Losses of long-established genes contribute to human evolution

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While it is well understood that the evolution of new genes leads to adaptations that help species survive, gene loss may also afford a selective advantage. A group of scientists at the University of California, Santa Cruz led by biomolecular engineering professor David Haussler has investigated this less-studied idea, carrying out the first systematic computational analysis to identify long-established genes that have been lost across millions of years of evolution leading to the human species. Their findings appear in the December 14 issue of *PLoS Computational Biology*.

Haussler and five others in his group—postdoc Jingchun Zhu, graduate students Zack Sanborn and Craig Lowe, technical projects manager Mark Diekhans, and evolutionary biologist Tom Pringle—are co-authors on the paper.

“The idea that gene losses might contribute to adaptation has been kicked around, but not well studied,” said Zhu, who is first author of the paper. “We found three examples in the literature, and all of them could have medical implications.”

To find gene losses, Zhu employed a software program called TransMap that Diekhans had developed. The program compared the mouse and human genomes, searching for genes having changes significant enough to render them nonfunctional somewhere during the 75 million years since the divergence of the mouse and the human.

“This is the first study designed to search the entire genome for recent loss of genes that do not have any near-duplicate copies elsewhere in the genome,” said Haussler. “These are likely to be the more important gene losses.”

Genes can be lost in many ways. This study focused on losses caused by mutations that disrupt the open reading frame (ORF-disrupting mutations). These are either point mutations, where events such as the insertion or substitution of a DNA base alter the instructions delivered by the DNA, or changes that occur when a large portion of a gene is deleted altogether or moves to a new place on the genome.

“We used the dog genome as an out-group to filter out false positives,” Sanborn explained, because the dog diverged from our ancient common ancestor earlier than the mouse. “If a gene is still living in both dog and mouse but not in human, it was probably living in the common ancestor and then lost in the human lineage.”

Using this process, they identified 26 losses of long-established genes, including 16 that were not previously known.

The gene loss candidates found in this study do not represent a complete list of gene losses of long-established genes in the human lineage, because the analysis was designed to produce more false negatives than false positives.

Next they compared the identified genes in the complete genomes of the human, chimpanzee, rhesus monkey, mouse, rat, dog, and opossum to estimate the amount of time the gene was functional before it was lost. This refined the timing of the gene loss and also served as a benchmark for whether the gene in question was long-established, and therefore probably functional, or merely a loss of a redundant gene copy. Through this process, they found 6 genes that were lost only in the human.

One previously unknown loss, the gene for acyltransferase-3 (ACYL3), particularly caught their attention. “This is an ancient protein that exists throughout the whole tree of life,” said Zhu. Multiple copies of the ACYL3 gene are encoded in the fly and worm genomes. “In the mammalian clade there is only one copy left, and somewhere along primate evolution, that copy was lost.”

“In our analysis, we found that this gene contains a nonsense mutation in human and chimp, and it appears to still look functional in rhesus,” said Sanborn. Further, they found that the mutation is not present in the orangutan, so the gene is probably still functional in that species.

“On the evolutionary tree leading to human, on the branch between chimp and orangutan sits gorilla,” explained Sanborn. Knowing if the gene was still active in gorilla would narrow down the timing of the loss.

Sanborn took to the wet laboratory to sequence the corresponding region in a DNA sample from a gorilla. The gorilla DNA sequence showed the gene intact, without the mutation, so the loss likely occurred between the speciation of gorilla and chimpanzee.

“Acyltransferase-3 was not the only lost gene that doesn’t have any close functional homologues in the human genome. A highlight of our research was that we were able to find a list of these ‘orphan losses,’” said Zhu. “Some of them have been functional for more than 300 million years, and they were the last copies left in the human genome.” While the copies of these genes remaining in the human genome appear to be nonfunctional, functional copies of all of them exist in the mouse genome.

“These orphan genes may be interesting candidates for experimental biologists to explore,” said Zhu. “It would be interesting to find out what was the biological effect of these losses. Once their function is well

characterized in species that still have active copies, we could maybe speculate about their effects on human evolution."

Source: University of California - Santa Cruz