Global co-evolution of human microRNAs and their target genes.

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Created 3/20/2014
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Abstract:

MicroRNAs (miRNAs) have presumably contributed to the emergence of the novel expression patterns, higher brain functions and skills underlying human evolution. However, it is incompletely understood how new miRNAs have evolved in the human lineage since their initial emergence predictably entailed deleterious consequences due to their powerful multi-target effects. Here, we report genetic variation and conservation parameters for miRNAs and their predicted targets in the genomes of 1092 humans and 58 additional organisms. We show that miRNAs were evolutionarily more conserved than their predicted binding sites, which were inversely subject to the accumulation of single nucleotide variations over short evolutionary timescales. Moreover, the predictably 'younger' human-specific miRNAs presented lower genetic variation than other miRNAs; their targets displayed higher genetic variation compared to other miRNA targets in diverse human populations; and neuronal miRNAs showed yet lower levels of genetic variation and were found to target more protein-coding genes than non-neuronal miRNAs. Furthermore, enrichment analysis indicated that targets of human-specific miRNAs primarily perform neuronal functions. Specifically, the genomic regions harboring the vertebrate-conserved neuronal miRNA-132 presented considerably higher conservation scores than those of its target genes throughout evolution, whereas both the recently evolved human miRNA-941 and its acquired targets showed relatively low conservation. Our findings demonstrate inversely correlated genetic variation around miRNAs and their targets, consistent with theories of co-evolution of these elements and the predicted role attributed to miRNAs in recent human evolution.

Journal:
Molecular biology and evolution

Date Published:
2014 Mar 4

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