

NEWS AND COMMENTARY

Human Evolution

Select your words carefully

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Heredity (2003) 90, 343–344. doi:10.1038/sj.hdy.6800267

Advanced speech and language skills are among the most striking traits that separate humans from all other forms of life. Now two groups, Enard *et al* (2002) and Zhang *et al* (2002), have taken a step forward towards identifying recent genetic changes that may provide the underpinnings of these uniquely human characteristics.

A major goal of human evolutionary biology is to identify the factors that contributed to the development of complex human traits. Both genetic and environmental factors influence our capacity for speech and language: one of the most striking human-specific traits. These new studies use statistical evolutionary genetics methods to identify one of the genes that may have played a key role in the evolution of the neural circuitry involved in human speech and language (Bishop, 2002; Fisher *et al*, 2003).

Both studies are based on the premise that an advantageous allele of a language-related gene will have fixed in the human lineage around the time of the emergence of three human language and left behind signatures of genetic selection in modern human DNA. The *FOXP2* gene is an attractive candidate gene to screen for selection since it is involved in a rare inherited human speech and language disorder (Fisher *et al*, 2003). For example, carriers of a missense mutation (Arg553His) have impairments in mouth control move-

ments required for speech, written language, and in the comprehension and production of grammar (Lai *et al*, 2001; Fisher *et al*, 2003).

Although its exact role in language development is unclear, it is known that *FOXP2* is a member of the forkhead/winged-helix (*FOX*) family of transcription factors that is expressed in fetal and adult human brain. Its expression pattern in mouse also implicates it in the development of lung, intestine, and cardiovascular tissue (Fisher *et al*, 2003).

FOXP2 amino-acid sequences are very conserved in mammals: it is among the 5% most-conserved proteins in a survey of 1880 pairs of human-rodent gene pairs (Enard *et al*, 2002). This makes it all the more significant that two of the three amino-acid differences between human and mice occurred in the human lineage after our separation from chimpanzees and bonobos, approximately 5–7 million years ago (Figure 1).

In both the new studies, statistical tests showed an increased rate of non-synonymous (amino-acid altering) to synonymous (silent) sequence changes only in the human lineages compared to other mammals. The two amino-acid differences between humans and mouse are closely spaced together (Thr303Asn and Asn325Ser) in exon 7. Zhang *et al* (2002) surveyed 20 mammalian *FOXP2* orthologs, finding that one of these changes (Asn325Ser) also occurs in

carnivore lineages. Thus, it is difficult to ascertain whether the Thr303Asn change alone was critical for selection or the presence of both the amino-acid changes were needed. Alternatively, both amino-acid differences may not significantly affect *FOXP2* function, and *cis*-acting elements in the promoter region or motifs in the 3'- and 5'-UTRs may be under selection.

One can test for selection in *FOXP2* in humans by comparing sequence variation in the gene between and within human and nonhuman primates (eg chimpanzees, bonobos, and gorillas). If an advantageous *FOXP2* allele became fixed in early human history, it should have caused a local loss of variation (selective sweep) limited to the selected site and its flanking region (Smith and Haigh, 1974). Selective sweeps in the *FOXP2* gene coinciding with the development of speech and language in modern humans in the past few hundred thousand years should be detectable because most existing human polymorphism arose between 0.5 and 2 million years ago and human population structure does not predate 200 000 years (Kreitman, 2000; Przeworski *et al*, 2000).

Both studies tested for selection by comparing levels of polymorphism near the *FOXP2* locus to those at other human loci. The introns flanking *FOXP2* exon 7 are less variable than most neutral noncoding regions examined in humans to date (Harris and Hey, 2001; Enard *et al*, 2002; Zhang *et al*, 2002) as expected if a selective sweep has occurred recently. Furthermore, much of the polymorphism that is present consists of a statistical overabundance of low-frequency alleles. The latter observation would also be expected, given that such alleles should have arisen since the fixation of the advantageous sequence change within or near-

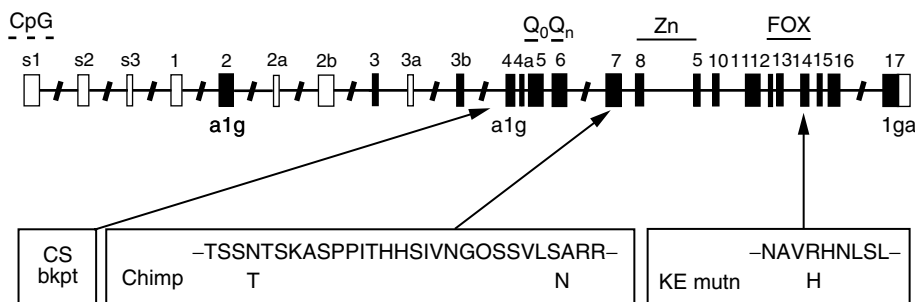


Figure 1 Schematic of the human *FOXP2* locus (reproduced from Fisher *et al* (2003)). White boxes represent noncoding exons, black boxes represent coding exons, and lines represent introns. The two human amino-acid substitutions relative to chimpanzees are marked along with the disease-causing mutation in the KE family. This figure is kindly provided by Dr Simon Fisher at the Wellcome Trust Centre for Human Genetics at Oxford University. With permission, from the Annual Review of Neuroscience, Volume 26 © 2003 by Annual Reviews www.annualreviews.org.

by the *FOXP2* locus. Since no other genes are located within 100 kb of this locus, both studies concluded that selection occurred due to the fixation of an advantageous *FOXP2* allele.

The analyses of polymorphism data indicate the selective sweep occurred in the last 100 000 (Zhang *et al.*, 2002) to 200 000 years (Enard *et al.*, 2002). The later dates are consistent with the emergence of modern humans and the development of the human language. However, given the limited resolving power of statistical tests involving cases of low genetic variation, these estimates must be regarded with caution (Harris and Hey, 2001).

Despite the importance of these studies, the real challenge is to establish a causal link between sequence changes at specific loci, like *FOXP2*, and the complex traits they are implicated in. Ethical considerations prohibit the genetic manipulation studies that would be the logical next step were we not dealing with humans and nonhuman

primates. However, there are several alternatives that could provide corroborating evidence of the importance of these genetic changes.

One possible strategy is to compare the relative activities of human and African great ape proteins *in vitro* and possibly *in vivo*, if nonthreatening to the health of the individual. Another fascinating option would be to engineer transgenic mouse models with human or African great ape copies of the gene of interest and then study the phenotype in detail. However, these experiments could be difficult to interpret given the different genetic and physiological background of rodents relative to higher primates.

Regardless of this, the studies by Enard *et al.* and Zhang *et al.* highlight the power that sequence comparisons among human and nonhuman primates have in identifying critical genomic regions that have been under selection in the human lineage. Altogether, the completed human genome sequence,

the impending release of draft sequence from the Chimpanzee Genome Project, (Olson and Varki, 2003) and the future rhesus monkey genome project will permit genomewide analysis of selection of human and nonhuman primates. These important studies should lead to fundamental insights into the nature of human genome evolution.

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