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MODELLING SELECTION FOR ADJUSTABLE GENES BASED ON SIMPLE SEQUENCE REPEATS.

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INTRODUCTION.

Although mechanisms that yield beneficial mutations can be selected indirectly if they are inherited along with favored alleles, the effectiveness of indirect selection as an agency for shaping adaptive mutation remains largely unexplored.

Several properties of simple sequence repeats (e.g., microsatellites) suggest a function in mutational modification of quantitative traits (1,2). Simple sequence repeats are integrated into many functional gene complexes, where the number of tandemly repeated units can exert a quantitative effect on gene expression. Since the most common effect of mutation in such sequences is the reversible addition or subtraction of a single repeat unit, mutations in such sequences can provide quantitative genetic variation with minimal risk of severely deleterious effect. This mode of mutation is intrinsic to repetitive sequences, and so is inherited along with each simple sequence repeat. Furthermore, mutation rate and typical mutation size are site-specific for reach such sequence, based on features such as motif length and purity of motif repetition. Could mechanisms of gene regulation involving simple sequence repeats be shaped by indirect selection to promote evolutionary adjustability of quantitative traits?

METHOD.

A computer simulation explores the effectiveness of indirect selection, using a simple stochastic model for a population of diploid individuals. Mutation effects are modelled after the properties of simple sequence repeats.

At each generation, a finite number of zygotes are produced by random pairing of parents. Those that survive selection become the parents for the next generation. Phenotype is determined by a single polymorphic locus. Alleles vary quantitatively, with corresponding quantitative effects on phenotype. Fitness values (probabilities of survival for the various phenotypes) have a normal distribution around a single optimal phenotype and may be reduced by competition among similar phenotypes. The model environment (i.e., the optimal phenotype around which fitness is distributed) can change gradually over time. As the environment fluctuates, optimal phenotypes may be accessible only through mutation.

Alleles mutate by random positive or negative increment in value. Mutation range (a limit on mutation magnitude) is hereditary and may be subject to infrequent random change. Mutation rate (the probability of mutation per allele per generation) is also hereditary and may also be subject to infrequent random change. Mutation range and rate have no direct effect on fitness; they are selected only indirectly as mutated alleles affect phenotype. These parameters are modelled as tightly linked to individual alleles, like the intrinsic mutational parameters of simple sequence repeats.

RESULTS.

When range and rate of mutation are assigned fixed values for all individuals in a population, simulations reveal a "mutational landscape" in which survivorship (average population fitness) depends on those parameters (Fig. 1, contours). The shape of the mutational landscape is determined by fluctuations over time in the model environment and by competition among similar phenotypes. Low survivorship can reflect not only excessive numbers of deleterious mutations but also paucity of mutational variation resulting in inability to track shifting fitness optima or to fill available niche breadth. When mutational parameters are free to vary and evolve, the population climbs uphill on the mutational landscape under the influence of indirect selection. Alleles that predominate after indirect selection have mutational parameters close to a peak or ridge of the mutational landscape (Fig. 1, dots). But this effect of indirect selection is dependent on linkage between mutational parameters and mutating alleles. Indirect selection is ineffective when mutational parameters are permitted to assort as independent characters, leading to extinction under stringent conditions of rapidly shifting fitness optima.

DISCUSSION.

Under simple simulated conditions, indirect selection can effectively shape mutational parameters but only when those parameters are linked to the mutating alleles. Indirect selection may also be an effective agency under natural conditions, whenever environmental change persists over time or heterogeneous conditions favor variation. Site specific modes of mutation such as those of simple sequence repeats may well be shaped by selection acting indirectly through the potential for adaptive adjustment that is provided by a reliable supply of quantitative variation. Indeed, simple sequence repeats may have an evolved function of mutationally adjustable gene regulation, while "the evolutionary plasticity of repeat sequence location in the genome could be regarded as a source of possibilities for new ontogenetic regulatory patterns" (3).

More speculatively, intricate contrivances for genetic manipulation (4,5) might evolve just as proficiently by indirect selection as do direct adaptations of morphology and behavior. And if this is so, then the remarkable engineering capacity of natural selection may depend, recursively, on sophisticated mutational mechanisms designed by indirect selection.

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