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Evolutionary insights from wild vervet genomes

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Abstract

A new study reports genome-wide variation in 163 vervet monkeys from across their taxonomic and geographic range. The analysis suggests a complex history of admixture and identifies signals of repeated evolutionary selection, some of which may be linked to response to SIV.

As our closest genetic relatives, non-human primates (NHPs) play a critical role in comparative evolutionary studies and as models for human disease. Over the past decade, a range of NHP reference genomes have been assembled, vastly increasing our understanding of primate genome dynamics and human-specific genomic features¹. The availability of reference genomes also opens the possibility for population resequencing studies, but so far few such studies of wild NHP populations have been conducted, especially outside the great apes. In this issue, Svardal and colleagues greatly expand the breadth of sequence data available for vervets², a diverse genus of Old World monkeys that are important biomedical research models. They analyze the genomes of 163 individuals sampled from 11 countries across their native range in Africa as well as the Caribbean, where vervets were introduced in the 17th and 18th centuries. This represents all vervet taxa and is one of the largest genomic samples of wild NHPs to date (Figure 1).

Resolving relationships

Vervets are generally divided into 5 or 6 taxa, but how these are related to each other, and whether they should be considered as species or subspecies has been a matter of debate. Relationships assessed by morphology, mtDNA and a small set of nuclear loci have come to different conclusions^{3,4}. Based on genotypes at 61 million SNPs, Svardal *et al.* use pairwise genetic distances and principal components analysis to offer the most thorough assessment of taxonomic relationships yet. On some aspects of the phylogeny, they find clarity: populations from the northern part of the vervets' range in Africa cluster into three groups corresponding to the morphologically distinct *sabaeus*, *aethiops* and *tantalus*. Strong support places the West African *sabaeus* as an outgroup to the other taxa, in contrast to some previous findings^{4,5}. They also find that the Caribbean populations are most closely related to the *sabaeus* group, corroborating historical records on their origin. Interestingly, genetic

evidence suggests independent founder events into the two Caribbean countries, Barbados and Saint Kitts and Nevis.

In other ways however, the taxonomic picture remains complicated. The taxa from the southern parts of the vervets' range in Africa (*cynosuros*, *hilgerti* and *pygerythrus*) show high levels of shared variation with correlated allele frequencies, and genetic distances do not always reflect morphological classification. More generally, multiple methods for detecting historical hybridization find evidence for gene flow. The average pairwise divergence between taxa is 0.4%, which is higher than across most taxa designated as subspecies, but lower than species-level comparisons. Although there is no evidence of recent interbreeding, all the vervet taxa show genomic signatures of historical admixture. This finding adds to a growing number of observations of gene flow between closely related primates⁶.

Living with SIV

Vervets are natural hosts of simian immunodeficiency viruses (SIVs), which are closely related to human immunodeficiency virus (HIV). Like other natural SIV hosts, vervets do not develop AIDS, and it has been hypothesized that host and virus are in a co-evolutionary arms race that has led to tolerance to infection. How might genes that have been under selection due to SIV be identified? Reasoning that the arms race scenario would lead to different variants favored in different populations, Svardal *et al.* chose to look for selection using XP-CLR, a test which compares populations to identify loci with unusually large allele frequency differences across linked variants, indicative of population-specific selection. They then combine XP-CLR results from pairwise taxon comparisons into a single score that is a measure of evidence for repeated population-specific selection. Indeed, the Gene Ontology (GO) categories that are enriched for high selections cores include several related with viral response.

To connect the selection scores more directly with response to SIV, Svardal *et al.* turn to a published dataset of gene expression measured throughout experimental SIV infection of vervets and rhesus macaques⁷. Rhesus macaques belong to another Old World monkey genus and are not natural SIV hosts; they do develop AIDS-like symptoms upon infection. Intriguingly, Svardal *et al.* find an enrichment of high selection scores in genes that change expression in vervets but not macaques. This suggests that selection has acted on genes that are involved in responding to SIV infection specifically in vervets. The selection scores are particularly enriched for genes that change expression at 6 or 115 days post-infection, pointing to particular time points that might be important in vervet-specific tolerance to SIV. This kind of integration between patterns of genomic variation in wild populations and lab-based phenotyping is a promising strategy towards deciphering the phenotypes underlying selection signals. The specific candidate genes and pathways can then be followed up back in the lab.

Both field and lab

The study by Svardal *et al.* greatly expands the genomic data available for wild vervets and provides new insights into their evolutionary histories². Another exciting development in vervet genomics is the application of high throughput sequencing to research animals, which will allow for a range of genotype-informed phenotypic studies under controlled conditions. In 2015, sequence data for 721 individuals from the Vervet Research Colony in the United States were reported⁸, and on page X of this issue, Jasinska *et al.* present a multi-tissue eQTL study in a subset of these sequenced vervets⁹. Although eQTL studies are now commonplace in humans, they have only recently begun to be applied to NHPs. As illustrated by the two studies in this issue, genomic analysis of NHPs offers a complementary approach to the work being carried out in humans to understand the evolution and genetic architecture of complex phenotypes. As accessibility of sequencing continues to increase, genotype-phenotype analyses in NHPs are likely to bring even more insights.

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Figure 1. Phylogeny and approximate numbers (order of magnitude) of published genome sequences for apes and common NHP biomedical research models. All listed species have at least a draft reference assembly. The vervet genomes, marked in red, are described in Svartal et al. 2. The left side of the figure is adapted from 1.