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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.

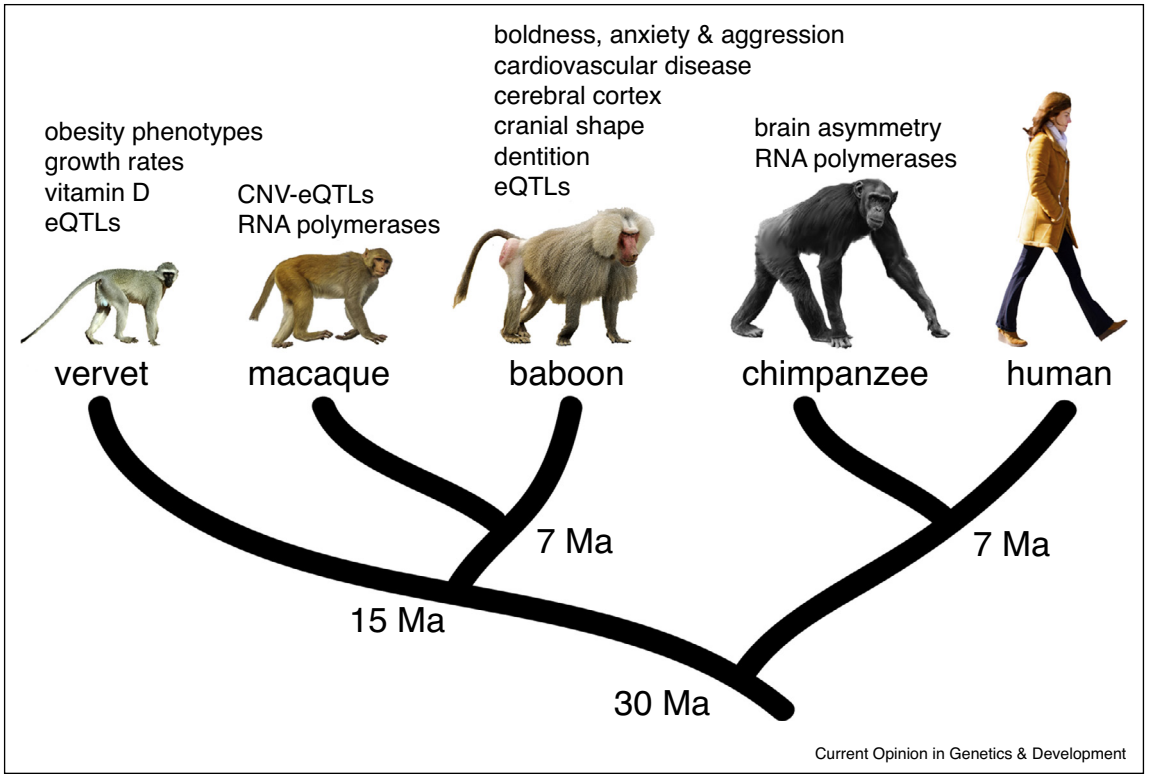
Crania and brains

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]).

Staying on the subject of fossils, a quantitative genetic approach was used to assess the evolutionary processes that may have led to the cranial variation observed across extant apes, using fossils to establish the rate of evolution [20]. There was evidence for strong stabilizing selection overall, but with two exceptions: selection for cranial vault expansion with the genus *Homo*, and selection for neurocranial reduction in the ancestor of the lesser apes. Another study focused on the evolution of the small brain and diminutive stature of *Homo floresiensis*, a hominid that existed on Flores Island in Indonesia between 10 000 and 60 000 years ago [21]. This analysis rejected neutral evolution and returned selection gradients that are not unlike those observed in natural populations today [21]. Perhaps most curious was the observation that the evolutionary trajectories for body and brain size differed, indicating that there may have been additional forces selecting for a particularly small cranial volume [21].

Teeth

Quantitative genetics and paleontology were also combined to elucidate the evolution of the primate dentition. As we learn more about the relationship between genotype and phenotype, it is imperative to consider trait correlations and the multivariate constraints they place on evolution [22]. My colleagues and I employed a series of bivariate analyses to estimate shared genetic effects across a wide range of dental measurements and body size in baboons. We found that teeth are not independent structures, but rather result from patterns of incomplete and complete pleiotropy [23,24]. We interpret variation in tooth size that results from completely overlapping genetic effects to likely be the output of a genetic patterning mechanism [25••]. Our goal was to devise simple phenotypic assessments that capture the output of these patterning mechanisms. We essentialized variation in the primate postcanine dentition into two ratios that are independent of sex and body size, one ratio captures the size differences across molars, and the other captures the size difference between premolars and molars [25••]. We then assessed these ratios across extant Old World primates, finding that genera occupy distinct morphospaces defined by the two traits. Disparities between taxa arose rapidly in the Middle to Late Miocene, precisely when the Messinian event triggered a much drier regional climate [25••]. Fossil data reveal that papionins now occupy the morphospace previously held by Miocene apes, having either displaced the apes or moved into their vacated niche. This study [25••], and those mentioned previously [20,21] demonstrate that quantitative genetic analyses can provide novel ways to assess morphological change through time in the fossil record, and represent a powerful tool for gaining insight into evolution [26].

Behavior

Behavior is also significantly influenced by genetic variation [27,28]. Accordingly, Johnson *et al.* [29] performed a multivariate factor analysis of individual response to novel objects and novel social partners within captive baboons. These factors provided a quantification of personality, the first two of which roughly characterized boldness and anxiety, and account for ~47% and ~19% of the variance respectively [29]. Both factors were significantly heritable and associated with cerebrospinal fluid neurochemistry and allelic variation in the gene *Synaptosomal associated protein 25* [29]. In contrast, a behavioral study of wild baboons returned a negative result. An association study of two polymorphisms in the serotonergic (5-HT) neurotransmitter with aggressive behavior across baboon species in Africa found no statistical significance despite a wide range of variation in aggressiveness [30••]. As hypotheses regarding human origins are starting to incorporate a finer understanding of the genetic influences on behavior [31], continued research on non-human primates will be essential.

Obesity and heart disease

As I mentioned in the introduction, while many quantitative traits are highly heritable, the loci identified through GWAS typically have low penetrance and, even cumulatively, still leave a substantial proportion of the genetic variance unexplained [2,7–9]. Another factor that might contribute to the 'missing heritability' may be the phenotypes explored, or rather, how we define them. As we saw with the dentition, quantitative genetic analyses can be used to reconceive how we assess phenotypic variation. Non-human primates provide a means through which to more comprehensively probe complex phenotypes, especially as it pertains to those implicated in complex diseases.

With this in mind, Schmitt and colleagues [32••] analyzed obesity-related phenotypes in a captive population of vervets and found two major childhood growth patterns, one of which is significantly more associated with adult obesity than is the other. These growth trajectories return heritability estimates in the range of those for body-mass-index [32••]. This finding echoes results from human research. But with the shorter generation times of vervets and the ability to homogenize their environment, we have an opportunity to investigate more intricate gene-by-age and gene-by-diet interactions. A harbinger of what is to come can be seen in a study of vitamin D in the same vervet colony. Chittoor *et al.* [33••] found a heritable component to serum levels of vitamin D with a significant genotype-by-diet-by-pregnancy status interaction, fascinating in light of the evidence of human adaptation to high latitude environments that combine high-fat diets with vitamin D deficiency [34].

The controlled environment of captive non-human primates, coupled with their physiological similarity to humans (given that we shared a last common ancestor ~30 Ma [35], compared to the ~70 Ma of mice and

humans [36]) also provided insight to the genetic architecture of cardiovascular disease. Following on a 7-week gene-by-diet study of SNPRC baboons that identified genetic influence on serum low density lipoprotein cholesterol [37], a subset was fed a high fat, high cholesterol diet for two years [38]. In this relatively short timeframe, the animals developed signs of cardiovascular disease risk similar to the early stages of atherosclerosis in humans [38].

Gene expression

Gene regulation clearly plays a fundamental role in the genetic architecture of complex traits [9]. Consequently, the study of eQTLs has been a fascinating addition to the phenotypic toolbox because they enable the identification of genetic variants that explain variation in gene expression [39]. Mapping of gene expression in a wild population of baboons yielded considerably more power to detect eQTLs compared to humans, likely a result of where baboons are located on the minor allele frequency spectrum — with more intermediate, and fewer low-frequency variants compared to humans [3]. Similar to what was found in the wild baboon population, eQTLs in captive vervets also have a higher signal-to-noise ratio than is observed in human studies despite a fairly small sample size [40••].

The baboon study also showed remarkable overlap with humans in the genes with eQTLs [3]. Similar to humans, *trans*-SNPs explain more (~24%) of the variation in expression than do *cis*-SNPs (~3%; *cis*- defined as being within 200 kb of a gene) [3]. The genes with eQTLs were also found to be less constrained at the sequence level compared to others, which may be evidence of conserved gene-specific robustness to genetic perturbation [3]. This result was prelude to the recent mapping of RNA polymerases in CD+4 T cells across humans, chimpanzees, and rhesus macaques [41••]. Danko and colleagues [41••] found that the genes that were regulated by larger numbers of enhancers are transcribed more similarly across taxa, regardless of the sequence variation of the individual enhancers. This result [41••], coupled with [3], suggests that there is pervasive compensation of enhancers for some genes, which would provide them with robustness to developmental perturbation.

Copy number variations (CNVs) were also associated with eQTLs across natural populations of the same macaque species in Southeast Asia [42••]. Results suggest that eQTL-CNVs may have more tissue-specific regulatory regions or enhancer elements, whereas eQTL-SNPs appear to be more general and tissue-independent regulatory elements [42••].

Over the next few years of research in non-human primate quantitative trait evolution we will likely also see exploration of epigenomic variation, as research in other organisms has already revealed it to be another heritable quantitative trait [43].

Conclusion

There are two themes present through all of the phenotypes discussed. First, we see that captive pedigreed breeding colonies are essential to the research [44,45]. For example, the baboons at SNPRC [11,12,13,14••,15,17,18,19,23,25••,29,37,38,44,46] and the animals at the Vervet Research Center [32••,33••,40••] were the foundation for many of the studies cited here. Pedigree analyses of non-human primates will likely continue to increase in number as more colonies increase availability. For example, the macaque colony at the Caribbean Primate Research Center [47•] has a recently published population genetic and pedigree structure [48•] and will hopefully recover from Hurricane Maria fully and quickly.

We also see that complex traits are, in some ways, becoming less complex thanks to research on non-human primate populations. There are two reasons for this. First, these populations enable the investigation of longitudinal and more nuanced phenotypes, and provide captive and wild settings in which to disentangle genetic, environment, sex, reproductive status, and age effects. This comparison between captive and wild populations may also prove essential to reconciling the incongruent strength of selection observed in natural versus controlled settings (reviewed in [49]). Second, the dramatic population expansion that characterizes human evolution since the Late Pleistocene compromises our ability to elucidate the genetic architecture of human complex traits [3,4]. Given the physiological similarities across primates, the demographic histories of non-human primates offer important opportunities to overcome the hurdles posed by our own species' dramatic reproductive success.

Conflict of interest statement

Nothing declared.

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