

Functional genomic insights into the environmental determinants of mammalian fitness

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Both the social and physical environment shape health, reproduction, and survival across many species, and identifying how these effects manifest at the molecular level has long been a priority in medicine and evolutionary biology. The recent rise of functional genomics has enabled researchers to gain new insights into how environmental inputs shape variation in gene regulation, and consequently, downstream organism-level traits. Here, we discuss recent work on this topic, as well as key knowledge gaps. Research in this area spans a wide range of taxa, but we focus our review on mammalian species because of their close evolutionary proximity to humans and because of their relevance for understanding human health. Improving our understanding of how the environment and the genome are connected promises to shed new light on the mechanisms underlying environmentally-induced disease in humans, as well as the evolution of environmental sensitivity more generally.

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Introduction

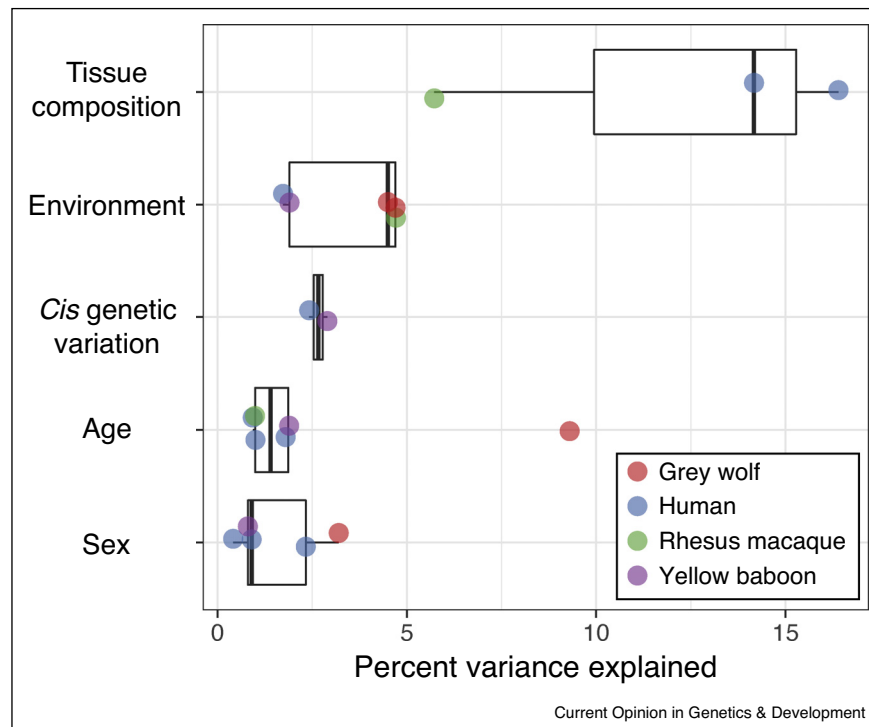
For decades, evolutionary biologists and medical scientists have asked how environmental variation shapes health, reproduction, and survival. Researchers have long appreciated that the physical environment (e.g., diet,

weather conditions, or pathogen exposure) has dramatic effects on fitness in mammalian species. For example, limited resource availability, both during development and later in life, predicts reduced fertility and mortality in humans [1,2] and in several wild mammal populations [3–6]. More recently, it has become clear that social components of the environment can also shape trait variation in ways that are equally profound. In social species, an individual's position in its social hierarchy (i.e., social status), as well as the degree to which the individual interacts with others (i.e., social connectedness), can predict disease risk and mortality [7–9]. Arguably, the strongest evidence for such social environmental effects comes from our own species [7,8].

Despite widespread and compelling evidence that environmental challenges affect fitness, we know relatively little about the molecular mechanisms that mediate these relationships, especially at the genome scale. Foundational work in molecular biology, genetics, and neuroscience has identified key molecules and candidate genes involved in sensing and responding to specific environmental inputs [10–12]. However, as new genomic methods have emerged over the last decade, the picture of how environmental variation affects our genomes has widened in scope. Specifically, using functional genomic tools, researchers have started to discover that environmental effects on organism-level traits are often mediated through changes in the way large, coordinated sets of genes are expressed, with environmental effects rivaling other well-known predictors of gene expression variation (e.g., demographic or genetic effects; [Figure 1](#)).

Here, we highlight recent research on how environmental signals affect genome-wide gene regulation, with a focus on select environmental effects that are well-linked to fitness variation and for which functional genomics has begun to provide new mechanistic insight. These examples are not meant as an exhaustive review (for other great reviews of this topic, see: [13–15]), but are instead meant to demonstrate the utility of functional genomics approaches for understanding how environmental variation 'gets under the skin' to affect health and survival. In discussing this work, we emphasize recent findings from humans as well as captive and laboratory mammalian models; however, we also identify gaps in our knowledge that could be better addressed using a more diverse set of non-model mammalian systems. Finally, we discuss new ways that functional genomics can be leveraged to understand connections between the environment and fitness,

Figure 1



The strength of environmental effects on gene regulation is comparable to other well-known predictors of gene regulatory variation. Using data from several published studies [36*,63,81–83], we estimated the mean percent variance in genome-wide gene expression levels explained (PVE) by tissue composition, demographic effects (age and sex), local genetic variation, and a range of social and physical environmental inputs (grey wolf = mangle and social status; rhesus macaque = social status; yellow baboon = maternal social connectedness; human = smoking). All studies were conducted in blood-derived samples, and mean PVE was taken from the text, supplementary information, or calculated using publicly available effect size estimates and data files. We note that PVE estimates are strongly influenced by the covariates included in models to detect environmental effects, and by the amount of variation in the environmental variable itself. However, across studies it is clear that environmental effects rival or exceed other widely accepted drivers of gene regulatory variation.

beyond study designs that correlate environmental variation with gene regulatory phenotypes (Box 1). Identifying the mechanistic path from environmental variation to fitness-related traits is important for treating and preventing environmentally-induced disease, and from an evolutionary perspective, for understanding how and when organisms evolve to sense and respond to their surroundings.

Environmental effects on genome-wide gene regulation

Mammals are able to dynamically respond to changes in their environment by tuning the expression levels of their genes. This ability relies on a diverse set of gene regulatory mechanisms, of which DNA methylation, chromatin accessibility, and histone modifications are the best studied to date. In particular, DNA methylation has received the most attention as a potential molecular mediator of environmental effects on gene expression levels, because of its demonstrated environmental sensitivity as well as the stability of environmentally-induced methylation changes [11,12]. Below, we highlight recent examples

of both physical and social environmental components that we have come to recently understand through studies of genome-wide gene expression, as well as the mechanisms that regulate gene expression.

Physical environmental effects on gene regulation

Variation in the physical environment—including what an animal eats, the weather it experiences, and the pathogens it encounters—is intricately connected to physiological change. In mammals, for example, seasonal changes in weather and resource availability can affect reproductive patterns [16], hormone levels [17], and disease risk [18]. It is becoming increasingly clear that these organism-level responses are implemented and maintained at the level of gene regulation. One recent study estimated that at least one quarter of the genes expressed in human blood varied in expression levels across seasons [19]. For instance, winter was associated with heightened expression of proinflammatory genes, which may contribute to higher rates of autoimmune and cardiovascular disease during these months. Interestingly, seasonal expression patterns observed in Europeans were

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