Epistasis in ultraconserved non-coding elements

Olga A. Vakhrusheva

Lomonosov Moscow State University, Leninskye Gory 1-73, Moscow, 119991, Russia, vakh57@gmail.com

Alexey S. Kondrashov

University of Michigan, Ann Arbor, MI 48109-2216, USA, kondrash@umich.edu

Georgii A. Bazykin

Lomonosov Moscow State University, Leninskye Gory 1-73, Moscow, 119991, Russia, gbazykin@iitp.ru

Human genome comprises hundreds of ultraconserved non-coding sequences. These elements typically defined as non-coding sequences longer than 200 base pairs with 100% identity to mouse, rat or chicken orthologous region (1). As negative selection associated with such extreme conservation should be of great strength, it was argued that such ultraconserved elements should be of great functional importance. Furthermore, selection acting on such elements was estimated to be much stronger than in protein-coding regions (2). However, experimental depletion of several ultraconserved elements resulted in viable mice (3).
We propose that such discrepancy between theoretical predictions and experimental observations might be explained by strong epistasis between individual sites in ultraconserved elements. In this case acquisition of any particular nucleotide substitution would destroy the element turning it unfunctional. In this scenario we would expect all mutations occurring next in this haplotype to behave in a neutral manner. Thus, we would expect individual SNPs to accumulate in the same haplotypes rather than to be independently distributed between different haplotypes. Here, we explore this scenario on the human polymorphism data from 1000 genomes project. Our findings are consistent with the hypothesis of strong epistasis acting in the ultraconserved elements.

1. G. Bejerano et al. (2004) Ultraconserved elements in the human genome, *Science,* **304**:1321–1325.

2. S. Katzman et al. (2007) Human Genome Ultraconserved Elements Are Ultraselected, *Science,* **317**:915–915.

3. N. Ahituv et al. (2007) Deletion of Ultraconserved Elements Yields Viable Mice, *Plos Biol,* **5**:e234.