phenotype	Type of evidence	Reference
Maize & Cocklebur	Herbicide resistance	Amino acid substitution	Bernasconi et al., 1995
Human influenza A	Virulence	Amino acid substitution	Brown et al., 2001
Bacteriophage ΦX 174	Thermotolerance	Nucleotide substitution	Bull et al., 1997
Bacteriophage ΦX 174	Host shift	Amino acid substitution	Crill et al., 2001
Bacteriophage T7	Fitness	Deletion/nucleotide Substitution	Cunningham et al., 1997
Escherichia coli	Drug resistance	Amino acid substitution	Levin et al., 2000
Bacillus subtilis KNTase	Thermostability	Amino acid substitution	Liao et al., 1986
Annual Sunflower spp.	Fertility	Genome composition	Rieseberg et al., 1996
Arabidopsis thaliana	Fitness	Genome composition	Ungerer, 2000
Bacteriophage ΦX 174	Thermotolerance/ host shift	Nucleotide substitution	Wichman, 1999
Flour Beetle	Pesticide resistance	Amino acid substitution	Andreev et al., 1999
Nematodes & Fungi	Pesticide resistance	Amino acid substitution	Elard et al., 1996
Coleopterans, Dipterans & Dictyopterans	Pesticide resistance	Amino acid substitution	ffrench-Constant, 1994
Arabidopsis thaliana	Flowering time	Deletion	Johanson et al., 2001
Wild Mice spp.	Immune response	Amino acid substitution	Jouvin-Marche et al., 1988
Human & Non-Human Primates	Blood groups	Nucleotide substitution	Kermarrec et al., 1999
Human & Old/New World Monkeys	Immune response	Nucleotide substitution	Kriener, 2000
Escherichia coli	Drug resistance	Nucleotide substitution	Low et al., 2001
Potato Virus X	Virulence	See Appendix 1	Malcuit et al., 2000
Human Immunodeficiency Virus (HIV)	Drug resistance	Amino acid substitution	Molla et al., 1996
Primates & Squid	Visual pigments	Amino acid substitution	Morris et al., 1993
Chimpanzee & Gorilla	Blood groups	Amino acid substitution	O'h Uigin et al., 1997
Human & Sooty Mangabey	Disease resistance	Deletion	Palacios et al., 1998
Escherichia coli	Virulence	Horizontal transfer	Reid et al., 2000
Escherichia coli	Thermotolerance	Duplication/deletion	Riehle et al., 2001
Cetaceans & Pinnipeds	Respiration	Amino acid substitution	Romero-Herrera et al., 1978
Human & Pea	Enzyme function	Amino acid substitution	Shafqat et al., 1996
Human, Marmoset & Squirrel Monkey	Visual pigments	Amino acid substitution	Shyue et al., 1995
Colobine Monkey, Ruminants & Hoatzin	Enzyme function	Amino acid substitution	Stewart et al., 1987; Zhang and Kumar, 1997
Human & Blind Cave Fish	Visual pigments	Amino acid substitution	Yokoyama and Yokoyama, 1990
Cowpea & Mung Bean	Seed weight	Comparative QTL mapping	Fatokun et al., 1992
Maize, Rice & Sorghum	Seed mass and dispersal	Comparative QTL mapping	Paterson et al., 1995
Silene vulgaris	Metal tolerance	Complementation test	Schat et al., 1996