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Genes 'for' Phenotypes: A Modern History View

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Abstract. We attempt to improve the understanding of the notion of a gene being 'for' a phenotypic trait or traits. Considering the implicit functional ascription of one thing being 'for' another, we submit a more restrictive version of 'gene for' talk. Accordingly, genes are only to be thought of as being for phenotypic traits when good evidence is available that the presence or prevalence of the gene in a population is the result of natural selection on that particular trait, and that the association between that trait and the gene in question is demonstrably causal. It is therefore necessary to gather statistical, biochemical, historical, as well as ecological information before properly claiming that a gene is for a phenotypic trait. Instead of hampering practical use of the 'gene for' talk, our approach aims at stimulating much needed research into the functional ecology and comparative evolutionary biology of gene action.

Key words: direct functions, evolutionary biology, genes for, genetic trait, molecular genetics, proper function, selection

Introduction

In this paper, we attempt to answer the following questions: What does it mean when we say that a gene is 'for' some trait? And, what do we have to know about the relationship between an organism's genotype, its phenotype, its environment, and its developmental and evolutionary history if we are to speak properly about some of its genes being 'for' certain traits? The distinction we wish to stress is between genes being 'for' particular traits and genes merely being 'associated with' particular traits. We can (and do)

know how to find genes associated with various phenotypic traits, and we in fact do know of a lot of genes so associated. But what do we have to know to make the *further* claim that the genes are *for* such a trait rather than merely being *associated* with it? We would first like to attempt to formulate an answer to these questions for the general case, and then bring out some of the implications of the answer we give for the human case.

We will argue that the best sense that can be made of the 'gene for *x*' locution is to treat it as a kind of functional talk, specifically the 'Modern History' version of functional talk that Godfrey-Smith developed for thinking about biological functions (aka 'direct proper functions': Godfrey-Smith 1994; see also Griffiths 1993). We can properly speak, we will argue, of a gene being 'for' some trait only when the gene was maintained by natural selection in the recent evolutionary history of the organism by its causal association with the trait in question (a more precise definition will be developed below). Based on this interpretation, it will turn out that to say that a gene is *for* some (variation on a) trait *x* is to say something about not merely what the gene happens to do in this particular case, but also something about what biological meaning that association has.[1]

On this 'Modern History' view of 'gene for' talk, it will turn out that we know of rather fewer genes that are *for* things (as opposed to merely being associated with them) than some might have thought or implied. Further, in many cases 'genes for' will turn out to be for less exciting things than we might have wished (contra Dawkins (1982), we will argue that there are no genes 'for' such things as reading-ability in humans). We think that the advantages to this view are many. Unlike views which conflate genes being for traits with genes being associated (even causally) with phenotypic traits, and unlike views which reject the legitimacy of any talk of genes being for phenotypic traits, the sort of work encouraged by the Modern History approach to thinking about 'genes for' in functional terms focuses attention onto biologically important questions. For example, this approach deals with how evolution changes the associations between genes and phenotypes, i.e., on how genes can evolve new functions (see below). This way of thinking about 'genes for' is, therefore, not merely cautionary in the way that a refusal to countenance any usage of 'gene for' talk would be, but rather would work to further the exploration of important avenues of research. Indeed, another reason to support the Modern History view is that while as yet there are few genes about which enough is known to justify thinking of them as 'for' particular phenotypic traits, research encouraged by the Modern History view would be useful for a variety of goals. It would for example aid in (a) discovering more such genes, (b) beginning to get a sense of how many such genes there likely are, and (c) beginning to get a sense of how important

such genes have been evolutionarily. It may be that on the Modern History view there will always be relatively few genes that are known to be 'for' particular traits; however, if these have been of great evolutionary significance, a language that encourages a program of looking for them is still to be recommended.

Unlike more permissive usages, this way of limiting 'genes for' talk would discourage the sorts of misconceptions about the relationship between genes and phenotypes so common in the contemporary culture and the popular media. For example, consider the naïve sort of genetic determinism and genetic essentialism encouraged by the bombardment of reports of the discovery of 'the gene for *x*' type (see note 5, below). While sharing this feature in common with those approaches that reject all 'gene for' talk, our approach recognizes that there are situations in which using such language seems natural and appropriate. While on the Modern History view the conditions on properly using the language of a gene being 'for' a phenotypic trait are restrictive, they are not impossible to meet. When we do meet these conditions, and hence can reasonably conclude that a given gene is *for* some phenotypic trait(s), we end up knowing something quite a bit more important and interesting than when we merely know of associations between genes and characters.

1. 'Genes for' or not 'genes for'?

Historically, arguments about whether it makes sense to claim that some gene is 'for' some trait have centered on two relatively extreme positions, namely that the 'genes for' concept is harmless and easily analyzed, and that the 'genes for' concept is pernicious and likely incoherent. There is a significant literature surrounding these positions, and so in the interests of space they will merely be sketched here, along with some of their most pressing difficulties. Richard Dawkins is usually taken (fairly or unfairly) as the representative of the first view, and as claiming that there are not only *lots* of 'genes for' phenotypic traits, but also that theorizing about the adaptive significance of traits is at least a good first step towards discovering that there are genes for it (see e.g. 1982, especially chapter 2). Broadly, Dawkins argues that finding genes statistically associated with particular variations in phenotypic traits is the equivalent of finding genes *for* those traits (1982: 21). Sterelny and Kitcher (1988) develop the "intuitive idea" that "we can speak of genes for *x* if substitutions on a chromosome would lean, in the relevant environments, to a difference in the *x*-ness of the phenotype" (1988: 348). More precisely, they claim that a particular locus L affects a particular trait *P* if there are

allelic substitutions at L that will result in differences in *P* in "standard environments" (1988: 349).

While there is plenty of room to quibble with the above definition (especially with respect to what is to count as a 'standard environment' and why such environments are to be privileged), the main difficulty we see with all such proposals is more basic. Both Dawkins's original definition, and Sterelny and Kitcher's rearticulation of the idea, fail to do justice to the notion of one thing being *for* another. It seems to us clear that 'being-for-ness' is not just a matter of association or of causal mechanisms. This is not an original observation: as far back as 1963, Lorenz has written that "unless selection is at work, the question 'What for?' cannot receive an answer with any real [biological] meaning" (Lorenz 1963: 14). If we want to use the phrase 'a gene for *x*,' then we have to take seriously the implications of the language involved in that phrase. "What's it for?" is not a question we can answer by pointing to a statistical association, or even by making use of causal connections that are not necessarily biologically significant. And, as Lorenz reminds us, the only biologically significant functions, the only answers to the question 'what's it for' that are biologically meaningful, are those that involve natural selection. There is nothing wrong with the suggestions made by Dawkins, Sterelny and Kitcher, if what they want to discuss are associations between genes and characters, but they ought not talk about finding genes *for* traits based on those suggestions.

On the other side, it is sometimes suggested that the attacks on 'adaptationism' and genetic determinism most closely associated with Gould and Lewontin (Gould and Lewontin 1979; see Pigliucci and Kaplan 2000 and cites therein) imply that the language of 'genes for' traits (at least if used at anything above the most straightforward biochemical level) is entirely misguided. Further, the attacks of Oyama and others on the supposed centrality of the gene, and their proposed alternative ("Developmental Systems Theory," henceforth DST), are sometimes thought to imply that the 'gene for' language is a failure (see for example Oyama 1985; Griffiths and Gray 1994, and related). Oyama, for example, attacks the idea that a gene could be for a trait by first arguing that the question "what for?" is an attempt at an "ultimate" causal explanation, and then arguing that "ultimate" causal explanations in this sense are not "best understood . . . through the genes" (Oyama 1985: 53, 126).

But most of the effort in DST is not directed towards arguing that it is impossible to properly speak of a gene being for some trait or other. The point is merely that this way of talking has been problematic in practice, because it has been interpreted to make genes out to have a special place in the developmental process, which is exactly what DST wants to

deny (see for example Griffiths and Gray 1994: 277). Gray for example writes, "I wish to dislodge the gene from the privileged site it has occupied in our accounts of development and evolution" (Gray 1992: 199). This dislodging task can be done without having to argue that there is no possibility at all of finding genes that actually are *for* traits, a position we think is untenable.

The position that it is impossible to find genes for traits in untenable not because the gene should hold a central place in our thinking, and not because we are old-fashioned adaptationists who want to make every trait out to have been the product of natural selection acting on genes. Rather, the problem is that there are cases where the locution seems to us entirely natural. While we would reject most of Dawkins's putative 'genes for' traits, there are cases where we think the locution is useful and informative. Consider the case of the FY-0 gene in human populations. This gene is all-but absent in populations where malaria has not historically been a problem, but is present in some 87% of the population in Sub-Saharan Africa (Cavalli-Sforza and Cavalli-Sforza 1995: 125). The primary effect of the gene is "the absence of the FY substance" and this absence "grants . . . a certain amount of protection against [*Plasmodium vivax*, a particular malaria parasite]" by making "it hard for the parasite to multiply" (Cavalli-Sforza and Cavalli-Sforza 1995: 125). If we ask of the FY-0 gene, "What's it for?" the answer that it is *for* (partial) malaria resistance seems entirely natural; such an answer addresses the functional ascription inherent in the phrase. An analysis of 'for-ness' of this sort can be carried out in a biologically meaningful way of just the sort that Lorenz suggested for biological functions more generally. It is for this reason that Dawkins's hypothetical gene *for* dyslexia could be no such thing (1982: 23). Whatever functions a gene might have acquired through selective regimes, causing dyslexia is surely not among them.

We believe that a good starting point for thinking about 'genes for' in a functional way is the "Modern History" approach to biological functions developed by Godfrey-Smith (Godfrey-Smith 1994; see also Griffiths 1993). Godfrey-Smith was attempting a definition of biological functions in general, and concluded that they are "disposition or effects a trait has which explain the recent maintenance of the trait under natural selection" (1994: 344). We want to say that we can properly speak of a gene being for some phenotypic trait within a population only when its association with that trait explains the recent maintenance of the gene in that population.[2]

In the next section, we will try to get clearer on just what we need to know in order to say that a gene is *for* some phenotypic trait in the Modern History sense described above. We will also provide an explanation of why the FY-0 case, as strong as it seems to be, represents a scenario where only

a minimum of the requirements are met, and we will argue that it should be thought of as a gene for partial malaria resistance only in a tentative way. It will become clear just how hard it is to claim that a gene is really for some trait (especially in the case of humans). In later sections, when we attempt to deal with those harder cases that for example DST proponents draw our attention to (plasticity, universal epistasis, pleiotropy, emergent properties, etc.), some of the conceptual limitations of this form of 'gene for' talk will become clearer.

2. Finding 'genes for' – the challenges of the Modern History view

Unless we accept the view that the entirety of talk of 'genes for' traits is misguided and should be given up, we need to find some way of distinguishing legitimate uses from uses that force us to take the gene as primary or central, or that force us into thinking in the adaptationist mold. Ideally, such a solution would permit us to speak sensibly of a gene being for a trait only where there was no risk of moving, as Sterelny and Kitcher put it, "from the 'genes for *P*' locution to the claim that selection can fashion *P* independently of other traits of the organism", a slippage that they say is "perennially tempting" (1988: 361). In this section, we will argue that the Modern History interpretation of talk of 'genes for' traits is far more resistant to this slippage than other views that have been proposed. In part, this will turn out to be because the work necessary to claim that there is a 'gene for' some trait in this view forces one to consider more facets of the relationship between the organism's development and its recent evolutionary history than would other versions of 'gene for' talk, or indeed even giving up 'gene for' talk altogether.

The first thing to notice is that no statistical correlation, no matter how strong, will be enough on the Modern History view to talk of there being a gene for some trait. Indeed, it will turn out that no single kind of evidence will ever be enough. Merely knowing something about the evolutionary history, or the population genetics, or the developmental pathways, or any other isolated bit of biological information, will not suffice. Some combinations of these will be required. Just what combination may well depend on the case, however.

So, what do we want to know in order to claim properly that a gene is *for* a trait? Ideally, we would want to know all of the following:

a) That the gene is statistically associated with the trait.
b) The most important aspects of the biochemical and developmental pathway from the gene to the trait.

c) That the trait in question really was the likely subject of natural selection in the species recent evolutionary history.
d) That the maintenance of the gene in the species in its recent evolutionary history can actually be the result of (c).

The first requirement, that there actually be an association between the gene and the phenotype, is the reason why it is sometimes suggested that a statistical approach may be a good 'first step' in finding genes 'for' traits. While this is necessary, it should now be clear that it is nothing like sufficient. It is worth noting, however, that there does not have to be a statistical association in the sense Dawkins developed, as one could have 'genes for' on this view even where there is no variation in the population for the genes involved or for the trait in question. Obviously, (b) is difficult from an experimental standpoint. There are not many organisms, nor many traits, for which we know most of the relevant biochemical pathways involved in moving from any given gene to any given trait. Part of the reason for this, we suspect, is that the complex relationship between genes and phenotypes will often not permit us to talk sensibly of genes for traits. For example, as will we see below, for traits in which complex epistatic effects play a role, the notion of them being 'polygenic' will prove inadequate and it will turn out best not to speak of their being specific 'genes for' the trait. Rather, it may be best to speak of the trait as an 'emergent' property of the epigenetic process (see below and Schlichting and Pigliucci 1998: 337). In these cases, we will not wish to speak of any particular genes 'for' the trait at all; some complexities at the level of ontogeny will be sufficient, on this view, to reject the use of 'for' talk. Nevertheless, there are some genes and some traits that we have a rather good handle on, and so for some kinds of traits, we can expect at least limited success in meeting the challenge of (b). However, the relationships that one finds out about in (b), even when coupled with (a) are not sufficient, either. The reason can be seen quite clearly – even where we know of a gene associated with a trait, and know the biochemical (developmental) pathways by which it is so associated, we do not yet have good reason to use the functional language implied by 'genes for ' talk because of the lack of information about the role of natural selection.[3]

The condition listed as (c) provides perhaps one of the most difficult challenges. We want to suggest by (c) that we need more than a good just-so story about how the trait might have been useful; we need to actually understand something about how it might have been the object of natural selection. This has to rely on a phylogenetically informed comparative analysis of the organisms in question; a necessity that originates from the core fact that evolutionary biology is a historical, not just experimental, science.

Finally, by (d) we need to know how natural selection on the trait in question could account for the prevalence of the corresponding gene. It may in fact be impossible to be certain that this requirement has been met (the difficulties are compounded by such phenomena as pleiotropy and allometry), but theoretical biology can be used to demonstrate at least the plausibility of this condition in each specific case. The recognition of these difficulties is a good reason to remain cautious about 'gene for' talk, even in those cases where the other requirements would seem to have been well met.

Rarely (if ever) will it be possible to fully meet all these criteria. In some cases, though, we may wish to cautiously suggest that a gene may be for some trait even though not all conditions have been adequately met. For example, in the cases of purported genes for phenotypic traits in humans, it would obviously be impossible (ethically and practically) to perform many of the experimental manipulations that are at the heart of figuring out (b). Gene knock-out experiments, gene substitution experiments, attempts to develop reaction norms for the relevant genotypes, environments, and traits in question, laboratory evolution experiments, etc., while part of the geneticist's and ecologist's standard tool kit for most organisms (see Schlichting and Pigliucci 1998: 16–20 and cites therein), are out of the question in humans. This is why, in part, all claims to have found genes for phenotypic traits in humans should be treated with caution. However, in other species more easily experimentally manipulated, claiming to have found a gene for some trait without performing such experiments would be over-bold at best.

There is, of course, nothing in the Modern History view which suggests that we should expect to find genes for those traits that we happen to find of immediate interest – indeed, quite the opposite. Many traits of interest to us (especially in the human case) were probably never under direct selective pressure, and so on the basis of the Modern History account, there could not be genes *for* them (examples in the human case might include reading ability, advanced mathematical aptitude, etc.). Also, in the case of many complex traits, we should not expect to find genes for the trait in question at all, but rather expect that genes associated with the trait will prove to be part of suites of genes with complex interactions such that the trait is best viewed as an emergent property of the epigenetic process. Further, while neither historical nor mechanistic (e.g. developmental) complexities alone will be enough to *rule out* the possibility of a gene or genes being 'for' a trait (see the discussion of gene complexes, below), these complications will tend to make possible 'genes for' harder to identify and the tests necessary to gain evidence for the relationship harder to perform adequately.

This may seem like a lot of work, and it clearly is. Recall, though, the point of pushing for a Modern History understanding of what it means for

genes to be for phenotypes. The work suggested by this method addresses some of the most fundamental questions in evolutionary biology, ecology, and developmental biology. Avoiding this work by refusing to talk about genes being 'for' phenotypes may be just as misguided as avoiding this work by pretending that mere statistical associations or mechanistic causal chains provide enough evidence to declare that a gene is for a phenotype. As yet, little of this work has been done; until more of it is, it will be hard to be sure about just how important those genes that are, in the Modern History sense, for phenotypes actually have been in an evolutionary sense. It is possible, though, that these genes, even if they turn out to be rare, could be some of the most interesting genes in an evolutionary sense.

3. Complications: Pleiotropy, epistasis, plasticity, QTLs, and emergent properties

If the idea of a gene being for some phenotypic trait runs into considerable problems when we think of simple, relatively straightforward cases of genotype-phenotype mapping functions, things become much more muddled (and interesting) when we turn our attention to some of the most complex (and of course, relevant) situations. We will discuss a few general categories below to illustrate that the more we think about it, the more we are forced to acknowledge how difficult it is to meet the challenges involved in taking the phrase 'gene for' seriously in many biologically meaningful contexts.

Perhaps one of the most universal and clearly understood properties of genes is the fact that they have pleiotropic effects. Pleiotropy is the phenomenon by which the effects of a gene can be measured not just on one trait (however we define "trait," see e.g. Gould and Lewontin 1979), but on several. For example, the Hb^S mutation of the globin gene coding for human hemoglobin causes a distortion of the three-dimensional structure of the molecule itself (the mutation changes a single base pair, from A to T, substituting a valine for glucine in the protein). This diminishes the ability of hemoglobin to exchange oxygen and carbon dioxide with the blood; however, in some instances the same structural defect alters the shape of the red cells, thereby preventing the agent of malaria from reproducing. What are these alleles at the Hb locus 'for'? Strictly speaking, they code[4] for a certain molecule with a given metabolic function, and they have presumably been selected in the past in order to perform this function. The alterations in the shape of the red cells and the consequent resistance to malaria are therefore not what the Hb^S allele was originally 'for'. But – depending on the environmental conditions – the mutation actually does confer a selective advantage in malaria-infested areas. Is it therefore now to be considered a

gene 'for' malaria resistance? Or rather for both resistance and gas exchange? Actually, the gas exchange function is impaired to some extent (so much so that homozygosity for the condition is lethal). A side effect of this mutation in heterozygote individuals is a mild form of anemia (due to the fact that only one of the two genes produces a functional allele for gas exchange). Surely, we would not speak of a gene for anemia, however, even though it is being maintained by selection favoring one of its other effects. So, one could think of this as an example of a gene for gas exchange, which later partially evolved into a gene for malaria resistance. In this way, the 'genes for' language we develop can account for constraints and trade-offs; a gene can be *for* a particular trait, and associated with another unfavorable trait, where the selective advantage of the trait it is for outweighs the disadvantage of the trait it is associated with.

The situation becomes even more complex when we take into account gene-gene interactions, i.e., epistasis. We are not referring here to epistasis in a statistical sense, a property studied at the population level in quantitative genetics. Instead, we are discussing what is sometimes termed "physiological" epistasis, i.e., actual physical interactions among gene products. If gene products would only interact in an additive manner, i.e., the metabolic or phenotypic results would be directly proportional to the action of each gene, we would still be able to talk about 'genes for' in some meaningful sense. For example, if ten genes affect flowering time in a plant, but each gene adds a fixed (not necessarily equal) number of days to the final phenotypic outcome, each of those genes would legitimately be considered a gene for delaying flowering. However, modern physiological and molecular biology teaches us otherwise. In the model plant *Arabidopsis thaliana*, for example, several genes interact in complex ways to determine the timing of flowering (Kuittinen et al. 1997). Some of these genes have antagonistic, or inhibitory, effects on each other. Therefore, some genes involved in flowering are actually 'for' inhibiting other genes involved in flowering, depending on the circumstances (usually, but not only, the conditions of the external environment, such as photoperiod, or temperature). Of course, each of these genes may also have (and in some cases demonstrably have) pleiotropic effects, thereby compounding the problems of pleiotropy and epistasis.

Closely related to issues surrounding the epistatic interactions of genes are those that concern the possibility that coadapted gene complexes might be the result of natural selection on particular kinds of traits. Given that many traits are associated not with single genes, but rather with complex suites of genes, it is worth considering whether such gene complexes could be 'for' particular traits in the sense we develop. It is certainly possible in principle that coadapted gene complexes might be the result of natural selection for a

particular trait they are associated with (statistically and mechanistically), and hence candidates for 'genes for' talk. However, it should be noted that, at least in the case of eukaryotes, almost nothing is known about such complexes or the role they play in the development of phenotypes. Until we have far more information, which may well require rather more technical know-how than is currently available, claims about the role that such complexes play will be conjectural at best. A partial exception is provided by the study of gene complexes in bacteria, often termed "operons", where the number of genes is reduced, their interactions fairly clear, and the phenotypes they induce are of a biochemical nature and therefore more easily dissected (see for example Silva and Dykhuizen 1993 and cites therein).

Pleiotropy and epistasis are also further complicated by phenotypic plasticity (Pigliucci 1996; Scheiner 1993). The environments in which the organisms live mediate the effects of genes as well as the interactions among genes. In a mathematical model of dominance and pleiotropy based on the details of the metabolic structure of organisms, Keightley and Kacser (1987) predicted that "dominance and any possible differences are thus a function of the environment in which organisms are operating as well as of their genes". This may be simply because enzymes (the direct product of many genes) are characterized by reaction curves that alter their efficiency in relation to environmental parameters such as temperature and pH, among others.

Another important point need to be discussed about plasticity, the fact that there are at least two types of it, for which our discussion of 'genes for' has very different implications. Smith-Gill (1983) discussed the difference between plasticity induced by phenotypic modulation and plasticity determined by developmental conversion. Schlichting and Pigliucci (1995) proposed an interpretation of the two categories in terms of modern molecular genetics, and this is the one we will follow here. Essentially, phenotypic modulation is the situation in which the phenotypic response to the environment is a continuous function proportional to the environmental input. For example, an animal's litter size may be directly proportional to the availability of food in the previous year. Schlichting and Pigliucci suggested that phenotypic modulation may be caused by allelic sensitivity, i.e., by a direct proportionality between the effects of gene products and the environment in which those products are expressed. Allelic sensitivity is very well known in biochemistry, where the reaction curves of enzymes are studied in response to a variety of environmental conditions such as temperature or pH. Smith-Gill's developmental conversion, on the other hand, occurs when the phenotypic response is stable over a range of environments, but is "converted" to a different phenotype if the environmental signal surpasses a given threshold. For example, some plants will flower only if the photoperiod

(day length) is longer than a certain number of hours, and will otherwise keep into the vegetative state indefinitely. Schlichting and Pigliucci suggest that developmental conversion may (but does not have to) be generated by specific plasticity genes, regulatory elements that essentially control the position of the threshold and trigger one of a series of alternative developmental cascades. It seems to us that while one can make a reasonable argument that genes controlling developmental conversion may be genes 'for' the plastic response (but see below our discussion of one of such examples), the argument is much more difficult to substantiate in the case of phenotypic modulation. This is because while environmental receptors do not make sense if they are not triggering a specific (and presumably adaptive) response, gene products may be environmentally sensitive as a matter of unavoidable physico-chemical properties, not because they were designed by natural selection. Of course, allelic sensitivity may be co-opted by selection to produce an adaptive plastic response. Indeed, Schlichting and Pigliucci (1995) proposed that this may be the intermediate step toward the evolution of developmental conversion. In such case, we would regard this as an instance of exaptation at the molecular level, as discussed below. Of course, genes 'for' a continuous plastic response can determine phenotypic modulation, if the usual conditions of causal connection and historical continuity discussed above hold.

Perhaps paradigmatic of the 'gene for' problem in modern biology is the current fashion of studies on QTLs, or Quantitative Trait Loci (see for example Phillips 1999 and cites therein). The basic idea is in fact very simple and very old, in that it has been used in some form or another throughout the history of transmission genetics. It boils down to the possibility of mapping (more or less accurately) the position of a gene statistically related to a given character by examining the recombinant progeny of a cross between parents variable for that trait and a series of unrelated markers. If the phenotype of interest is significantly correlated with some markers rather than others, one can provisionally conclude that the genomic regions thus identified include one or more genes whose effects alter the phenotype of interest. Originally, this technique was used with phenotypic and then chromosomal markers. Today, it is much more effective (and almost as cheap) to use it with molecular markers.

However, there are some fundamental limitations inherent in the QTL approach. Firstly, it can be carried out only on one cross at a time, thereby limiting the extent of natural variation that can be sampled. Secondly, it biases the outcome toward the discovery of a few genes with large effects, because the power of the analysis is directly proportional to the sample size used in assaying the progeny. Nevertheless, QTL analysis allows the researcher to

identify genes associated to trait variation in nature. But is a given QTL a gene 'for' the phenotype under study? Not in any biologically meaningful sense of the term, and certainly not as it is developed here. For one thing, QTL analysis only identifies chromosomal regions that contain the relevant gene(s); it can rarely pinpoint a specific gene due to the limited number of markers and progenies usually tested. This, however, is only a technical limitation related to the power of the analysis and the sample sizes used. A more serious problem arises when one considers that QTL studies, as much as they are based on the apparently mechanistic approach of molecular mapping, are in fact the application of a statistical technique. As such, QTL mapping does not tell us anything at all about the function of the candidate genes, although it can provide a preliminary screen toward further, more mechanistically oriented, studies. Therefore, claims such as those in Wu (1998) that plasticity genes with regulatory functions have been identified and mapped through QTL studies are, to say the least, premature. (Notice that it would have been in the interest of one of the authors if Wu had in fact succeeded, his results being confirmatory of the author's published models of the genetics and evolution of plasticity) This claim stems from the confusion between statistical and physiological epistasis referred to above, where the first has been detected and improperly translated into the second (the latter being the one required by the current theory of plasticity genes; see for example Pigliucci 1996; Schlichting and Pigliucci 1995 and cites therein).

All of the above problems are compounded by the fact that phenotypes are actually the result of the emergent properties of developmental systems, not just of gene actions. Evolutionary biologists have recently accepted this conclusion by taking into account the role of "epigenetics" or "epigenetic rules". What is an epigenetic rule? While it is still frustratingly difficult to accurately pinpoint it, the idea is that phenotypes and behaviors are the result of a complex and continuous (but not necessarily unintelligible) interaction between genes and environments. Perhaps one of the best conceptualizations of epigenetics comes from the work of Atchley and Hall (1991). They pointed out that tissue-tissue communication (as in the induction of the formation of eyes in vertebrates by the adjacent neural crest) is not a genetic effect in the strict sense, but a response to the internal environment of the embryo. Furthermore, this epigenetic effect catalyzes further gene action, necessary for the production of proteins specific to the new structure being developed (e.g., the crystalline in the eye). Local (intracellular) genetic effects, internal environments (cell-cell or tissue-tissue interactions), and external environments therefore all combine to produce the phenotype and behavior of the organism. In cases of this sort, it will be difficult to make good sense of

the idea of genes being 'for' specific attributes of those phenotypes and behaviors.

A particularly well-understood example of a gene that can have many, possibly evolutionarily profound effects, while it cannot be thought of as a gene 'for' those effects, is the *hsp90* gene of *Drosophila*. This gene codes for a protein that is part of the complex heat-shock response present not only in fruit flies, but in virtually every organism in which it has been searched for (see Rutherford and Lindquist 1998 and cites therein). Rutherford and Lindquist (1998) described flies in which the function of the HSP90 protein has been impaired, either by mutation or by chemicals. These animals display an array of morphological changes, spanning virtually every aspect of *Drosophila*'s adult phenotype. The specific effects of mutations at the *hsp90* locus depend on the genetic background being considered. Most interestingly, selection can stabilize these effects so that after a few generations they are present even if HSP90 is functional. Rutherford and Lindquist conclude that HSP90 buffers *Drosophila*'s developmental machinery against this variation, thereby allowing other loci to behave neutrally and to accumulate mutations. A mutation at the *hsp90* locus or certain environmental conditions can "release" this hidden variation, promoting evolutionary change in spite of a conservative developmental system.

From our perspective, one can certainly argue that *hsp90* is 'for' buffering the fly's developmental machinery from heat shock. However, it would be hard to claim that *hsp90* is also 'for' accumulating a reservoir of genetic variation, or 'for' the occurrence of alternative phenotypes under certain environmental conditions, since natural selection is by definition not teleological. Yet, these additional roles may make *hsp90* and similar genes crucial for understanding long-term phenotypic evolution.

4. Genes for, exaptations, and genetic piracy

The Modern History view of genes being for phenotypes is a powerful tool for thinking through the way in which evolution can work to change the biological significance of various genes. On this view, genes that were for a particular phenotype can, in time, become for other phenotypes entirely, or indeed, for nothing at all (e.g., they may become pseudogenes). Similarly, genes that were not in fact 'for' anything in particular (at least at the gross phenotypic level) can, over time, gain that sort of biological significance.

An example of gene that may once have been for some phenotypic trait but no longer is may be that of the alleles associated with cystic fibrosis (CF). It has been suggested that the prevalence of genes associated with cystic fibrosis in some populations is due to the heterozygote superiority such alleles

afford. Heterozygotes for alleles associated with cystic fibrosis may well be highly resistant to typhoid fever, but homozygotes for genes associated with CF generally acquire the disease and die young (see Pier et al. 1998). If true, the situation would be analogous to that of alleles associated with sickle cell anemia, discussed above with respect to pleiotropy. However, in contemporary western populations, the continued existence of the alleles associated with CF *cannot*, in all likelihood, be explained by the selective advantage heterozygosity provides. Resistance to typhoid fever has not been a major selective pressure in the very recent history of most western populations; the existence of such genes in modern populations at detectable frequencies is probably due to simple inertia. Therefore, genes that may once have been *for* something, e.g. resistance to typhoid, are now not for anything at all. If at some future time, typhoid once again will become a major threat and exerts a significant selective pressure, and the maintenance of the alleles associated with resistance to it in the population will be once again actually due to the resistance they afford, the genes might de novo become for something.

A similar example is provided by one of the current conjectures attempting to account for the prevalence of genes associated with HIV resistance (the so-called CCR5-Delta32 'AIDS-resistance' allele) in certain populations (see Stephens et al. 1998). If the prevalence of this gene in some populations were the result of selective pressure for resistance to the bubonic plague (as some researchers have conjectured), then it seems that at some time in the recent past (about 600 years ago) the gene may well have been at least partially for resistance to the bubonic plague. More recently, however, its maintenance in the population has presumably not been due to any active selection for it at all, but rather to evolutionary inertia. If this scenario is correct, the gene's usefulness in providing resistance to HIV might make that feature out to be an *exaptation* in the sense developed by Griffiths (1992; see also Gould and Vrba 1982). If the prevalence of the gene in extant populations is not being actively maintained by natural selection, we would have what Griffiths calls an 'exaptation'. If at some later date, the gene's association with HIV resistance is responsible for its maintenance due to selective pressures associated with that resistance, the gene would be in Griffiths's terms an 'exadaptation' (Griffiths 1992: 119). In our view, in that later case of an 'exadaptation' the gene in question would have become a plausible candidate for being a 'gene for HIV resistance'. Obviously, this is very speculative, but the basic idea, that on the Modern History approach to 'gene for' talk a gene that was for some trait can lose that (functional) association and later become 'for' some other trait, is intriguing.

Indeed, this aspect of the Modern History approach to thinking about genes 'for' traits is especially useful for considering the way in which new

gene functions can (and do) evolve. Roth (1988) presents an interesting scenario in her discussion of genetic piracy. According to Roth's definition, genetic piracy is the process by which:

> New genes, previously unassociated with the development of a particular structure, can be 'deputized' by evolution; that is, brought in to control a previously unrelated developmental process, so that entirely different suites of genes may be responsible for the appearance of the structure in different contexts. (Roth 1988: 7; see also Schlichting and Pigliucci 1998: 144–146; Ganfornina and Sanchez 1999)

Roth cites de Beer on the eyeless mutants of *Drosophila*, in which it is possible to select for other genes which result in "a fly with restored eyes that still has the original mutation" (1988: 7). From this, Roth concludes that in these cases "new genes are involved in the formation of eyes that previously had not been" (1988: 7). In this way, a different set of genes may become associated with the formation of a trait, and in some of these cases, different genes may end up being for the 'same' (homologous) phenotypic trait. Interestingly, one of Davies's criticisms of functional ascriptions in biology that appeal to evolutionary history ("Direct Proper Functions" in the literature) is the difficulty in specifying identity conditions for traits throughout recent evolutionary history (Davies 1994). By forcing the researcher who wishes to claim to have found genes 'for' traits into focusing on the recent evolutionary history of the relationship between the gene and trait in question before making any such claims, the Modern History approach we advocate focuses attention onto the way in which this relationship is somewhat fluid. Indeed, this very fluidity is the key to understanding the evolution of 'new' gene functions and associations.

5. Genes for: A case study of how far we can push the concept

Philosophical discussions of the type we are engaged in used to be limited by the scant availability of actual hard data pertinent to the subject matter. Modern molecular and evolutionary biology, however, afford us a unique opportunity to probe the advantages and limitations of the concept of a 'gene for' by testing it against concrete examples about which we know a great deal. Of course, in none but a few simple cases we know all or even most that there is to know about the genotype-phenotype mapping function. The black box of epigenetics has just recently being tackled by molecular developmental biologists, and a dim light is been shed on its interior. In the following, we will discuss the example of a gene, the *phyB* locus, in the weedy crucifer plant

Arabidopsis thaliana, as a guide to a more concrete understanding of what do we really mean by genes for something.

The *phyB* locus codes for one of five alternative forms of a class of molecules named phytochromes. Phytochromes are light-harvesting molecules that function as photoreceptors in *A. thaliana* and in many other organisms, including all flowering plants, non-flowering plants, green algae, and cyanobacteria. The specific functions and effects of these photoreceptors differ to some extent, but the PHYB gene product is sensitive to the ratio of Red to Far-Red (R:FR) wavelengths of light. The molecule can exist in the cell in two forms, one capable of absorbing red light and thereby switching conformation to the alternative form; the other sensitive to far-red light and shifting to the red-form. PHYB is present in *A. thaliana* in both forms, whose chemical equilibrium depends on the R:FR ratio (Ballarè 1999). Phytochrome B has been associated with a number of phenotypic effects, generally grouped under the label of "shade avoidance response". The idea is that under natural conditions the R:FR ratio is an indicator of impending competition: the surrounding vegetation absorbs the red component of the spectrum, which is photosynthetically active, but reflects the far red, too weak to be energetically useful. This alters the R:FR ratio from about 1:1 under normal sunlight to values below one, in proportion to the density of the vegetation. If a plant can sense the level of competition before it becomes too strong (i.e., before actual competition for light, water, or nutrients ensues), it may be able to adopt alternative growth strategies to minimize the damage. These strategies include suppression of branching to concentrate resources on vertical growth of the main stem and accelerated flowering to complete the life cycle before the quality of the environment deteriorates further (see Schmitt and Wulff 1993 and cites therein).

Indeed, physiological studies have confirmed that phytochrome B affects a variety of plant phenotypes: seed germination, cell elongation, cotyledon expansion, seedling appearance, flowering time, as well as leaf production and branching pattern (see Pigliucci and Schmitt 1999 and cites therein). Furthermore, evolutionary biologists have amassed convincing evidence that the shade avoidance response is indeed adaptive, not only in *A. thaliana* but in other plants as well (see Schmitt 1997 and cites therein). Finally, molecular genetic investigations have demonstrated that the mechanics of action of the *phyB* locus are complex. Its gene product interacts with a light-labile phytochrome termed PHYA (see for example Reed et al. 1994 and cites therein), with at least another phytochrome, named C (see Halliday et al. 1997 and cites therein), and with a completely different class of photoreceptors sensitive to blue light and known as cryptochromes (Casal and Boccalandro 1995). Phytochromes A and B interact with blue receptors in a complex manner,

both synergistically and antagonistically, depending on the environmental situation and the characters studied (see Callahan et al. 1999). Of course, photoreceptors by themselves do not actually exert any biological function, and they have to act together with other gene products to do so. Here the literature is much more vague and incomplete, although we know that there are several "transduction genes" whose products carry the information from the phytochromes to other molecules (Ang and Deng 1994; Quail et al. 1995). Eventually, the bio-effectiveness of light perception and transduction is mediated by one or more plant hormones such as gibberellin (see for example Chory and Li 1997 and cites therein), although other hormones (e.g., cytokinin) affect some of the same traits altered by light signals independently of the phytochromes (Su and Howell 1995).

So, what is the *phyB* locus 'for'? The obvious answer is that its function is to gauge the R:FR ratio. But surely light perception per se cannot be the target of natural selection, unless the information so acquired is actually used in some biological function related to fitness. Plants, after all, are not just curious about their environment. And here is where the trouble begins. If we use the studies associating mutations at the phytochrome B locus with their phenotypic effects, we are led to conclude that the gene is for the control of germination, cell elongation, leaf production, flowering time, apical dominance, branching pattern, and reproductive output – to say the least. One problem with this sweeping generalization is that in fact a lot of other genes also seem to be 'for' the same characters, with only partial (and sometimes contrasting) overlap with the effects of *phyB*. Furthermore, some of these traits (e.g., leaf production) are altered by mutations at the phytochrome B locus not because the phytochrome has much to do directly with leaf production, but more likely because the general growth rate of these mutants is slower than the wild type plants (this may also account for part of the differences in flowering time). That is, some of the alterations associated to changes at the *phyB* locus are bound to be accidental byproducts of the mutation, and not indicators of the wild type function of the gene.

Another level of complication in order to attribute a specific function to the phytochrome B gene arises when we consider that its biological activity is strictly environment-dependent: under a variety of environmental circumstances (i.e., unless the R:FR ratio is altered) the gene does not really do anything at all. That is why this locus has been proposed as one of the best candidates for the role of "plasticity genes", genes whose effect makes sense only under environmentally heterogeneous conditions (Pigliucci 1996).

Even the wealth of molecular information accumulated on the action of *phyB* does not seem to help clarify things much. One could say, for example, that the gene product of this locus is 'for' stimulating a transduction cascade

that eventually triggers the action of the gibberellin hormone. But more precisely one would have to say that *phyB* is for triggering gibberellin through the use of intermediary molecules (and specify this mediation effect). How far from the immediate effect of the phytochrome transcript can we go and still meaningfully speak of its function? On the other hand, surely it would be limiting to say that the gene is for photoreception and activation of a transducer (which is all the gene product of the *phyB* locus really does). Ignoring the fact that these actions have biological consequences affecting the plant's fitness would be as absurd as ascribing the entire plant phenotype to the action of this particular gene. Yet, the reality is that one can place the PHYB molecule on any point of the sliding scale defined by this continuum. The problem is that genes do not do anything by themselves, but only in relation to their environment, both the external one, and the one provided by the actions of other genes.

Evolutionary and phylogenetic information, also available for *phyB*, does not solve the problem either. We know that it belongs to an ancient family of genes, certainly predating the origin and evolution of flowering plants. We also know that these genes have diversified their biological effects, which are now only partially overlapping. If we go back far enough in time, the phytochromes can be thought of as very ancient photoreceptors, whose DNA sequence has been highly conserved for the past billion years at least (see Ballarè 1999 and cites therein). Such a long phylogenetic history also strongly suggests that they must have been maintained by natural selection, or they would have been lost (or at least their sequences would have been much more dramatically altered). Therefore, one could safely conclude that the phytochrome genes are really 'for' photoreception. However, their other functions/effects have changed considerably throughout the evolution of cyanobacteria, algae, and plants. Therefore, they have always been more than just photoreceptors, but this additional component has been constantly shifting through evolutionary time. This is exactly what we mean by the Modern History view that considers the idea of a gene for something more fluid and fuzzy than the classical rendition. In our specific example, the *phyB* gene controls photoreception and – indirectly – a series of environment-dependent changes in the phenotype and phenology of the plant. This flexibility does increase the fitness of the plant and the gene does qualify as a plasticity gene. However, which bits of the response are adaptive and which are allometric byproducts of altered growth rates remains to be established, and it is a very difficult empirical question.

6. Conclusions: The advantages of the Modern History approach to 'genes for'

We have argued that no approach to finding genes that relies on their merely being correlated with phenotypic traits can properly claim to have found genes for those traits. To conclude that a gene is not merely associated with a trait, but rather is actually for that trait, one needs significant amounts of evidence about not only the association, but also the biochemical pathways involved, and the recent evolutionary history of the organism in question (see Table 1). The Modern History approach demands that to speak properly of genes for a trait, the frequency of the genes in question was maintained in the population because of their association with that trait, and the resulting positive selective pressures for that trait. That is, in moving from the discovery of a candidate gene to a 'gene for' some trait, one needs at least information on the biochemical pathways the gene is involved in, on the epigenetic effects (including pleiotropy, epistasis, regulatory plasticity, etc.), on the functional ecology of the phenotype in question, and on the phylogenetic history of the organism and of the gene (or gene family). Finding these things out demands painstaking work: one cannot substitute assumptions, no matter how attractive, as many 'sociobiologists' and people partaking in 'evolutionary psychology' have tried to do. While we expect that it is impossible to know all of the above in any particular case, a consilience of evidence may move us to speak (albeit cautiously) of a gene being 'for' a trait where some of the above evidence is wanting. These are not easy things to find out even in organisms in which experimental manipulations are possible. In the case of humans, where experimental manipulations are out of the question, they are more difficult still, perhaps so much so that we can never be confident to have found a gene 'for' a reasonably complex phenotypic trait in humans. However, we do not think that this is a reason to despair, or that this places undue burdens on current research.

Indeed, as noted above, we feel that the recognition that we can rarely find genes 'for' specific phenotypic traits is valuable for many reasons. This recognition will, we hope, focus attention on the evolutionary relationship between phenotypes and genes, including the fascinating ways in which genes can acquire new functions and 'old' structures become associated with different genes. Such recognition would also focus more attention on the relationship between the organism and its environment, and the way in which gene-environment interactions shape the ontogenetic pathways and evolutionary histories of organisms (Schlichting and Pigliucci 1998). In focusing attention on the relationship between genetic and phenotypic development in an evolu-

Table 1. A checklist for 'genes for'

Type of necessary evidence	Methods to gather the evidence
Statistical association	Quantitative genetics, QTL analysis
Identification of candidate genes	QTL analysis, mutagenesis
Information on gene regulation (developmental and environmental)	Molecular and ecological genetics
Information on epigenetic effects (pleiotropy, epistasis, and high-level interactions)	Quantitative and molecular genetics
Functional ecology of associated phenotypes	Field studies on fitness consequences, experimental manipulations. Functional ecology and quantitative genetics
Phylogenetic history (of both the organisms and of the gene or gene family)	Molecular systematics. Phylogenetic comparative methods

tionary context, this view of 'genes for,' as challenging as it may be, keeps the attention where it ought to be. These are positive benefits of this way of thinking about 'genes for' traits. But the dangers that this way of thinking avoids are equally significant.

The number of purported discoveries of 'genes for' various complex traits, often in humans, that are reported in the media (both popular and scientific) is simply staggering.[5] Even in the scientific literature, we feel that such reports often give a misleading picture of the current state of research into the relationship between genes and phenotypes. But the misunderstandings and confusions that reports in the popular media engender, and, indeed, engender because of the very language of 'genes for,' is if anything even more worrisome. These misunderstandings are problematic because they systematically mislead the public. They raise illegitimate expectations about the power of genetic research,[6] and these misunderstandings end up actually influencing public policy decisions, and doing so in ways that a proper appreciation of the current state of knowledge about the relationship between genes and complex phenotypic traits in humans would not countenance. To claim, as Dawkins does, that when a geneticist says 'gene for' what they mean is 'a statistical association with' a phenotype is, we believe, difficult to maintain. Geneticists (and other researchers), especially those that talk to the media, do not get to play Humpty Dumpy – their words do not get to mean whatever they choose them to.

Notes

[1] The sort of functional talk developed by Godfrey-Smith (and other authors, such as Griffiths 1993) has come under attack by e.g. Davies (1994, forthcoming) and others. These attacks, for the most part, do not apply to the problem we are working on. For example, the main foci of Davis (1994), the (claimed) inability of historical views of functions to deal with identity issues over time and the (claimed) inability of historical views of functions to deal with complex (empirical) genetic issues, are both difficulties that we embrace. We think that our way of conceiving of 'genes for' aids the proper conceptualization of these issues. Davis (forthcoming), on the problem of 'malfunctions,' is also not an issue for the sort of 'genes for' talk we develop, for reasons that are related to the way that evolution can and does change the relationship between phenotypes and genes (see below).

[2] Agar (1996) suggests a somewhat similar approach to interpreting 'genes for' in his critique of the approach recommended by Dawkins and to a lesser extent the one of Sterelny and Kitcher. In arguing that the sense of a gene being 'for' a trait suggested by those views is too weak, Agar proposes that a better approach might recognize that genes "depend for their existence on phenotypes which [license] a kind of functional ascription to them" (1996: 295). More formally, "G is a gene for [a phenotypic trait] P, if G is selected for the production of P" (1996: 295). While we feel that this analysis is on the right track, Agar's articulation of the view is problematic. The most important difficulty, from our perspective, is that Agar's analysis seems to underestimate the complexity of the relationship between genes and phenotypes. Indeed, Agar sometimes suggests that a possible-worlds analysis would show that genes which are associated with, e.g., the development of healthy hearts are "highly likely" for "building hearts" (1996: 297, 298). Below, we will give some explicit arguments against moving from an association with biologically important features to conclude that it is this association that is responsible for the gene's maintenance in the population. We think that there are far fewer 'genes for' traits than Agar seems to imply. Further, we explicitly reject Agar's pluralism about 'genes for' talk; while some researchers "may want to include neutral and deleterious effects" in their 'gene for' talk (Agar 1996: 299), for the reasons above we should reject such talk in these situations as misleading.

[3] For example, imagine a particular ocean current strongly associated with beach erosion in a particular area. Imagine in fact that we learn how, from a mechanistic standpoint, that particular current has resulted in this particular erosion. It is clear that we still have no reason to claim that the tide is for the erosion of the beach. This is the situation we find ourselves in when we understand the developmental pathways a particular gene and gene product are involved in, and how those pathways result in a particular trait, but do not understand the recent evolutionary history of the organism with respect to the trait in question. (The authors would like to thank Richard Aquila for this example.)

[4] We use the phrase 'code for' here in the strict historical sense of the word recently developed by Godfrey-Smith (2000) and which we feel is the most common use in the molecular genetics community. We mean by it only that it is the DNA sequence that explains the presence of that particular protein, the one it 'codes for' (but does not 'resemble' – hence the 'code' metaphor). We agree with Godfrey-Smith that this interpretation does justice to the way the term is actually used by careful molecular biologists (and follows early uses of the word).

[5] In the popular media, many very bold versions of 'gene for' claims can be found. Some relatively recent examples include: "A gene for social behavior rather than a gentler upbringing could explain what makes women so much nicer than men" (Mallalieu reporting for the Guardian 1997); "Scientists find a gene for intelligence" (Conner, reporting for the Times 1997); "Gene for 'evening people' found" (The Globe, no byline 1998); "A gene for high

sex drive and another for promiscuity, have been discovered by scientists in America" (Irwin reporting for the Telegraph 1998). Quick full-text database searches turn up many reports like these in newspapers and magazines every year. However, the popular media is not alone in using this language; claims in the same style often appear in respectable peer-reviewed research journals as well. For example Marian argues for "RS [right shift, a theory of handedness] as caused by a gene for left hemisphere advantage" (1998: 459). Lee et al. claim that their research "may lead to cloning of a susceptibility gene for schizophrenia" (1998: 123). Gershon et al. claim to be "closing in on genes for manic-depressive illness and schizophrenia" (1998: 233).

[6] It is somewhat of an open question if these illegitimate expectations are raised by the carelessness of scientists when talking to the media, or by a more or less conscious effort to justify the public interest and therefore divert funding to otherwise intellectually less than fertile projects such as the human genome initiative.

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