A dead gene comes back to life in humans

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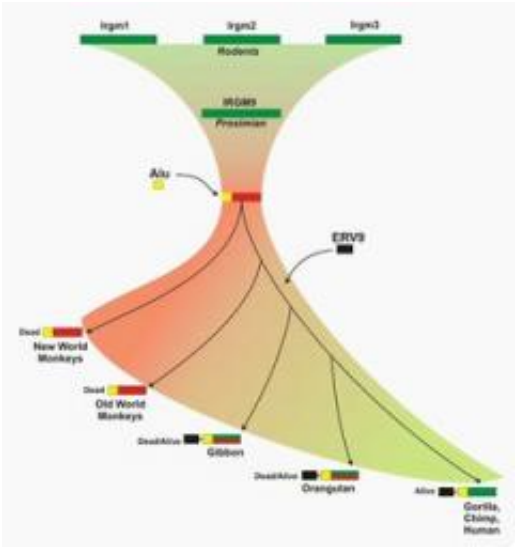

The figure summarizes the death and resurrection of Human IRGM gene. The functional gene (green) and the non-functional dead copy (red) are shown within the context of the generally accepted primate phylogeny. Genetic analyses suggest that that gene died approximately 50 million years ago as a result of genetic changes that disrupted its expression and function. In all Old World and New World monkeys, the gene is non-functional. However, in the ancestor of the apes and humans, mutations occurred to restore its function. This restoration of the protein's reading frame was gradual and some species such as gibbon and orangutan carry a living and dead copy.

(PhysOrg.com) -- Researchers have discovered that a long-defunct gene was resurrected during the course of human evolution. This is believed to be the first evidence of a doomed gene - infection-fighting human IRGM - making a comeback in the human/great ape lineage.

The study, led by Evan Eichler's genome sciences laboratory at the University of Washington and the Howard Hughes Institute, is published March 6 in the open access journal *PLoS Genetics*, in the article, "Death and Resurrection of the Human IRGM Gene." The first author of the study is Cemalettin Bekpen, a UW senior fellow in genome sciences.

The truncated IRGM gene is one of only two genes of its type remaining in humans. The genes are Immune-Related GTPases, a kind of gene that helps mammals resist germs like tuberculosis and salmonella that try to invade cells. Unlike humans, most other mammals have several genes of this type. Mice, for example, have 21 Immune-Related GTPases. Medical interest in this gene ignited recently, when scientists associated specific IRGM mutations with the risk of Crohn's disease, an inflammatory digestive disorder.

In this latest study, the researchers reconstructed the evolutionary history of the IRGM locus within primates. They found that most of the gene cluster was eliminated by going from multiple copies to a sole copy early in primate evolution, approximately 50 million years ago. Comparisons of Old World and New World monkey species suggest that the remaining copy died in their common ancestor.

The gene remnant continued to be inherited through millions of years of evolution. Then, in the common ancestor of humans and great apes, something unexpected happened. Once again the gene could be read to produce proteins. Evidence suggests that this change coincided with a retrovirus insertion in the ancestral genome.

"The IRGM gene was dead and later resurrected through a complex series of structural events," Eichler said. "These findings tell us that we shouldn't count a gene out until it is completely deleted."

The structural analysis, he added, also suggests a remarkable functional

plasticity in genes that experience a variety of evolutionary pressures over time. Such malleability may be especially useful for genes that help in the fight against new or newly resistant infectious agents.

More information: Bekpen C, Marques-Bonet T, Alkan C, Antonacci F, Leogrande MB, et al. (2009) Death and Resurrection of the Human IRGM Gene. PLoS Genet 5(3): e1000403. doi:10.1371/journal.pgen.1000403, www.plosgenetics.org/article/i … journal.pgen.1000403

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