Human Diversity: Sequence and Functional Variation in APOBEC3 Genes

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G Brennan

Human APOBEC3 is a family of seven proteins that block replication of retroviruses and retrotransposons (mobile DNA elements in the genome) by mutating DNA during reverse transcription. Lentiviruses have evolved APOBEC3 antagonists to escape this restriction, and the conflict between APOBEC3 and these antagonists has driven rapid evolution of some APOBEC3 family members. At least one of the APOBEC3 genes, APOBEC3H, is polymorphic in human populations, and a large percentage of people encode alleles with poor antiviral activity. (OhAinle, et al., 2008). In a recent paper published in Virology, Drs. Nisha Duggal (Molecular and Cellular Biology Program, Division of Human Biology) and Michael Emerman (Divisions of Human Biology and Basic Sciences), with collaborators from the University of Washington, define the extent of APOBEC3 allelic diversity in the human population. “Many studies have identified genetic differences in humans; however, few studies have investigated the functional consequence of these mutations. Here, we identify mutations in innate immune genes and functionally test their impact on viral replication,” said Dr. Duggal.

To examine human APOBEC3 diversity, the authors evaluated 913 individuals of European, African, or Asian descent from the 1000 genome project (www.1000genomes.org). This dataset contained 21 total variants in the APOBEC3 locus with an allele frequency >1%; 12 had been previously identified, while nine variants were new. Moreover, the authors found that a deletion of ABOBEC3B, and single nucleotide variants (SNVs) in APOBEC3F and APOBEC3H were more common in individuals of European or Asian ancestry, while SNVs in APOBEC3A, APOBEC3C, APOBEC3D, and APOBEC3H are more frequent in individuals of African ancestry. These allelic differences suggest that demographic events or selection may have acted on the APOBEC3 locus in a population-specific manner, and therefore some or all of these variants may result in functional differences.

To define the functional impact of the newly identified APOBEC3 alleles, Duggal et al. measured the ability of different alleles to inhibit either retrotransposons or viruses. APOBEC3D activity was especially interesting to test because human APOBEC3D is not very active against lentiviruses such as HIV compared to the chimpanzee APOBEC3D protein. Thus, the authors wanted to know if human APOBEC3D variants existed with increased activity. However, they found that the two SNVs in APOBEC3D decreased this protein’s antiviral activity even more than the activity of the most

commonly encoded protein. On the other hand, the ability to restrict retrotransposons is more frequently conserved in human APOBEC3D alleles.

In order to determine if selective pressures have recently acted on the human APOBEC3D gene, the authors calculated the interspecies divergence (human-chimpanzee) and intraspecies nucleotide diversity for each human population. While the interspecies divergence was similar for each human population, APOBEC3D had significantly lower than expected intraspecies nucleotide diversity (HKA $\chi 2 = 4.31$, $p < 0.05$) in all three human populations. Moreover, APOBEC3D exons had lower nucleotide diversity than introns, indicative of purifying selection acting on the coding sequence of APOBEC3D, rather than a selective sweep fixing a single haplotype across the population. While APOBEC3D has been shown to evolve under positive selection during the human-chimpanzee divergence, these current data suggest that human APOBEC3D has been optimized for a specific cellular function and that continuous selective pressure is acting to conserve this gene. Because the authors demonstrate that APOBEC3D is under recent purifying selection in humans, they suggest that it has a critical cellular function, likely as a host-defense against genomic parasites such as the retrotransposons, while the chimpanzee version of this gene has gained a function to protect against viral infections.

Duggal NK, Fu W, Akey JM, Emerman M. 2013. Identification and antiviral activity of common polymorphisms in the APOBEC3 locus in human populations. Virology. Epub before print, doi: 10.1016/j.virol.2013.05.016.

See also: OhAinle M, Kerns JA, Li MM, Malik HS, Emerman M. 2008. Antiretroelement activity of APOBEC3H was lost twice in recent human evolution. Cell Host Microbe. 11;4(3):249-59.

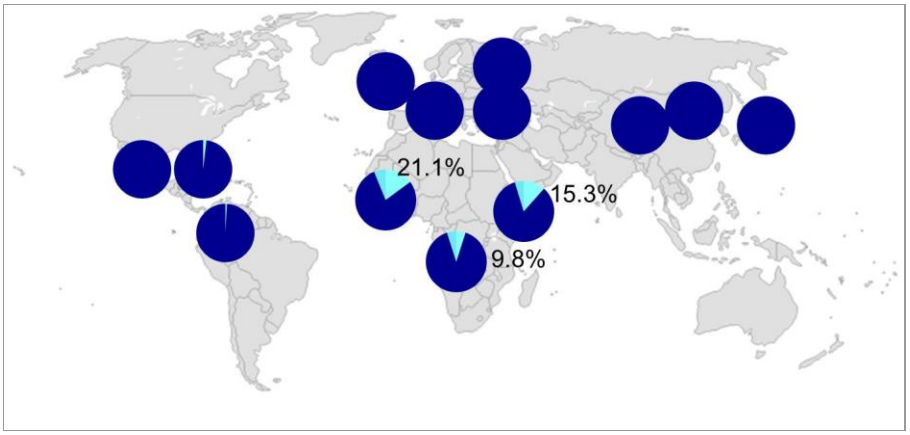

Image courtesy Dr. Nisha Duggal.

Worldwide distribution of wildtype (purple) or deleterious (blue) APOBEC3D alleles.