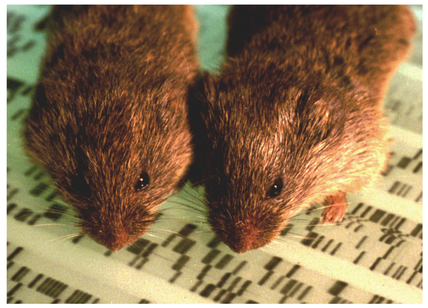

Repeat-based variation in a vasopressin receptor gene influences intra- and interspecific variation in social behavior among voles [13]. *Image courtesy L. Young*

Why do so many neurodevelopmental genes contain repeat-based mutable sites?

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Background

SSRs (SIMPLE SEQUENCE REPEATS) are integrated into many genes that affect nervous system function and development.

- Notoriously, mutations in triplet repeats are responsible for many genetic neuropathologies [1].
- SSRs with various motifs (not just triplet repeats) appear to be responsible for normal variation in many neural and behavioral traits [2].
- Histidine repeats are overrepresented in proteins expressed in the nervous system [3].

SSRs equip genes with mutable sites.

- 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.
- Many SSRs are located in functional domains, within exons and introns as well as in upstream and downstream regulatory regions.
- The number of motif repetitions can influence practically any aspect of gene function [4].
- SSRs experience frequent, reversible, site-specific mutations which add or subtract motif units.
- SSRs supply abundant genetic variation with minimal risk of severely deleterious effects.
- SSRs can contribute to adaptive evolution [5, 6].

Selection can favor SSR mutability.

- INDIRECT SELECTION occurs when a phenotype is closely and causally linked with a genomic trait (such as site-specific mutability) which does not directly affect phenotype.
- Each SSR encodes both a particular phenotype (represented by the number of repeats) and also a specific mutation rate (encoded by motif length and purity of motif repetition). These dual representations are inextricably linked.
- SSR mutability can be favored by INDIRECT SELECTION when circumstances repeatedly favor mutant alleles.
- Thus INDIRECT SELECTION can plausibly exploit SSRs to provide a reliable supply of low-cost genetic variation [7].

A puzzle, and a hypothesis

Why should a peculiar, mutation-prone pattern of genetic information be especially common in genes associated with neural function?

- As reported to SfN several years ago [8], computer simulations of population genetics have suggested that repeated bouts of adaptive stress can indirectly select alleles that are susceptible to frequent, small mutations.
- SSRs appear to confer onto real genes the mutability characteristics that are favored in such simulations.
- SSRs provide genetic "tuning-knobs" for efficient adaptation in shifting environments [9].

SSRs may be associated with neural function because behavioral traits are especially critical for evolutionary adaptation.

New clues

Riley & Krieger recently reported a peculiar category of SSR, found predominantly in genes involved in nervous system function and development [10].

- These genes contain dinucleotide repeat (diSSR) sites with highly conserved upstream flanking sequences in their untranslated regions.
- Among all the examples whose functions are known, most either are critical for mammalian nerve cells (such as ion channels, synapse-associated proteins, neurotransmitter receptors, axon pathfinders) or are expressed during embryonic nervous system development.
- (The function for such diSSRs remains unknown, but they are expected to influence folding of transcribed single-strand RNA.)

Remarkably, most of these mutation-prone diSSR sites are conserved over deep evolutionary time.

- It is the diSSR sites, not their specific motif sequences nor their numbers of repeats, that are conserved.

Conserved diSSR sites display recurring patterns of motif replacement in various mammalian lineages [11].

- "Some function is evidently being preserved in the repetitive (and hypermutable) nature of these sites, one which can persist through, or perhaps even exploit, the accumulation of sequence-transforming mutations" [12].

Simulation results

Can these new clues be integrated with a hypothesis of "tuning knob" function for SSRs, as suggested by prior simulations?

- Extending prior pop-gen simulations indicates that mutationally unstable ("tuning knob") alleles, once established within a population, are not effectively eliminated during intervals of stability lasting hundreds of generations.
- However, "tuning knob" alleles can individually experience variation and drift, while maintaining their function as prolific sources of genetic variation.
- These simulations show that various high-mutation-rate alleles can replace one another during repeated periods of stability and adaptive stress.

Such results appear consistent with motif replacement at conserved diSSRs sites, as reported by Riley & Krieger [10, 11].

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Conclusions:

A "tuning knob" function, implemented by SSRs, can persist through deep evolutionary time.

Such an evolutionary role appears especially advantageous for neural and developmental mechanisms.

Pay attention to repeats whenever they appear in or near a gene of interest.

Simple sequence repeats can act as general-purpose tuning knobs for adjusting gene function [9].