Parallel Selection: Evolution’s Surprising Predictability

The mechanistic basis of how polygenic traits respond to selection is not well understood. New research provides compelling evidence for widespread parallel selection in independent mouse strains selected for extreme body weight.

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Although it has been over 150 years since Charles Darwin and Alfred Wallace first described their independent discovery of the theory of natural selection [1], understanding the molecular and mechanistic basis of adaptation remains a fundamental goal of evolutionary biology. Since this time, many beautiful and illuminating examples of adaptation at the molecular level have been described for a wide variety of phenotypes, including beak morphology in Darwin’s finches [2], coat color in beach mice [3], skin wrinkling in Shar-Pei [4,5], and lactose tolerance in humans [6]. A common characteristic of these phenotypes is that they have a relatively simple genetic architecture; however, the vast majority of agricultural, evolutionary, and biomedical phenotypes of interest are polygenic and influenced by genetic variation at many loci [7]. Thus, it is unclear whether these examples are representative of the evolutionary dynamics at play for adaptively evolving polygenic traits. For example, outstanding questions include: does selection primarily act on newly arisen advantageous mutations or alleles already segregating in the population (also referred to as ‘standing variation’); is the response of a polygenic trait to selection driven by a small number of alleles with large effects or by many alleles with small effects; and finally, are there particular genes, or regulatory sequences, that are recurrent targets of selection? In a recent issue of Current Biology, Chan et al. [8] provide insight into these questions by comprehensively identifying and analyzing loci that contribute to body weight in mice.

A formidable barrier to understanding the molecular basis of polygenic adaptation has been the difficulty in genetically dissecting such traits. To improve their chances of mapping loci that influence body weight, Chan et al. [8] studied seven previously developed mouse strains that had been independently subjected to long-term artificial selection for increased weight and size (Figure 1). Indeed, the effects of artificial selection were impressive, with some lines increasing in body weight by as much as 240% compared to unselected controls. Because these seven selected lines were derived from several common stocks, they inherited shared genetic variation. Chan et al. [8]
leveraged the common ancestry of these strains to specifically test the hypothesis of whether the same polymorphisms that experienced selection in one strain also experienced selection in other strains. In other words, they were interested in determining if artificial selection led to parallel genetic changes across the seven mouse lines. Such parallel responses to selection would result in shared variants found at high frequency in the selected lines and low frequency in the control unselected lines.

To find this signature of parallel selection, Chan et al. [8] genotyped nearly 600,000 SNPs and developed a novel statistical approach to formally assess patterns of allele sharing between selected and control mice. In total, they found 67 significant parallel selected regions that ranged in size between 50 kb and 1 Mb. This is a remarkable result for several reasons: first, in typical gene mapping experiments of polygenic traits, large numbers of offspring need to be analyzed to have sufficient power to identify variants with even modest effect sizes. Chan et al. [8] studied only seven selected lines, but identified a substantial number of quantitative trait loci (QTL) for body size and weight, highlighting the power of parallel selective mapping. Reassuringly, many parallel selected regions overlapped with previously identified body weight QTLs in mice and could accurately predict weight in independent mouse panels.

Second, the genomic intervals spanned by parallel selected regions were substantially smaller compared to the often poor resolution afforded by many QTL mapping approaches. The higher resolution of parallel selection mapping is attributable to taking advantage of the history of recombination events that had occurred during the course of the long-term artificial selection experiments. The ability to localize QTL more precisely is of considerable practical importance because it accelerates the identification of causal genes and polymorphisms influencing the trait of interest. For example, Chan et al. [8] were able to obtain single gene resolution for several parallel selected regions, including GPR133, a locus that has also been robustly associated with height in humans [9].

Third, and most importantly, the results of Chan et al. [8] provide clear evidence that a substantial component of the response to selection for larger and heavier mice was due to parallel changes acting on standing genetic variation. The reuse of existing variation as substrates of selection in these independently evolving lines suggests that, at least in some circumstances, evolution may be more predictable than perhaps expected. Although evolution is inherently a stochastic and historically contingent process, a deeper understanding of the molecular basis of parallel selection may provide insights into when, and perhaps why, selection can yield reproducible genetic changes.

An important question moving forward is whether the widespread parallel selection observed by Chan et al. [8] is a common mechanism underlying polygenic adaptation, or if it was the result of the specific phenotype studied or study design employed. In particular, does strong artificial selection for increased weight and size in mice provide any insight into the molecular and mechanistic basis of how natural selection acts in the wild? Interestingly, Chan et al. [8] provide evidence that the parallel selected regions they identified have also experienced positive selection in several large-sized wild mice. Even more provocatively, they found weak but statistically significant overlap between their parallel selected regions and 180 loci that have been associated with human height. Moreover, evidence for parallel selection has been found in a number of species, including humans [10,11], threespine sticklebacks [12,13], and Caenorhabditis elegans [14]. In many of these cases, parallel selection is likely acting on standing variation, which stands in stark contrast to the predominant theoretical model that adaptation is driven by selection on newly arisen advantageous mutations [15]. In fact, most statistical tests of neutrality are designed to detect classic signatures of selection predicted by this model [16]. The results of Chan et al. [8] and others suggest that perhaps many signals of selection have gone undetected and new methods tailored to more realistic models of adaptation are needed.
Although considerable work remains in the continued quest to delineate the molecular and mechanistic basis of evolutionary change within and between species, the work of Chan et al. [8] provides some of the best evidence yet that parallel genetic changes in the response to a selective pressure may be an important component in the adaptive evolution of polygenic traits. In many ways, the more we learn about evolution the more it resembles François Jacob’s famous analogy that evolution is a tinkerer [17], an imperfect process that makes do with the parts (genetic variation) that are available to it.

References

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Pronuclear Migration: No Attachment? No Union, but a Futile Cycle!

How do pronuclei migrate towards each other? The zebrafish *futile cycle* gene is shown to encode a maternally expressed membrane protein required for nuclear attachment and migration along the sperm aster.

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During fertilization, the male and female pronuclei migrate toward each other and congress to mix genetic materials from both parents. In many animal species, the sperm donates the sole pair of centrioles. The centrosome — essentially centrioles coated with microtubule-nucleating material — thus assembles near the male pronucleus and nucleates microtubules for the sperm aster [1]. Once contacted by the expanding sperm aster, the female pronucleus moves along the microtubules toward the centrosome, close to the male pronucleus (Figure 1A), in a dynein-dependent manner [2–4].

One approach to elucidate pronuclear migration mechanisms is forward genetics. This requires maternal effect mutations that alter the molecular composition of the egg while allowing the mother and her eggs to develop. The maternal-effect mutation *futile cycle* in the zebrafish zygote abolishes pronuclear congression and DNA segregation in subsequent mitoses. Early embryonic cell cycle progresses normally and cytokinesis still occurs, orchestrated by centrosomes and microtubule asters without DNA, thus resulting in enucleated cells [5]. In this issue of *Current Biology*, Lindeman and Pelegri trace the *futile cycle* mutation to a gene encoding a vertebrate-specific lymphoid-restricted membrane protein (Lrmp) [6]. Lrmp protein localizes mainly to the nuclear envelope. In the metaphase spindle, where nuclear envelope is absent, the Lrmp protein is found juxtaposed with the centrosomes at the spindle poles. In *futile cycle* mutant zygotes, centrosomal material is detached from both pronuclei, which stay far apart from each other, and no detectable Lrmp protein localization is observable. Using various localization approaches in fixed embryos and a novel method to genetically rescue the maternal effect mutation, the authors suggest that Lrmp provides a physical link between the nuclear envelope and microtubules [6].