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TRIPLET-REPEAT DNA: UNSTABLE REGULATORY GENES COULD BE EVOLUTIONARY "TUNING KNOBS".

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Excessive expansion of triplet repeat DNA sequences causes several neurological diseases (Martin, *Science* 262:674). But the length of these mutational unstable sequences also modulates normal gene transcription activity (Gerber, et al., *Science* 263:808), as predicted from the basic principle that site-specific mutation can offer significant evolutionary benefits (King, *Science* 263:595). The concept that highly mutable genes can be adaptively advantageous has not yet been widely applied in genetic neurobiology, presumably because it contradicts the common opinion that mutation in any form is almost always deleterious. In computer simulations, however, deterministic selection at a single locus can favor unstable alleles, if the quantitative phenotypic effects of individual mutations are small and if competing Mendelian alleles are not optimally fit, especially if the adaptive peak fluctuates over time. Natural selection might similarly favor mutation-prone genes if the usual consequences of mutation were suitably constrained. Regulatory genes based on unstable triplet-repeat length could thus function as evolutionary "tuning-knobs", efficiently establishing adaptive genotypes in a shifting environment. This idea may offer a useful paradigm for studying patterns of genomic organization underlying innate but evolutionarily flexible patterns of behavior.