

Highly similar noncoding genomic DNA sequences: ultraconserved, or merely widespread?

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Abstract: In this note, I propose an explanation for the seeming contradiction between bioinformatics-based predictions of an essential function for ultraconserved DNA sequences, and the lack of an experimental demonstration of such function.

Key words: transposon, mobile genetic element, human genome, nongenetic.

Résumé : Dans cette note, l'auteur propose une explication pour l'apparente contradiction entre les prédictions fondées sur la bio-informatique voulant que les séquences d'ADN ultraconservées aient une fonction essentielle et l'absence d'appui empirique pour une telle fonction.

Mots-clés : transposon, élément génétique mobile, génome humain, non génétique.

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The large-scale comparison of genomic DNA sequences between vertebrate lineages has revealed the presence of highly similar noncoding DNA sequences between lineages that diverged hundreds of millions of years ago (Bejerano et al. 2004; Pennacchio et al. 2006). Taken at face value, such high levels of sequence similarity reflect an equally high degree of sequence conservation since the divergence of the lineages in question. Sequence conservation can, in turn, be taken as an indication of functional constraint on the accumulation of new mutations, suggesting that these sequences are essential for critical biological functions (Drake et al. 2006; Katzman et al. 2007). Although this line of reasoning is perfectly logical, it appears to be contradicted by recent experimental results showing that deletions of these genomic DNA sequences have no detectable functional consequences (Ahituv et al. 2007). Here, I suggest a resolution of this paradox based on the observation that many of these sequences appear to be related to transposable genetic elements (Nishihara et al. 2006; Pennisi 2007).

It is well known that transposable genetic elements may be transferred between lineages (Clark et al. 1994) and that, once transferred, they can rapidly spread to all members of a sexual outbreeding population (Hickey 1982). This combination of inter-lineage transfer and intraspecies proliferation leads to unexpectedly high levels of sequence similarity between element copies in different lineages, given the divergence times of the host genomes (Sánchez-Gracia et al. 2005). For example, a recent report (Piskurek and Okada

2007) shows that poxviruses are possible vectors for horizontal transfer of retrotransposons from reptiles to mammals. In other words, the high levels of sequence similarity may reflect a transfer of these sequences between genomes long after the genomes themselves diverged from their common ancestor. Not only can we explain the seemingly high levels of sequence conservation by the horizontal transfer of transposons between diverse lineages, but the rapid intra-genomic turnover of such transposons would also generate patterns of allelic variation that mimic purifying selection.

Of course, if these horizontal transfer events were *very* recent, i.e., within historical time, the situation would be trivially obvious. It is not so obvious, however, to distinguish between the consequences of a horizontal transfer that occurred twenty million years ago and a divergence that occurred two hundred million years ago. This is because the transferred sequences would have undergone significant divergence, albeit less than expected based on the species divergence times. Finally, it is worth noting that all transposon sequences are themselves subject to selective constraint, but this is selection for transposon function rather than cellular function. What is lacking in the current analyses is a critical consideration of the complexities that are introduced by the potential interspecies transfer and intraspecies proliferation of these sequences.

In conclusion, the observed high sequence similarity between noncoding genomic DNA sequences in diverged vertebrate lineages may not, after all, be an indication of an

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important organismic function for “junk” genomic DNA (Pennisi 2007). Instead, it may simply reflect the fact that “genomic weeds” can be transferred between lineages and flourish within genomes during the course of long-term evolution.

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