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Functional genomic insights into the environmental determinants of mammalian fitness

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Abstract

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.

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

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Conflict of Interest

The authors declare no conflict of interest.

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 [10,11].

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 [12–14]. 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: [15–17]), 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, 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 [13,14]. 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 [18], hormone levels [19], and disease risk [20]. 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 [21]. 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 reversed in samples collected from Australians, where the seasons are the opposite of the Northern Hemisphere [21]. Other mammals are less well-studied with respect to seasonal effects on gene regulation, although seasonal expression variation has been documented in the snowshoe hare [22] and some hibernators, including the dwarf lemur [23], and European [24] and Siberian hamsters [25].

Food resource availability, which need not covary with season, also leads to changes in metabolism, life history, and longevity in a range of organisms [1–6]. One of the most dramatic effects is associated not with *what* you eat, but *how much* you eat. A 10-40% reduction in caloric intake can lead to a 4-45% increase in lifespan in mammalian species ranging from rodents [26] to rhesus macaques [27]. These dramatic shifts in survival are also reflected in the epigenome of calorically restricted animals: calorically restricted mice and macaques exhibit DNA methylation profiles that mimic those of younger animals [28]. These observations highlight one potential mechanism, delayed epigenetic aging [29], through which caloric restriction may lead to a longer, healthier life. It is important to note, however, that the effects of caloric restriction are not always beneficial. For example, work on the Dutch Hunger Winter, a severe wartime famine, has linked extreme maternal caloric restriction (400-800 calories/day) with an increased risk of insulin resistance, obesity, and cardiovascular disease in offspring conceived during famine [30]. These health consequences are thought to be mediated by changes in DNA methylation that occur near growth and metabolism-related genes in offspring in response to famine [31,32], though the evidence for causal links between *in utero* caloric restriction, DNA methylation, and metabolic disease has been called into question [33].

In addition to the number of calories consumed, the nutritional content of food resources can alter gene regulation. For example, mice fed a ketogenic diet (characterized by low carbohydrate, moderate protein, and high fat intake) exhibited decreased expression of genes involved in aging-related biological pathways, including insulin signaling and TOR (target of rapamycin) activation; these effects persisted into old age, which may mechanistically explain the link between a ketogenic diet and decreased mortality, improved cognition, and better memory in aging animals [34].

Social environmental effects on gene regulation

For social animals, interactions with conspecifics are one of the most salient components of the environment [35]. In these species, recent evidence points to the importance of gene regulation for translating social environmental variation into variation in reproduction, health, and survival. For instance, social status has been linked to changes in gene expression in species ranging from mice to macaques to humans [36–39]. Specifically, these studies have found evidence that the chronic stress of low social status leads to an increase in the expression of proinflammatory genes both in circulating immune cells [16,38] as well as in brain regions important for memory and cognition [40,41]. In one extreme example of social subordination, the reproductive suppression of subordinate, “non-breeder” naked mole rats is apparent at the level of gene expression in reproductive organs [42]. Subordinate female naked mole rats also exhibit different gene expression profiles in the brain — particularly at genes involved in dopamine metabolism, which is implicated in a range of functions from sexual arousal to aggression to cognition [42].

The effect of the social environment is not limited to social standing. The quality and quantity of social relationships has been shown to alter gene expression as well. For example, in humans, loneliness is associated with increased expression of proinflammatory genes in peripheral blood [16,43] and the brain [44]. Further, a study that experimentally manipulated social status in rhesus macaques found that variation in affiliative relationships partially accounted for the effect of social status on gene expression variation at one third of status-associated genes [38]. Because the gene regulatory effects of social adversity (both low social status and social isolation) are so common across species, and are often concentrated in proinflammatory or innate immune genes, this signature is sometimes called the ‘conserved transcriptional response to adversity’ (CTRA; [45]).

Open questions about environmental effects on gene regulation

While progress has been made toward understanding how gene expression connects environmental insults with fitness-related traits, several key gaps emerge from the summaries provided above. First, it is relatively rare for researchers to investigate both environmentally responsive gene expression patterns and their underlying gene regulatory mechanisms in a single system. Studies that have done so have almost universally focused on DNA methylation [31,46–49] (but see [50] for a study showing effects of social status on chromatin accessibility and gene expression). However, there is no reason to think other regulatory mechanisms are not equally environmentally responsive. For example, human dendritic cells can remodel their transcription factor binding, chromatin, histone, and DNA methylation profiles over the course of a few hours in response to bacterial infection [51,52]. To date, however, the degree to which these same mechanisms also respond dynamically to social and other physical environmental stimuli remains largely unknown, as does the degree to which environmentally-associated variation in gene regulatory mechanisms are causal to changes in gene expression and organisms-level phenotypes [33]. Studies that utilize time course experiments [52], Mendelian Randomization or other causal inference tools [33,53,54], and manipulation of epigenetic marks [55,56] promise to help further our

understanding of the causal chain linking variation in the environment with variation in gene regulatory mechanisms, gene expression, and ultimately fitness.

A second open question is to what degree are the same environmentally-responsive genes affected across similar contexts, tissues, or species? While some progress has been made in identifying proinflammatory and innate immune genes as common targets of social adversity in mammalian blood [45], this work is so far limited to captive animals and humans, and more work is needed to understand the generality of this framework. It is possible that there is a conserved molecular "toolkit" that underlies shared gene regulatory responses to environmental variation [57]. However, because of the limited taxonomic diversity of gene regulatory work, little progress has been made in understanding how or why a given set of genes evolve to sense and respond to environmental variation.

Finally, we do not yet understand when in the lifespan animals are most sensitive to social or physical environmental inputs. Mounting evidence suggests that some environmental stressors encountered early in life may permanently alter gene regulatory programs, and thus go on to shape physiology and health across the lifecourse. For example, a groundbreaking study in laboratory mice found that maternal diet during pregnancy influenced offspring methylation near the *agouti* gene, which in turn affected *agouti* gene expression, fur color, body mass, and susceptibility to diabetes later in life [12,58]. More recently, these findings have been extended to a diverse set of early life environmental contexts [31,47,59,60]. However, evidence that gene expression programs dynamically react to the current environment has also been growing in parallel [38,61], leaving open the question of which environments, genes, and organisms are governed by 'early embedding' of environmental variation into the genome versus dynamic responses. Addressing this gap is essential for understanding when in the lifespan environmental improvements or interventions are likely to have the biggest impact.

Mammalian systems inform our understanding of evolution and human health

As models for human health, studies of mammals can help us to understand the most salient features of an individual's environment, including how they mechanistically alter health and survival. Remaining challenges include (i) understanding the gene regulatory mechanisms that causally link environmental effects to gene expression variation and, ultimately health and survival; (ii) identifying the specific genes that are most strongly affected by environmental challenges; and (iii) understanding how the answers to (i) and (ii) vary across the lifecourse. Addressing these challenges will require multiple approaches, including longitudinal, prospective work in humans as well as studies of animal models. While work in humans can struggle with retrospective reporting of environmental circumstances, as well as confounded relationships between key environmental components (e.g., social adversity can be associated with reduced access to healthcare and poor nutrition [62]). These issues can be circumvented in animal models. Further, in captive situations, experimental manipulations can identify causal links between the environment and gene regulation — experiments that would be difficult or impossible to conduct in humans.

However, it is important to point out that certain questions will be difficult to answer in the handful of popular mammalian models researchers have focused on to date, namely laboratory rodents and captive primates.Though powerful, these systems (i) do not capture the full range of physical and social environmental variation that exists in nature, (ii) typically focus on isolating the effects of one environmental variable, and may therefore miss key interactions among different environmental components [38,63,64], and (iii) are not sufficient to support comparative work on the evolution of environmentally sensitive gene regulatory programs. Thus, without expanding genomic work to a larger set of environments and species (including wild populations), we will remain unable to understand how genomic plasticity evolves in response to the complex environmental variation observed in nature. While a few steps have been taken in this direction (e.g., [23,46,54,65]), more needs to be done. Fortunately, there is a rich history of studying environmental effects in natural systems, and modern genomic tools are rapidly becoming more streamlined and optimized for samples collected in the wild or in species without existing genomic tools [66,67]. Thus, non-model, natural systems appear ripe for molecular analysis of well-understood environment-fitness relationships.

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Emerging questions about the relationship between the environment and fitness that can be answered with genomic tools

As genomic work has progressed, it has become clear that the environment and the genome are intertwined in diverse and important ways, beyond 'simple' main effects of environmental variation on gene regulation. Here, we discuss three research areas that explore new types of environment-genome connections – the microbiome, indirect genetic effects, and gene × environment interactions – and address how functional genomic tools can help unravel these emerging links.

The microbiome.

The microbiome (the collection of microbes that live in and on an organism) sits at the interface of the outside environment and internal physiology. Variation in both the physical [68,69] and social environment [70–72] can shape the bacterial communities that exist within an individual, with consequences for physiology, health, and behavior [73,74]. The environmental dependence of the microbiome is thus particularly clear and exciting, and researchers are increasingly turning to functional genomic datasets to understand how the two are mechanistically linked. In particular, researchers are beginning to sequence bacterial RNA (an approach known as 'metatranscriptomics') to gain insight into the genes that are actively expressed by the microbes in these complex communities [75]. This approach thus allows researchers to capture information about environmental effects on bacterial function and activity, rather than simple presence/absence.

Indirect genetic effects.

The genotypes of those around you can also influence your behavior and your genome — a concept called indirect genetic effects (IGEs; [76]). For example, using genotype data from over 20,000 parent-offspring pairs, Kong et al. found that genetic variants that exist in parents, but are not transmitted to their children, had an effect on their children's educational attainment that was ~30% stronger than direct genetic effects [77]. Thus, the parental environment is both profoundly important for educational attainment and affected by parental genotypes — even those genetic variants that are not directly passed on to the offspring. Work in laboratory mice has also found that the impact of IGEs on physiology, behavior, and gene expression can rival or exceed that of direct genetic effects [78,79]. Further, one recent study attempted to map specific loci that affect phenotypic variation in social partners, in an effort to understand the genetic architecture of IGEs ([78] though larger samples will likely be needed to make progress in this area). Moving forward, it will be particularly interesting to expand this work beyond humans and model laboratory systems, and to use functional genomics to trace the mechanistic pathway from genetic variants that exist in social partners to their effects on focal individuals.

Genotype × environment interactions.

There is substantial heterogeneity in how individuals respond to the same environmental challenges. One explanation for this observation is that genetic variation controls each

individual's response. This phenomenon, known as a genotype × environment (G × E) interaction, has captured the attention of evolutionary and health researchers alike, as it has the potential to explain why particular individuals are especially vulnerable (or resilient) to environmental challenges. One effective tool for mapping G × E effects on gene expression is to expose cells from a given individual to contrasting environmental conditions *in vitro*, and identifying genetic variants that affect gene expression in one condition but not the other. Using this paradigm, researchers have uncovered substantial genetic variation for the way humans respond to bacterial and viral infections, stress hormones, and environmental toxins [80–82]. Importantly, this work has allowed us to begin to understand why responses vary among individuals (e.g., because of ancestry), which genetic variants account for such differences, and how evolutionary processes (e.g., selection or introgression) have established these variants in human populations [17]. As culturing cells from non-model systems is becoming increasingly achievable, it will be important to expand GxE work beyond humans (and eventually, beyond the laboratory). Doing so will allow us to understand whether genetic variation for environmental sensitivity is prevalent across species and environmental contexts; this information will allow us to ask whether the evolutionary processes maintaining genetic variation for plasticity in humans [17] extends to other mammalian and natural systems.

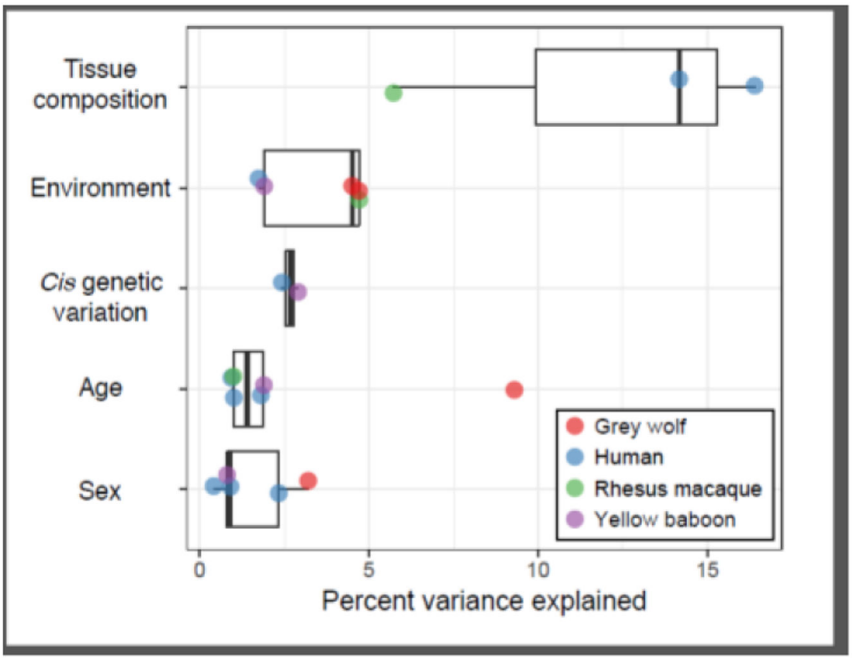

Figure 1. The strength of environmental effects on gene regulation is comparable to other well-known predictors of gene regulatory variation.

Using data from several published studies [38,65,83–85], 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 = mange 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.