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HARdly a monkey's uncle

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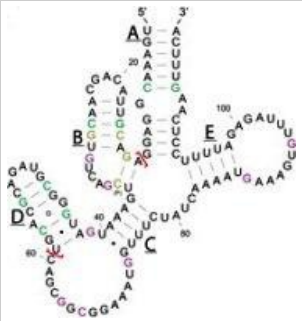
A non-coding, evolutionarily conserved gene expressed in cells that are important for human neuronal development shows accelerated change in humans relative to other species.

Which genes specify the differences between humans and chimpanzees? Pollard *et al.* report that the non-coding gene *HAR1F* has an increased rate of sequence changes in humans relative to other species in a recent issue of *Nature*.



The structure for HAR1F is unique and differs between humans (shown here) and other species in the region labeled D.

The authors searched for highly conserved genes and found 35,000 sequences in the chimpanzee with at least 96% identity to mouse and rat sequences. Forty-nine had increased rates of sequence substitutions in the human relative to other amniote species, which include mammals and reptiles, and were therefore named 'human accelerated regions' (HARs). Ninety-six percent of HARs were non-coding sequences and most were adjacent to genes commonly described by the Gene Ontology terms 'DNA binding' and 'transcriptional regulation.' Twenty-four percent of HARs were adjacent to genes involved in neuronal development.

HAR1 had the most accelerated changes in humans relative to other amniote species. Based on the low rate of non-adjacent sequence substitutions in HAR1 between most amniote species, the authors predicted 0.27, but found 18 substitutions in human relative to chimpanzee HAR1. In contrast, the authors found two substitutions in chimpanzee relative to chicken HAR1.

The 118-base pair HAR1 region is present in *HAR1F* and *HAR1R*, two overlapping, non-coding genes transcribed in opposite directions. The authors found a stable secondary structure for *HAR1F* that differed from any transcript previously reported. The structure for *HAR1F* also differed between humans and other amniotes. All 18 human-specific HAR1 substitutions change A or T to G or C, which stabilizes and strengthens RNA structure.

Cajal-Retzius neurons produce reelin and are important in cortical development. More reelin is produced in humans relative to other amniotes, and reelin is therefore thought to be important in the evolutionary development of the brain. *HAR1F* expression localized to Cajal-Retzius cells as early as the ninth gestational week in the human brain. By 17–24 gestational weeks, *HAR1F* no longer localized to Cajal-Retzius neurons, but was found in the developing cerebellar cortex, hippocampus, and hindbrain olivary complex. In the adult, *HAR1F* and *HAR1R* localized to cerebellum, hippocampus, thalamus and hypothalamus as well as to ovary and testes.

Expression of *HAR1R* in the developing brain was 50-fold lower

than expression of *HAR1F* and difficult to localize. Similarly, in the adult, *HAR1F* expression was greatly elevated relative to *HAR1R* in almost every tissue. In contrast, *HAR1F* and *HAR1R* were equally expressed in both the adult and the embryonic mouse brain, suggesting that the regulated expression of *HAR1F* may be important to its human-specific function.

It is tempting to speculate that *HAR1F*, like reelin, is important in the complex development of the human cortex, which is both larger and more specialized than the cortices of most other species.

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1. Pollard, K. S. *et al.* An RNA gene expressed during cortical development evolved rapidly in humans. *Nature* (2006). doi: 10.1038/nature05113 | Article |