

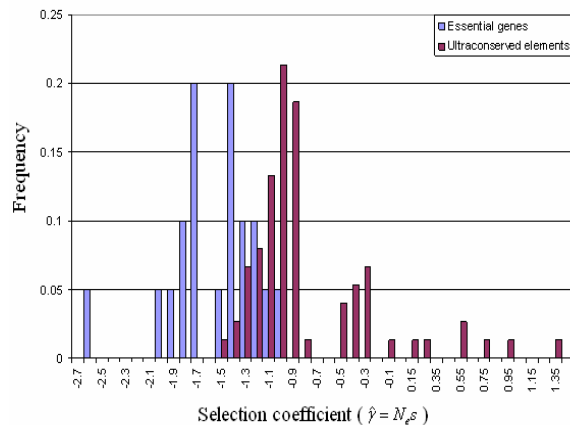
The strength of selection on ultraconserved elements in humans

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Ultraconserved elements are stretches of consecutive nucleotides that are 100% conserved in multiple mammalian genomes [1]. A basic tenet of comparative genomics is that sequences which contribute to the fitness of an organism will diverge slowly through evolutionary time. Thus, the ultraconserved elements, which seem to evolve exceptionally slowly, might encode important functions. The theoretical functions of these elements, however, remain unknown. Although the ultraconserved elements are identical in the reference human, mouse, and rat genomes, we identified numerous polymorphisms within these regions in the human population. We genotyped unrelated human DNA samples at loci within these sequences to determine whether polymorphisms in ultraconserved elements affect fitness. For all SNPs tested in ultraconserved regions, individuals homozygous for derived alleles (alleles that differ with the mouse and rat reference genomes) were present, viable, and healthy. The distribution of allele frequencies in these human samples argues against strong, ongoing selection preserving the conservation of these sequences. By examining the distribution of polymorphisms within these elements and exploring nucleotide differences in these sequences in the chimpanzee genome, we estimated the strength of selection consistent with the maintenance of these elements in multiple mammalian genomes.

Figure 1 Distributions of selection coefficient acting on ultraconserved elements and essential genes



Our data indicate that most ultraconserved regions are under relatively weak purifying selection. Despite the lack of fixed differences in these sequences between humans and rodents, the average level of selection on ultraconserved elements is less than that on essential genes (**Figure 1**). In addition, a small number of ultraconserved elements actually show more substitutions than expected, which is a hallmark of positive selection. The strength of selection that is associated with ultraconserved elements suggest that deleting these regions may have only subtle phenotypic consequences not easily detected in the laboratory.

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