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Recent insights into the evolution of quantitative traits in non-human primates

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The past few years of genetic research on primate quantitative trait variation have been notable in the diversity of phenotypes explored, ranging from classic skeletal measurements to behavior, through to levels of gene expression, and with observations from both captive and wild populations. These studies demonstrate the importance of captive pedigreed breeding colonies, populations that can be matched to their wild counterparts to enable comparison of genetic architectures. Non-human primate genotype:phenotype maps are essential for placing human variation within an evolutionary framework as well as for gaining insight to human biology. While the demographic history of most primates has been fairly stable since the Late Pleistocene, humans experienced a dramatic population expansion that increased the number of rare, mildly deleterious mutations. These rare genetic variants complicate the genotype:phenotype association because they account for a disproportionate amount of the genetic variance and are harder to detect. The similar physiologies of our closest living relatives may prove to be key for overcoming the hurdles posed by humans' peculiar demographic explosion.

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Introduction

As we approach the centennial anniversary of the infinitesimal model of continuous variation [1], we pause to reflect on recent research that bears the fruit of 100 years of effort. Research on non-human primates represents a small slice of a much larger discipline, but it merits specific review because of its particular relevance to human biology and evolution.

There is a mystery that hinders the translation of discoveries in human genetics to clinical use — the case of the 'missing heritability' [2–4]. Heritability estimates from human twin and family studies often far exceed the genetic variance explained by known variants identified through genome wide association studies (GWAS) [2,5,6], not infrequently by as much as an order of magnitude [2]. Proposed solutions to the conundrum range from larger biomedical data sets [7], to analytical methods that include both additive and non-additive genetic effects [2], and models that allow for the effects of genes outside core regulatory pathways, adding the 'omnigenic' to the polygenic and oligogenic models of complex traits [8]. Epistatic and epigenetic factors may also explain some of the discrepancy [9]. However, it is quite likely that much of the missing heritability arises from the peculiar demographic history of our species [4].

Rapid population growth, as experienced by humans over the last 50 000 years, significantly increases the number of weakly deleterious mutations in a population because selection is less effective on weaker compared to more harmful mutations [4]. These rare alleles do not seem to add to the overall genetic variance for a particular phenotype, but they do contribute to a large proportion of it, and are much harder to detect through association studies [3,4]. Non-human primates — who have not experienced demographic expansions — have fewer low-frequency genetic variants compared to humans, which means that the influence of allelic variation on quantitative traits is easier to detect [4]. Combine this population history with the physiological similarity to humans, and our fellow primates may well help solve the missing heritability problem in the genotype:phenotype mapping of quantitative trait variation. In this brief review, I touch on some of the most recent advances in this field.

I will not distinguish between quantitative traits and complex phenotypes, but rather use the terms interchangeably as I focus on phenotypes that vary continuously within a population and are influenced by many genetic and environmental effects, and their interactions. Much attention is placed on elucidating the genetic architecture of these phenotypes because their variation can contribute to disease risk in humans and provides the substrate on which evolution occurs.

One of the most remarkable, recent advances in non-human primate quantitative genetics derives from technological and analytical innovation that enabled a dramatic

expansion of what we mean by the term 'phenotype,' as this is now approaching the totality of the expression of the genotype [10]. The last few years of research on non-human primates explored a wide range of phenotypes, from classic skeletal measurements to behavior, through to levels of gene expression, with observations from both captive and wild populations. With an eye towards highlighting this breadth, this review is organized by phenotype, starting with crania and brains, and then moving to teeth, behavior, growth rates, cardiovascular phenotypes, and ultimately expression quantitative trait loci (eQTLs). An overview of the non-human primates mentioned in this review, their phylogenetic relationships, and the phenotypes mentioned for each, is provided in Figure 1. At the end, I highlight two themes that pervade the research.

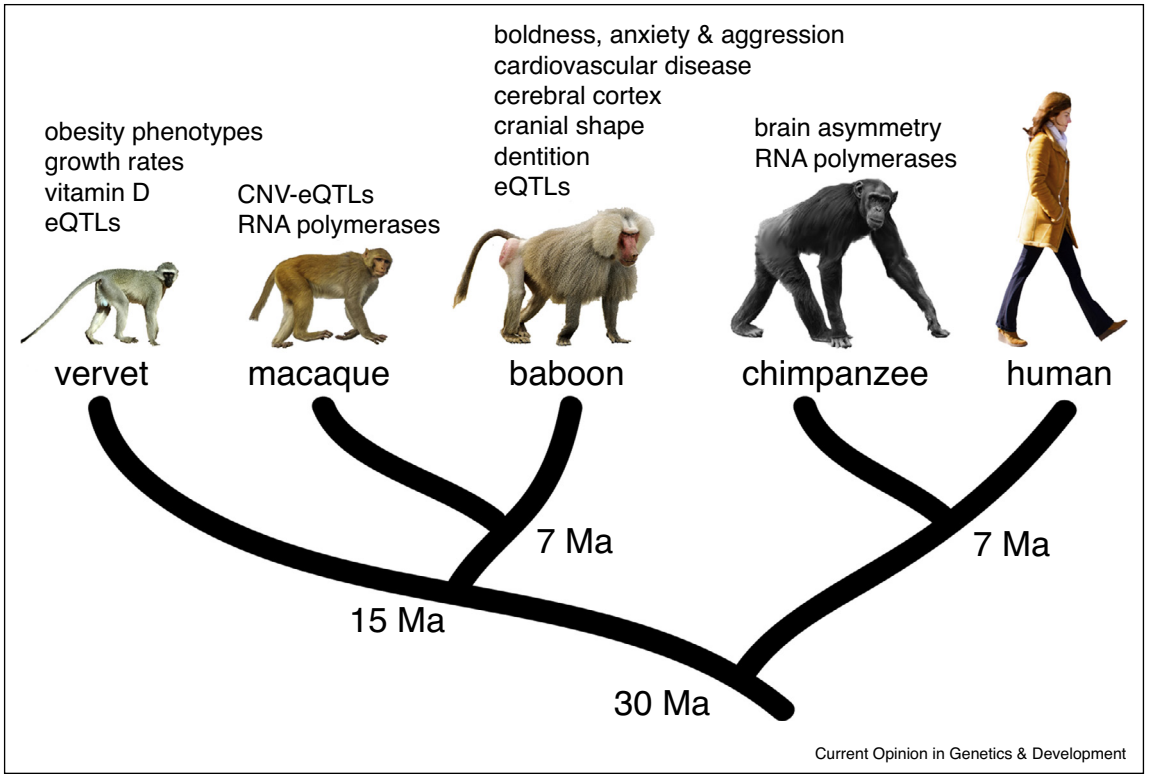
Crania and brains

Building on a decade of prior research on the cranial variation of baboons from the Southwest National Primate Research Center (SNPRC)'s captive pedigreed breeding colony [11–13], Joganic and colleagues [14••] recently estimated shared genetic effects across interlandmark distances from skulls. Baboons are characterized by their extended muzzles and significant sexual dimorphism. Consequently, the finding that body mass is genetically correlated with cranial shape indicates that selection on one phenotype would influence the other over evolutionary time, and may explain the convergence in craniofacial morphology observed in the two large-bodied papionins (baboons and mandrills) that have these extended muzzles [14••].

Variation on the inside of the skull was also studied. The endocranial surface from the same baboon skull collection [14••] enabled a study of variation in cerebral cortex folding [15]. The cerebral cortex has evolved in tandem with brain size in primate evolution, leading to a non-linear increase in cortical surface area (where neuronal cell bodies are located) [15]. Variation in cortical gyrification is heritable with modular structure, and is in part influenced by genetic effects that are independent of brain volume [15]. In interesting contrast, a study of chimpanzees and humans found that brain asymmetry is not heritable, a somewhat unexpected result given their strong behavioral lateralization (e.g. handedness) [16].

Baboons are famous for their natural hybridization zones that provide natural experiments through which to explore genetic architecture. Ackermann and colleagues [17,18] found that the F1 hybrid olive and yellow baboons have larger nasal cavities, an observation with interesting implications for the particularly larger nasal cavities observed in Neanderthals compared to modern humans [19].

Figure 1



Overview of genetic studies of quantitative traits in non-human primates highlighted in this review. The focal phenotypes are organized by taxa, and the taxa arranged according to phylogenetic relationship (last common ancestor estimates are from [35,36,50]).