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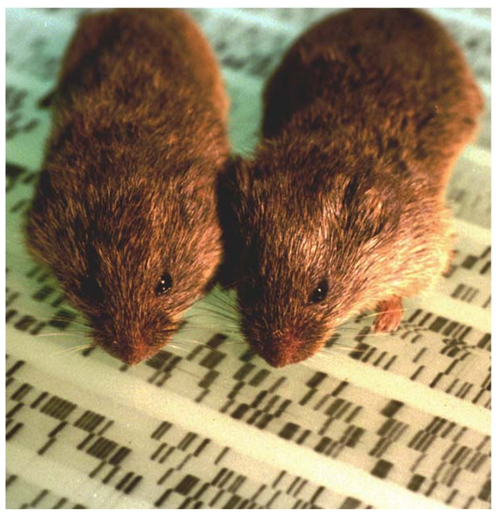

SSR variation in a vasopressin receptor gene is responsible for intra- and interspecific variation in social behavior among voles (Hammock & Young 2005).

Image courtesy L. Young

Facilitating Evolution:
Simple Sequence Repeats Make Genes Adjustable.

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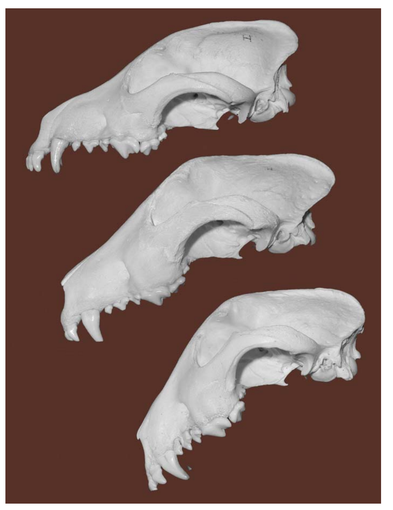
The evolutionary plasticity of repeat sequence location in the genome could be regarded as a source of possibilities for new ontogenetic regulatory patterns. E.H. Davidson, 1982



SSR variation within developmental control genes underlies morphological differentiation among domestic dog breeds (Fondon & Garner 2004).

Image courtesy J. Fondon III

SIMPLE SEQUENCE REPEATS (SSRs) **can enhance the evolutionary plasticity of developmental processes.**

SSRs supply abundant genetic variation with minimal risk of severely deleterious effect.

Many SSRs are located in functional domains, within exons and introns as well as in upstream and downstream regulatory regions.

SSRs experience frequent, reversible, site-specific mutations which add or subtract motif units. The number of motif repetitions can influence practically any aspect of gene function.

SSRs (also called MICROSATELLITES and MINISATELLITES) are DNA tracts in which a relatively short base-pair sequence, or MOTIF, is repeated over and over in tandem.

Although SSRs are often mischaracterized as "junk", their exceptional mutability can contribute genetically meaningful variation.

When integrated into functional gene complexes, SSRs act as general-purpose **TUNING KNOBS** for adjusting gene function (King *et al*. 1997, Kashi & King 2006).

TRIPLET REPEAT (trinucleotide SSR) mutations can alter the length of an encoded homopolymeric amino acid stretch without shifting the reading frame.

Transcription factors frequently incorporate homopolymeric stretches encoded by variable triplet repeats (e.g., Gerber *et al*. 1994).

Abundant triplet repeat variation in developmental regulatory genes provides the basis for rapid morphological evolution of domestic dog breeds (Fondon & Garner 2004).

The phylogenetic origin of insects is marked by the appearance of a triplet repeat in a Hox gene (Galant & Carroll 2002).

SSRs contribute to EVOLVABILITY by conferring properties of adjustability, modularity, and exploratory behavior.

SSRs' site-specific, repeat-based mutability can facilitate efficient adaptive adjustment at any level in a regulatory hierarchy.

Mutation rate and typical mutation size are based on heritable parameters of each SSR site, such as motif length and purity of motif repetition.

Individual SSRs can arise spontaneously, replace one another, and vanish without altering basic gene function.

Mutability based on SSRs may be evolutionarily advantageous.

INDIRECT SELECTION can plausibly shape SSR mutability and location so that these sequences provide a reliable supply of low-cost genetic variation.

A selective advantage based on SSR mutability has been experimentally demonstrated for the CONTINGENCY GENES of pathogenic bacteria (Bayliss & Moxon 2006).

Although similar evolutionary benefit for eukaryotes has not yet been conclusively established, several examples of adaptive variation provided by SSRs have been reported (reviewed in Kashi & King 2006; King, Trifonov & Kashi 2006).

INDIRECT SELECTION of a genomic trait such as site-specific mutability (which does not directly affect phenotype) occurs when the trait is closely and causally linked with beneficial mutant phenotypes.

At SSR loci, mutability is encoded by motif length and repeat purity while phenotype is encoded by the number of repeats. Repeat-number stability will be favored only when an ancestral number of repeats consistently yields higher fitness than do variants with altered repeat numbers. Mutability will be selected (indirectly) when changing circumstances repeatedly favor mutant alleles.

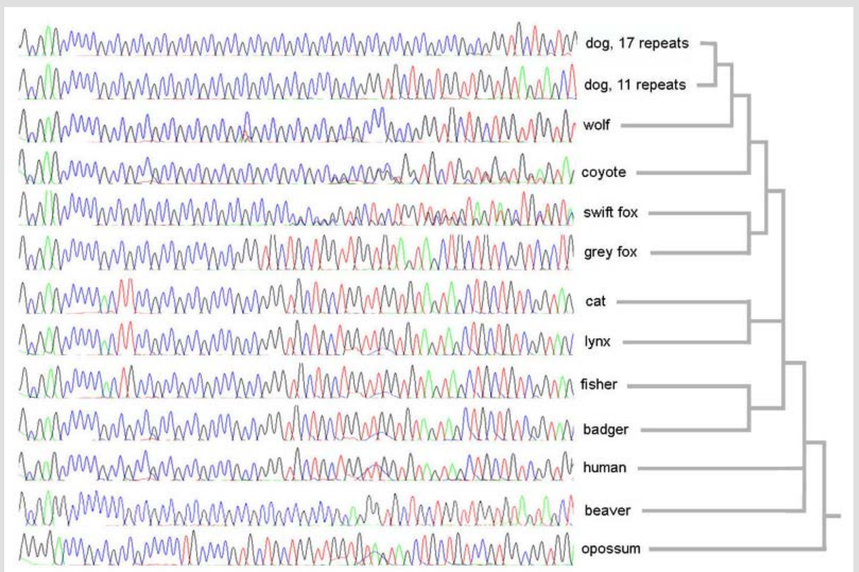
Mutationally variable SSRs *may be a common and beneficial feature of adjustable genes, just as* TUNING KNOBS *are a common and useful feature of adjustable instruments.*

SUPPORTING MATERIALS

Repeat-Number Mutations	***vs.***	**Classical Point Mutations**
Repeat-number mutations involve addition or subtraction of repeating motifs. Any gain or loss in the number of repeats can be readily reversed by subsequent loss or gain.		Multiple types of point mutation (substitutions, insertions, and deletions) make reversal of any particular mutation unlikely. Reversal of multiple mutations is highly improbable.
SSR repeat-number mutations occur at rates orders of magnitude higher than those for point mutations. Yet such extreme mutability seems not to be substantially deleterious.		Point mutations typically occur at extremely low rates. Such rates apparently result from natural selection favoring the highest practical level of replication fidelity.
Variation in repeat-number mutation rate is due to attributes which are intrinsic to each SSR site. Thus site-specific mutation rates are heritable along with particular SSR alleles.		Variation in point mutation rate typically involves mechanisms whose effects on replication fidelity are not site-specific but distributed throughout the genome.
Phenotypic effects of SSR mutation are often quantitative and small, with reasonably high likelihood of adaptive advantage. Reversible switching occurs in contingency genes.		Phenotypic effects of point mutations range from neutral to lethally disruptive, with beneficial effects occurring only rarely.

An SSR Phylogeny

The mammalian gene *Dlx-2* exemplifies conservation of SSR location and motif together with variation in number of repeats and purity of repetition.



Data courtesy J. Fondon III

If you would like more information . . .

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