

G

Genetics of Social Behavior



Timothy A. Linksvayer
Department of Biology, University of
Pennsylvania, Philadelphia, PA, USA

What does the “genetic basis” or simply “genetics” of a trait mean? Two alternative definitions are commonly used and sometimes confounded: (1) The full set of genes and molecular pathways underlying the *expression* of a trait. (2) The set of variable DNA sequences in a population that contribute to trait *variation* in that population. In any population, only a subset of locations in the genome that can potentially influence a trait are variable and contribute to trait variation and trait evolution. For this reason, while molecular biologists traditionally focus on characterizing the molecular pathways underlying trait expression (definition 1), geneticists and evolutionary biologists traditionally focus on elucidating how genetic variation contributes to trait variation and trait evolution (definition 2).

Social behavior has long and commonly been regarded as being that part of the phenotype that is furthest away from DNA [20]. Indeed, theory and empirical studies indicate that both the molecular mechanisms underlying the expression of social behavior as well as the genetic variation underlying variation in social behavior are more complex than the corresponding genetic basis of traits that are not influenced by social interactions. Here the

theoretical reasons why behavioral traits, and social behaviors in particular, are expected to be particularly genetically complex are explained, and quantitative genetic, transcriptomic, and comparative genomic empirical studies of the genetic basis of social behavior are summarized.

The Genetic Basis of Behavior Is Likely Relatively Complex

When compared to many other types of traits (e. g., morphological or physiological traits), all behavioral traits may have added genetic complexity in terms of the numbers of genes and molecular pathways that influence them. Behavioral outcomes are influenced by an array of organismal processes and systems, including all aspects of organismal physiology and development, and involving many organismal systems, including endocrine, nervous, and immune systems. For example, all the molecular pathways that influence organismal metabolism are also likely to influence overall activity rate as well as specific behavioral outcomes. Overall, any gene that influences any organismal trait may be expected to influence behavioral traits to some degree as well, so that the majority of genes in the genome may be expected to influence the expression of behavior to some degree. Thus, the molecular mechanisms influencing behavior are expected to be very diverse and widespread. The relative contribution of genetic variation to

phenotypic variation for behavior (i.e., the heritability of behavior) is also likely different from that of other traits, because animal behavior is fundamentally responsive to immediate internal and external environmental conditions and in many organisms includes learned components. Indeed, estimates of heritability for behavioral traits across animals are typically lower than morphological or physiological traits.

The Genetic Basis of Social Behavior Is Especially Complex

By definition, social behavior involves interaction between two or more individuals. Behavior, as well as other traits, can be *influenced* by social interactions or *defined* by them. For example, an individual ant worker's foraging or exploratory behavior may be influenced by physical or chemical interactions with nestmates. Some other behaviors can only be defined in the context of social interactions, such as dominance interactions or collective behaviors, such as ► [colony-level defense](#) or nest construction that emerge from the collective activities of many individuals in the colony.

As a result of the dependence on social interactions, social traits are the property of the genomes of multiple interacting individuals. These complications are formally studied in the interacting phenotypes framework, where an individual's traits are *directly* affected by its own genotype and *indirectly* affected by the genotypes of social partners [13, 21]. While this approach is focused on characterizing the genetic contribution to trait variation and trait evolution (definition 2 of genetic basis), it is readily conceptually extended to also include the full set of molecular pathways underlying trait expression.

In social insect colonies, where multiple castes and age classes of individuals interact and influence colony-level functions, a complex network of genes existing in many interacting individuals can potentially influence the expression of traits. For example, the foraging behavior of an individual honey bee worker may depend on her own current nutritional and physiological state, which

is influenced by the pattern of expression of genes in many of her tissues (e.g., brain, gut, ovaries). In addition, the individual's foraging behavior is likely strongly influenced by the current nutritional state of nestmates and the colony as a whole, as well as by local interactions with other foragers (e.g., through physical interactions, the ► [waggle dance](#), etc.), and by ► [pheromones](#) produced by nestmate ► [brood](#), other workers, and the queen [12]. Importantly, all these features of the social environment experienced by the focal individual result from the collective traits and genes of nestmates.

As a result of the web of social interactions and social interdependency of individuals within social insect colonies, the molecular mechanisms underlying the expression of social behavior – and other traits – in social insect colonies are likely much more complex, involving genes and pathways distributed across multiple interacting individuals, when compared to the traits of solitary organisms that are at least less influenced by interactions with conspecifics [4, 13]. Furthermore, genetic variation in the genomes of both the individual expressing the trait and her/his social partners (i.e., through direct or indirect genetic effects, respectively) may contribute to trait variation for individual-level traits, as well as for colony-level traits. Thus, even though ► [social insect genomes](#) have a similar number of genes as the genomes of solitary insects, the genetic basis of many social insect traits is likely to be relatively more complex.

Progress Toward Characterizing the Genetic Basis of Social Insect Behavior

Given the daunting biological complexity of social insect colonies surveyed so far, it may not be surprising that researchers have typically used reductionist approaches that seek to control or ignore social complexity in order to study the genetic basis of individuals' social behavior. In particular, researchers seeking to elucidate the genetic basis of social insect traits have often turned to approaches developed for solitary organisms that do not explicitly consider the

genetic contributions of the social environment, and that only consider the direct links between individuals' traits and their own genes. That is, most social insect genetic research has not addressed the critical genetic contribution of the social environment.

Despite this, a major finding that has emerged from sociogenomic research over the past decade is that the patterns of gene expression that characterize the neurogenomic state of individuals (as well as patterns of social behavior and other social traits) critically depend on the details of the social environment, including the precise genotypes of nestmates and their traits, and the composition of the colony [5]. This result provides a nice validation of the biological reality of the colony's social complexity. The remaining paragraphs survey quantitative genetic, transcriptomic, comparative genomic, and population genomic research focused on elucidating the genetic basis of social insect traits, in particular social behavior.

For several decades honey bee researchers have used quantitative genetic approaches to characterize how the genotype of individual workers and the genetic composition of the colony influence honey bee foraging, defensive behavior, and hygienic behavior. This research includes artificial selection studies that show how social behavior is heritable and can rapidly evolve in response to selection, as well as a series of studies identifying variable regions of the genome (i.e., quantitative trait loci; QTL mapping) and candidate genes underlying this variation in social behavior [7, 8]. For example, these studies identify regions of the genome that differ between honey bee lineages with respect to colony-level aggression, degree of pollen hoarding, or expression of hygienic behavior. These studies have also found that the effect of an individual's genotype on its own behavior is often conditional on the genotypes of nestmates, and more generally the genetic composition of the colony.

Even though these studies have made progress in identifying candidate genes underlying variation in social behavior, the precise genetic details have remained largely elusive. However, this is not surprising: the precise genetic variants that cause variation in behavior in any animal species

have only been characterized in a handful of cases [3].

In the past two decades, social insect researchers, starting with honey bees, have used transcriptome sequencing technologies (e.g., RNA sequencing) to simultaneously quantify expression levels of all genes in the genome in order to gain insight into the molecular mechanisms associated with the expression of social insect division of labor [2, 19]. Comparing patterns of gene expression between two types of individuals (e.g., honey bee nurses versus foragers, or queens versus workers) identifies differentially expressed genes that are putatively related to functional differences underlying division of labor. Note that this approach focuses on elucidating the molecular mechanisms of trait expression (definition 1 of genetic basis) and does not by itself identify which locations in the genome are variable and can contribute to trait evolution.

That said, other studies have sought to make evolutionary inferences about the molecular mechanisms underlying social traits by comparing sets of differentially expressed genes across multiple species or lineages (e.g., between honey bees and ants) [1, 18]. Some transcriptomic and comparative transcriptomic studies have emphasized the importance of certain highly conserved functional classes of genes and molecular pathways (e.g., those with inferred functions relating to metabolism) and have found evidence for significant overlap of these pathways between distinct social lineages, while others have emphasized that novel genes that are not highly conserved may also play major roles in the genetic basis and evolution of social life, especially for novel communication functions [9].

More recently, studies have begun to compare the genomes of social insect species in order to make inferences about evolutionary changes in gene content and patterns of molecular evolution that have occurred in social insect lineages [10, 15]. These studies have emphasized changes in gene families with chemosensory functions, which may underlie the complex system of chemical communication found in insect societies. These studies have also identified rapidly

evolving genes that may be associated with the evolution of social adaptations.

One limitation of these studies is that so far they have been restricted to only a few species. Because each species and lineage has a large number of distinct genes scattered across the whole genome, only some of which are causally related to the phenotypic differences of interest (e.g., related to differences in social behavior), it is difficult to identify the genetic differences that matter. Population genomic studies have also made progress in identifying specific genes that show signatures of positive selection, or relaxed purifying selection, which may contribute to genetic changes underlying the evolution of social complexity [6, 17].

Genome-wide association studies (GWAS) have begun to identify variable regions of the genome that contribute to variation in social behavior among individuals and colonies in natural populations [11]. These approaches, together with traditional controlled crosses between lineages that differ for social traits of interest and subsequent QTL mapping, can also be used in concert with transcriptome profiling (i.e., expression QTL or eQTL mapping) to elucidate how DNA sequence variation affects patterns of gene expression and subsequently contributes to variation in social behavior and other traits.

Finally, with both traditional and newly developed genetic approaches, researchers have begun to experimentally manipulate candidate genes to confirm their effects on social behavior [14, 16]. Because the genetic bases of social behavior are apparently very complex, these experimental studies, which are typically limited to one or a few genes that are a priori of interest, will need to be coupled with the unbiased approaches described above in order to gain a full understanding of the genetic basis and evolution of social behavior.

References

- Berens, A. J., Hunt, J. H., & Toth, A. L. (2015). Comparative transcriptomics of convergent evolution: Different genes but conserved pathways underlie caste phenotypes across lineages of eusocial insects. *Molecular Biology and Evolution*, *32*, 690–703.
- Chandrasekaran, S., Ament, S. A., Eddy, J. A., Rodriguez-Zas, S. L., Schatz, B. R., Price, N. D., & Robinson, G. E. (2011). Behavior-specific changes in transcriptional modules lead to distinct and predictable neurogenomic states. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 18020–18025.
- Ding, Y., Berrocal, A., Morita, T., Longden, K. D., & Stern, D. L. (2016). Natural courtship song variation caused by an intronic retroelement in an ion channel gene. *Nature*, *536*, 329–332.
- Friedman, D. A., Johnson, B. R., & Linksvayer, T. (2019). Distributed physiology and the molecular basis of social life in eusocial insects. *Hormones and Behavior*, *122*. <https://doi.org/10.1016/j.yhbeh.2020.104757>.
- Grozinger, C. M., Sharabash, N. M., Whitfield, C. W., & Robinson, G. E. (2003). Pheromone-mediated gene expression in the honey bee brain. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(Suppl 2), 14519–14525.
- Harpur, B. A., Kent, C. F., Molodtsova, D., Lebon, J. M. D., Alqarni, A. S., Owayss, A. A., & Zayed, A. (2014). Population genomics of the honey bee reveals strong signatures of positive selection on worker traits. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 2614–2619.
- Hunt, G. J., Page, R. E., Jr., Fondrk, M. K., & Dullum, C. J. (1995). Major quantitative trait loci affecting honey bee foraging behavior. *Genetics*, *141*, 1537–1545.
- Hunt, G. J., Amdam, G. V., Schlipalius, D., Emore, C., Sardesai, N., Williams, C. E., Rueppell, O., Guzmán-Novoa, E., Arechavala-Velasco, M., Chandra, S., Fondrk, M. K., Beye, M., & Page, R. E., Jr. (2007). Behavioral genomics of honeybee foraging and nest defense. *Naturwissenschaften*, *94*, 247–267.
- Jasper, W. C., Linksvayer, T. A., Atallah, J., Friedman, D., Chiu, J. C., & Johnson, B. R. (2016). Large-scale coding sequence change underlies the evolution of postdevelopmental novelty in honey bees. *Molecular Biology and Evolution*, *33*, 1379.
- Kapheim, K. M., Pan, H., Li, C., Salzberg, S. L., Puiu, D., Magoc, T., Robertson, H. M., Hudson, M. E., Venkat, A., Fischman, B. J., Hernandez, A., Yandell, M., Ence, D., Holt, C., Yocum, G. D., Kemp, W. P., Bosch, J., Waterhouse, R. M., Zdobnov, E. M., Stolle, E., Kraus, F. B., Helbing, S., Moritz, R. F. A., Glastad, K. M., Hunt, B. G., Goodisman, M. A. D., Hauser, F., Grimmelikhuijzen, C. J. P., Pinheiro, D. G., Nunes, F. M. F., Soares, M. P. M., Tanaka, É. D., Simões, Z. L. P., Hartfelder, K., Evans, J. D., Barribeau, S. M., Johnson, R. M., Massey, J. H., Southey, B. R., Hasselmann, M., Hamacher, D., Biewer, M., Kent, C. F., Zayed, A., Blatti, C., III, Sinha, S., Johnston, J. S., Hanrahan, S. J., Kocher, S. D., Wang, J., Robinson, G. E., & Zhang, G. (2015). Social evolution. Genomic

- signatures of evolutionary transitions from solitary to group living. *Science*, *348*, 1139–1143.
11. Kocher, S. D., Mallarino, R., Rubin, B. E. R., Yu, D. W., Hoekstra, H. E., & Pierce, N. E. (2018). The genetic basis of a social polymorphism in halictid bees. *Nature Communications*, *9*, 4338.
 12. Lemanski, N. J., Cook, C. N., Smith, B. H., & Pinter-Wollman, N. (2019). A multiscale review of behavioral variation in collective foraging behavior in honey bees. *Insects*, *10*. <https://doi.org/10.3390/insects10110370>.
 13. Linksvayer, T. A. (2015). Chapter 8 – The molecular and evolutionary genetic implications of being truly social for the social insects. In A. Zayed & C. F. Kent (Eds.), *Advances in insect physiology* (pp. 271–292). London: Academic Press.
 14. Roth, A., Vleurinck, C., Netschitailo, O., Bauer, V., Otte, M., Kaftanoglu, O., Page, R. E., & Beye, M. (2019). A genetic switch for worker nutrition-mediated traits in honeybees. *PLoS Biology*, *17*, e3000171.
 15. Simola, D. F., Wissler, L., Donahue, G., Waterhouse, R. M., Helmkampf, M., Roux, J., Nygaard, S., Glastad, K. M., Hagen, D. E., Viljakainen, L., Reese, J. T., Hunt, B. G., Graur, D., Elhaik, E., Kriventseva, E. V., Wen, J., Parker, B. J., Cash, E., Privman, E., Childers, C. P., Muñoz-Torres, M. C., Boomsma, J. J., Bornberg-Bauer, E., Currie, C. R., Elsie, C. G., Suen, G., Goodisman, M. A. D., Keller, L., Liebig, J., Rawls, A., Reinberg, D., Smith, C. D., Smith, C. R., Tsutsui, N., Wurm, Y., Zdobnov, E. M., Berger, S. L., & Gadau, J. (2013). Social insect genomes exhibit dramatic evolution in gene composition and regulation while preserving regulatory features linked to sociality. *Genome Research*, *23*, 1235–1247.
 16. Trible, W., Olivos-Cisneros, L., McKenzie, S. K., Saragosti, J., Chang, N.-C., Matthews, B. J., Oxley, P. R., & Kronauer, D. J. C. (2017). Orco mutagenesis causes loss of antennal lobe glomeruli and impaired social behavior in ants. *Cell*, *170*, 727–735.e10.
 17. Warner, M. R., Mikheyev, A. S., & Linksvayer, T. A. (2017). Genomic signature of kin selection in an ant with obligately sterile workers. *Molecular Biology and Evolution*, *34*, 1780–1787.
 18. Warner, M. R., Qiu, L., Holmes, M. J., Mikheyev, A. S., & Linksvayer, T. A. (2019). Convergent eusocial evolution is based on a shared reproductive groundplan plus lineage-specific plastic genes. *Nature Communications*, *10*, 2651.
 19. Whitfield, C. W., Cziko, A.-M., & Robinson, G. E. (2003). Gene expression profiles in the brain predict behavior in individual honey bees. *Science*, *302*, 296–299.
 20. Wilson, E. O. (1975). *Sociobiology: The new synthesis*. Cambridge, MA: Harvard University Press.
 21. Wolf, J. B., Brodie, E. D., III, Cheverud, J. M., Moore, A. J., & Wade, M. J. (1998). Evolutionary consequences of indirect genetic effects. *Trends in Ecology & Evolution*, *13*, 64–69.