

The Molecular and Evolutionary Genetic Implications of Being Truly Social for the Social Insects

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Abstract

The social complexity that characterizes the eusocial insects strongly affects all aspects of social insect life, including the molecular and evolutionary genetic basis of social insect traits. Quantitative genetic theory and empirical approaches have been developed over the past 60 years specifically to study the genetic implications of social interactions. Surprisingly, given the obvious biological importance of social interactions in social insects, this research tradition has been and continues to be widely overlooked throughout the social insect literature, including in recent sociogenomic studies focused on understanding the molecular underpinnings of social life. Instead, the overwhelming majority of social insect genetic research has relied on conventional genetic approaches developed for solitary organisms focused on the one-to-one association of an individual's genes to its own traits. I survey social insect studies that conclusively demonstrate the importance of indirect genetic effects (IGEs), which arise from social interactions, for social insect trait expression and evolution. I explain why these genetically based social effects are expected to be ubiquitous in social insects and I explain the relevance of the IGE framework, originally developed within quantitative genetics, for molecular genetic studies of social insect traits such as behaviour and caste. I discuss the problems of ignoring IGEs and relying solely on conventional direct genetic effect approaches. Finally, I discuss the strong potential of using the IGE approach and other

more systems-level-focused approaches to complement conventional reductionist approaches in elucidating the genetic basis of social insect trait expression and evolution.

Eusocial insects are by definition “truly social” (Hölldobler and Wilson, 2009). Even the simplest eusocial insect colonies, consisting of small groups of individuals, are characterized by some degree of division of labour and group co-ordination by means of chemical and physical social signals. The largest and most complex insect societies teem with millions of individuals with highly specialized roles. Individuals within these societies are in almost constant social contact with colony members from a range of different functional groups and life history stages (Hölldobler and Wilson, 2009). An array of social signals acts to functionally integrate individuals within these complex societies to such an extent that it is difficult to conceptualize the physiology and behaviour of individuals in isolation (Hölldobler and Wilson, 2009; Le Conte and Hefetz, 2008; Seeley, 1995). Such social complexity is expected to profoundly affect all aspects of life, including the genetic basis of traits (e.g. Bloch and Grozinger, 2011; Johnson and Linksvayer, 2010; Kent and Zayed, 2013; Linksvayer and Wade, 2005).

However, research into the genetic basis of social insect traits has overwhelmingly relied on conventional reductionist genetic approaches. These approaches were originally developed for solitary organisms, where there is a simple one-to-one mapping of an individual’s genes to its traits (Falconer and Mackay, 1996). In contrast, in social organisms—especially in tightly socially integrated organisms such as social insects—traits are the properties of the genomes of multiple interacting individuals (Fig. 1; Linksvayer, 2006; Linksvayer et al., 2009; Moore et al., 1997; Wolf, 2003). Notably, even though sociogenomic studies have used conventional approaches that do not explicitly consider the genetic implications of social interactions, one of the major findings of 10 years of sociogenomic research is that physiology, development, gene expression profile, neurogenomic state and behaviour critically depend on the social environment (Manfredini et al., 2014; Robinson et al., 2005, 2008).

Generally speaking, traits that depend on social context—both traits that are *defined* by social interactions and traits that are *affected* by social interactions—have long been recognized as presenting a special difficulty for conventional genetic analysis (Cheverud and Moore, 1994; Griffing, 1981; Hahn and Schanz, 1996; Moore et al., 2002). Fortunately, theoretical

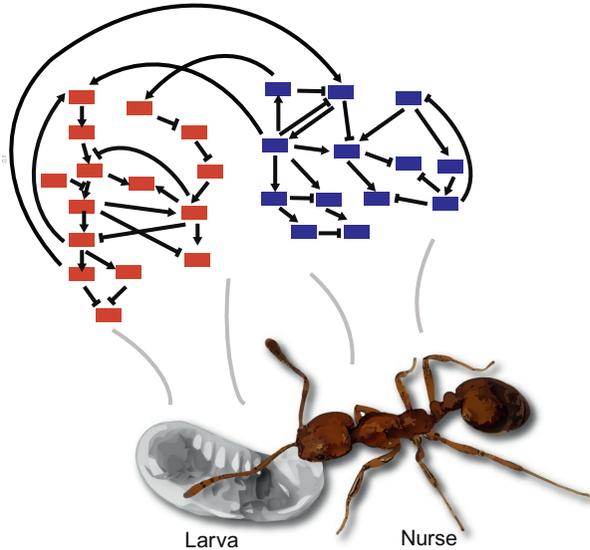


Figure 1 Genes affecting trait expression can be conceptualized as existing within a gene regulatory network. Here, a hypothetical gene regulatory network affecting ant larval traits (behaviour, development, physiology, etc.) is shown. Genes expressed in the larva (red (grey in the print version) boxes) directly influence its traits through *direct genetic effects*. Genes expressed in the nurse worker (blue (black in the print version) boxes) affect the larva's traits indirectly, via social interactions (transfer of proteins, brood care behaviour, etc.), through *indirect genetic effects*. Similarly, genes expressed in the larva feedback to indirectly influence the nurse's expressed traits through social interactions (begging behaviour, brood pheromone, etc.). Edges between boxes of the same colour represent conventional within-organism gene regulation and edges between boxes of different colours represent socially acting, intergenomic regulation. Realistically, genes expressed in foragers, the queen and other brood stages likely also influence the traits expressed by the pictured larva and nurse.

and empirical approaches tailored exactly for this problem have been developed within the field of quantitative genetics over the past 60 years. Indeed, well before W. D. Hamilton developed his famous theory of inclusive fitness for how social interactions affect fitness and expected social evolutionary outcomes (Hamilton, 1964), quantitative geneticists had begun developing models of how social interactions affect trait expression and trait evolution (Dickerson, 1947; Falconer, 1960; Willham, 1963). These models have led to the development of the interacting phenotypes/indirect genetic effect (IGE) framework, which provide formal theory and empirical approaches for studying how an individual's traits and fitness are affected by the genes of social partners (McGlothlin et al., 2010; Moore et al., 1997; Wolf et al.,

1998, 1999). Within this framework, *direct genetic effects*, the focus of conventional genetic approaches, occur when an individual's genotype affects its own traits. In contrast, *IGEs* occur when the traits of an individual depend on social partners' genotypes. These effects are labelled "indirect" because they act indirectly on traits, by shaping the environment (e.g. nutritional, chemical, physical environment) experienced by the focal individual.

Despite this long and rich history of IGE research focused on the genetic implications of social interactions and more recent calls for social insect researchers to consider IGEs (Helanterä, 2011; Johnson and Linksvayer, 2010; Keller, 2009; Linksvayer and Wade, 2005; Linksvayer et al., 2009), only a relatively small proportion of studies of the genetic basis of social insects' traits have explicitly used the IGE framework (e.g. Gempe et al., 2012; Linksvayer, 2006, 2007; Linksvayer et al., 2009, 2011; Teseo et al., 2014; van Zweden et al., 2010; Vojvodic et al., 2014; Wang et al., 2008). Surprisingly, the framework has until very recently (Malka et al., 2014) had seemingly little influence on sociogenomic research, the stated goal of which is to understand the molecular basis of social life (Robinson et al., 2005). Most recent reviews of the genetic basis of social behaviour and division of labour in social insects do not even mention IGEs (Bloch and Grozinger, 2011; Lattorff and Moritz, 2013; Libbrecht et al., 2013; Oldroyd and Thompson, 2007; Page et al., 2012; Smith et al., 2008; Yan et al., 2014; Zayed and Robinson, 2012), despite their certain importance.

These reviews typically do explicitly refer to the effect of the "social environment" on trait expression by indicating that an individual's traits, such as its behaviour, neurogenomic state or caste, are influenced by both its own genotype and the social environment it experiences. However, this basic genotype/environment partition is inadequate for social traits. As described further below, the critical missing point is that we know what makes up the social environment: the traits and genes of assorted types of social partners. Instead of simply conceptualizing these as the "social environment" and then moving on to study the direct genetic basis of response to these factors (Fig. 2A), we can explicitly study the genetic contribution of these "extrinsic factors present in the social environment" (Zayed and Robinson, 2012) to trait expression and evolution (Fig. 2B).

The omission of IGE-related theory and empirical studies from much of the literature on the genetic basis of social insect traits may in part be because researchers have often used either quantitative genetic approaches (e.g. Graham et al., 2011; Hunt et al., 1998; Kovacs et al., 2010;

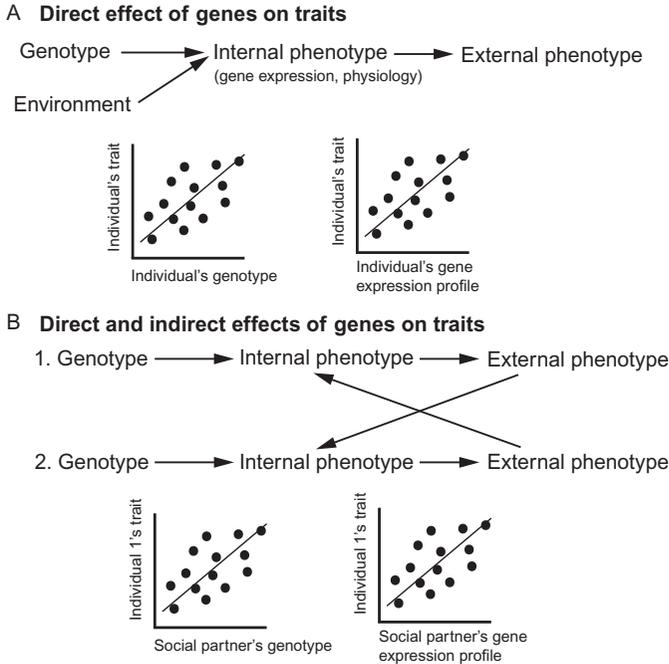


Figure 2 An individual's expressed behavioural and morphological traits (i.e. its external phenotype) depend on its own genotype and the environment it experiences. Here, an internal phenotype that can be quantified by measuring gene expression profiles or physiological traits is modelled as mediating genotypic and environmental effects on trait expression. (A) Direct effects of genes on traits. Conventional quantitative genetic approaches can elucidate the relationship between an individual's genotype and its traits (left graph); alternatively, conventional transcriptomic approaches can elucidate the relationship between an individual's gene expression profile and its traits (right graph). Note that with these approaches, it is possible to study the effects of the social environment on an individual's gene expression profile or other traits, but it is not possible to determine which genes and traits of social partners that make up the social environment are playing a role. (B) Direct and indirect effects of genes on traits. Alternatively, it is possible to explicitly study the indirect genetic effects of social partner genes on the traits of focal individuals. Here, the traits of individual 1 are affected by its own genotype and internal phenotype (patterns of gene expression, physiological traits, etc.), and its external phenotypic traits are also affected by the traits of its social partner, individual 2. As in panel (A), an internal phenotype (e.g. gene expression profile) is modelled as mediating genotypic and environmental effects on trait expression, so that the genetic effects of individual 2 on the traits of individual 1 first flow through the external traits of individual 2 and then to the internal and external traits of individual 1, and vice versa for IGEs of individual 1 on 2. Under this scenario, it is possible to determine how an individual's genotype and gene expression profile influence its own traits (left and right graphs in panel A), but it is also possible to study how the genotype and gene expression profiles of social partners influence the traits of each individual (left and right graphs in panel B).

Oldroyd et al., 1991; Page et al., 2000; Rueppell et al., 2004) or molecular genetic/transcriptomic approaches (e.g. Grozinger et al., 2003; Manfredini et al., 2014; Toth et al., 2007; Whitfield et al., 2006), with seemingly relatively little cross-talk. This is likely at least in part because the approaches are typically used to answer different but complementary questions about the genetic basis of trait variation versus trait expression, respectively. As a result, some researchers may be relatively unfamiliar with the existing quantitative genetic theoretical and empirical literature. Thus, one goal of this chapter is to introduce unfamiliar readers with the IGE literature specifically relevant to social insects.

Most importantly, I seek to explain how the IGE framework, originally developed within a quantitative genetic context, has strong potential to complement conventional approaches to elucidate the complex molecular and evolutionary genetic basis of trait expression and evolution in social insects (Linksvayer et al., 2012). I begin by briefly surveying the IGE literature and social insect studies that explicitly or implicitly studied IGEs. Next, I briefly survey studies of the molecular genetic basis of social insect traits, which have increasingly sought to study how the “social environment” affected trait expression but typically have done so without a formal framework. I explain why a formal theoretical and empirical framework such as the IGE framework is useful and often is necessary for both motivating and interpreting studies of the molecular and evolutionary genetic basis of social traits. Finally, I describe how the IGE framework is currently being extended in concert with emerging transcriptomic and genomic approaches to study the molecular basis of social interactions (Vojvodic et al., 2014), and how these approaches can lead to exciting social systems-level insight into the molecular and evolutionary genetic basis of social insect traits.

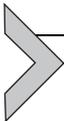


1. INTRODUCTION TO IGEs

The first models to explicitly consider the genetic implications of social interactions were developed by animal and plant breeders and focused on maternal effects, which occur when offspring traits depend on maternal traits, for example, as a result of maternal care (Cheverud, 1984; Dickerson, 1947; Falconer, 1960; Kirkpatrick and Lande, 1989; Willham, 1963). For example, in mammals, offspring size is strongly influenced by the quantity and quality of milk produced and provided by the mother (Bijma, 2006; Bouwman et al., 2010). Such maternal effects typically are highly heritable

(i.e. affected by maternal genotype), so that the maternal effect can evolve. Maternal genetic effects have been shown to strongly contribute to total heritable variation for many offspring traits and hence strongly affect evolutionary responses to selection (Wade, 1998). As a result, estimating maternal genetic effects has long been considered crucial and also routine for plant and animal breeders (Bijma, 2006; Bouwman et al., 2010).

Maternal effects models were extended to include other types of genetically based social effects (Cheverud and Moore, 1994; Griffing, 1977, 1981; Lynch, 1987), in particular within the interacting phenotypes/IGE framework (McGlothlin et al., 2010; Moore et al., 1997; Wolf et al., 1998, 1999). The “social environment” provided by conspecifics (e.g. in social insect colonies, the mother queen, sibling adults, sibling brood) depends on the traits and genes of social partners. In this way, the social environment contains genes and can itself evolve (Wolf, 2003). This is not the case for abiotic environmental factors, explaining why the social environment is fundamentally different than the abiotic environment. As discussed further below, the simple fact of “genes in the environment” can have profound implications for the molecular and evolutionary genetic basis of traits that are influenced or defined by social interactions as well as for approaches required to study these traits (Fig. 2). Note that IGEs are perhaps most intuitive when considering different classes or life history stages of conspecifics (e.g. parents and offspring; adult nurse worker and immature sibling; Fig. 1) but clearly can occur even when interacting individuals are homogeneous in terms of age, caste, etc. For more detailed reviews of the IGE theory and the IGE empirical literature, see Bleakley et al. (2010), McGlothlin et al. (2010), Wolf et al. (1998) and Wolf and Moore (2010).



2. SURVEY OF STUDIES OF IGEs IN SOCIAL INSECTS

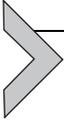
The maternal effect quantitative genetic models described above were first extended to study the genetic basis of honey bee colony-level traits such as honey production that are likely primarily influenced by queen and worker genotypes (Bienefeld and Pirschner, 1991; Bienefeld et al., 2007; Chevalet and Cornuet, 1982; Cornuet and Chevalet, 1987).

IGE approaches have also been developed and applied to social insect traits that can be measured on individuals, such as body size and caste (Linksvayer, 2006). Linksvayer and Wade (2005) described the theoretical implications of using an explicit IGE perspective for understanding the genetic basis of social insect traits and the evolution of eusociality (see also

Kent and Zayed, 2013; Linksvayer and Wade, 2009), and several subsequent empirical studies have explicitly used an IGE perspective to study the genetic basis of social insect traits (Gempe et al., 2012; Linksvayer, 2006, 2007; Linksvayer et al., 2009, 2011; Teseo et al., 2014; van Zweden et al., 2010; Vojvodic et al., 2014; Wang et al., 2008). Linksvayer (2006) estimated heritability and genetic correlations for direct and IGEs on body size and caste in an ant population, and Linksvayer (2007) and Linksvayer et al. (2009, 2011) studied the contribution of IGEs to divergence between ant species and honey bee lineages, respectively. Similar to these studies, Teseo et al. (2014) recently showed that reproductive traits in a clonal army ant depend on the interaction between direct and IGEs. Van Zweden et al. (2010) demonstrated that both direct and IGEs contribute to heritable variation in ant hydrocarbon profiles, with the most heritable hydrocarbons being those that were readily transferred among nestmates. Notably, Wang et al. (2008) was the first study to show that gene expression profiles depend strongly on IGEs (see also Gempe et al., 2012): in fact, the gene expression profiles of ant workers depended more strongly on the genotype of worker nestmates at the Gp-9 locus than the worker's own genotype.

These studies explicitly using the IGE framework build on a long series of social insect studies that implicitly considered IGEs. These studies recognized the special difficulty of heritable effects of the social environment (i.e. IGEs) for studying the genetic basis of social insect traits, and also demonstrated that these effects strongly contribute to heritable variation for a range of social insect traits (e.g. Allsopp et al., 2003; Beekman and Oldroyd, 2003; Beekman et al., 2000; Calderone and Page, 1992; Calis et al., 2002; Gotzek and Ross, 2008; Guzmán-Novoa and Page, 1994; Hunt et al., 2003; Keller and Ross, 1995; Melnichenko and Burmistrova, 1963; Moritz and Southwick, 1987; Moritz et al., 1987; Oldroyd et al., 1991; Osborne and Oldroyd, 1999; Pankiw and Page, 2001; Pankiw et al., 2002; Rinderer et al., 1986; Ross and Keller, 2002; Rüppell et al., 2001). These studies have often used a cross-fostering approach to experimentally disentangle the contribution of an individual's own genotype (direct genetic effects) versus the genotype of social partners (IGEs) to its traits.

Altogether these empirical studies which explicitly or implicitly studied IGEs provide strong empirical support for the notion that IGEs are very widespread and strongly contribute to heritable differences within and between social insect populations. Below, I explain why IGEs are actually expected to be ubiquitous in the truly social insects.



3. IGEs ARE EXPECTED TO BE UBIQUITOUS IN SOCIAL INSECTS

Maternal care guarantees maternal effects on offspring trait expression (Wade, 1998). Similarly, cooperative brood care (sib care), a defining feature of eusociality, guarantees sib effects on the traits expressed by developing brood (Linksvayer, 2006; Linksvayer and Wade, 2005). The importance of such sib effects on social insect traits is perhaps best illustrated by studies of honey bee caste development and caste-related traits. It has long been known that honey bee nurse workers regulate the development and caste fate of larvae by controlling whether larvae receive qualitatively and quantitatively distinct queen or worker diets (Haydak, 1970). When larvae are reared in the lab so that this social control is not possible, strict queen-worker dimorphism disappears (Linksvayer et al., 2011). Similarly, when social regulation of the larval nutritional environment is artificially manipulated, caste-related characters are affected (Dedaj et al., 1998; Wang et al., 2014). This also occurs when provisioning is more naturally manipulated, by cross-fostering larvae between honey bee strains (Allsopp et al., 2003; Linksvayer et al., 2009, 2011; Osborne and Oldroyd, 1999). These studies demonstrate that the caste developmental programme includes nurse worker genes with IGEs on caste, so that focusing solely on direct genetic effects expressed in developing larvae yields an incomplete picture of the genetic basis of caste. Some of the putative honey bee genes with IGEs on caste have been identified, including two major royal jelly protein genes (Huang et al., 2012; Kamakura, 2011), and hundreds of additional genes with putative IGEs on caste have recently been identified through RNA sequencing of the heads and royal jelly producing glands of nurse bees feeding queen- versus worker-destined larvae (Vojvodic et al., 2014). These nurse worker genes presumably affect larval development by affecting the quality and quantity of provisioned food as well as by affecting the provisioning behaviour of nurse workers.

The social mechanisms by which colony members regulate the development of brood are also known in a range of other social insects, and these mechanisms provide straightforward means by which IGEs act on the traits expressed by developing brood (Fig. 1). For example, in several ant species, nurse workers manipulate larval caste fate through biting developing larvae (Brian, 1973; Penick and Liebig, 2012); nurse *Polistes* wasps influence larval

caste fate through antennal drumming (Suryanarayanan et al., 2011); and *Melipona* stingless bee workers influence caste fate via a glandular secretion that is fed to larvae (Jarau et al., 2010). At the same time, larvae can indirectly affect the provisioning behaviour of nurse workers (Fig. 1) and hence affect their own caste fate through begging behaviour (Kaptein et al., 2005) and brood pheromone (Le Conte et al., 1995; Sagili and Pankiw, 2009).

Other types of social signalling mechanisms used in social insect colonies provide additional mechanisms for IGEs on a wide range of social insect traits. By definition, pheromones are chemical signals produced by one individual that affects the behaviour or physiology of the individuals who receive and respond to the signal (Le Conte and Hefetz, 2008; Slessor et al., 2005). Thus, genes underlying pheromone production and signalling can have IGEs on the traits of individuals receiving and responding to the pheromone. As ants are considered to be walking batteries of exocrine glands (Hölldobler and Wilson, 1990, 2009), producing an array of pheromones, there is enormous potential for pheromone-mediated IGEs on the expression of ant traits. Many social insect pheromones have been identified that originate from queen, worker or brood nestmates and affect the physiology, behaviour or development of recipients (Hölldobler and Wilson, 1990; Le Conte and Hefetz, 2008; Slessor et al., 2005).

This range of specific social mechanisms by which social insect individuals communicate—exchange of food, biting, exchange of pheromones, etc.—all provide mechanisms by which genes expressed in nestmate workers, brood and queen(s) have IGEs on development, physiology and behaviour. Indeed, the social mechanisms described above that characterize insect societies virtually guarantee that most, if not all social insect traits, are affected to some degree by IGEs originating in various types of nestmates. Despite the clear implication of the ubiquity of IGEs for social insect traits, the functional and evolutionary importance of IGEs has only rarely been acknowledged (Helanterä, 2011; Hunt, 2012; Johnson and Linksvayer, 2010; Keller, 2009; Kent and Zayed, 2013; Linksvayer and Wade, 2005; Linksvayer et al., 2009). In the following sections, I discuss why this omission is problematic.



4. IMPLICATIONS FOR THE MOLECULAR GENETIC UNDERPINNINGS OF SOCIAL INSECT TRAIT EXPRESSION

While past quantitative genetic research in the social insects sought to identify the causal allelic variants underlying trait variation, an alternative

molecular genetic approach is to identify and functionally describe the full set of genes and molecular interactions that influence trait expression, regardless whether any particular loci harbour allelic variation (Fig. 1). Increasingly, researchers study the transcriptomic profiles of individuals expressing certain traits (e.g. behaviours, developmental trajectories, etc.) as a first step to identify the set of genes and molecular mechanisms associated with trait expression (Chandrasekaran et al., 2011; Evans and Wheeler, 1999; Feldmeyer et al., 2014; Ferreira et al., 2013; Whitfield et al., 2006).

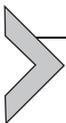
The first such social insect sociogenomic studies searched for associations between an individual's behaviour or caste and its genome-wide transcriptional profile (Fig. 2A), often while experimentally controlling the social environment (e.g. using colonies containing only a single age cohort of workers; Barchuk et al., 2007; Evans and Wheeler, 1999; Whitfield et al., 2003, 2006). These studies, many of which have focused on the genetic basis of social behaviour, have identified a large number of candidate genes expressed in individual's brains that are associated with their behavioural state (Chandrasekaran et al., 2011). As an aside, an IGE-motivated version of these studies would ask how well an individual's behaviour is predicted by its own versus its social partners' gene expression profiles in order to identify genes with putative direct versus IGEs on behaviour (Fig. 2). Subsequent studies have shown that the neuro-genomic state of workers is highly responsive to social signals, such as honey bee queen mandibular pheromone and forager-produced pheromones, which are known to affect colony-level division of labour (Alaux et al., 2009; Grozinger et al., 2003; Manfredini et al., 2014). These studies provide exciting first steps to elucidating the molecular genetic basis of individual's response to social signals. Other studies have begun to elucidate the molecular genetic basis of pheromone production (Malka et al., 2009, 2014).

Social insect colonies typically contain multiple types of individuals (e.g. various brood stages, queens, workers of different functional groups) and social signal production, reception and response occurs dynamically and simultaneously in these various interacting groups (Fig. 1). Studying signal production, reception and response separately, and in one group at a time, is likely to miss biologically important complexity. An alternative way to study this dynamic process involving signalling and response among multiple life history stages and functional groups within a colony is to use more systems-level approaches (Linksvayer et al., 2012). The IGE approach takes a step in this direction by considering the effect of multiple interacting individuals on each other. While the IGE approach has usually been applied in the context of quantitative genetic studies, the framework can also be readily applied to

study the full set of genes expressed in interacting social partners underlying trait expression (Linksvayer et al., 2012; Vojvodic et al., 2014). For example, by simultaneously studying the transcriptomic profiles of interacting nurse workers and developing larvae (Fig. 1), it is possible to identify genes expressed in both larvae and their care-giving nurses that directly, and indirectly, respectively, affect larval development (Vojvodic et al., 2014; Fig. 2).

As RNA sequencing costs continue to drop, it will increasingly be feasible to simultaneously study gene expression profiles of multiple categories of socially interacting individuals within social insect colonies, to provide social systems-level insight into the molecular basis of social regulation of the behaviour, physiology, development and fitness of colony members. Such a more systems-level focused strategy of profiling gene expression of multiple interacting organisms simultaneously has already been used to study the molecular mechanisms underlying host–pathogen interactions (Kollmus et al., 2014; Reid and Berriman, 2012; Tierney et al., 2012; Westermann et al., 2012), and this approach is a conceptually straightforward next step to study the molecular mechanisms underlying social interactions (Linksvayer et al., 2012; Vojvodic et al., 2014). Once candidate genes and gene networks are identified in the various classes of interacting individuals, gene-level approaches can be used to experimentally manipulate expression and quantify effects at the individual- and colony-levels.

Furthermore, there is increasingly exciting potential to link molecular-genetic and evolutionary-genetic approaches to identify how allelic variation within the colony-level network of genes underlying trait expression leads to phenotypic variation for both individual- and colony-level traits. These approaches have been described as “systems genetics” or “genetical genomics” (Ayroles et al., 2009; Mackay et al., 2009) and fit within the rapidly growing field of evolutionary systems biology (O’Malley, 2012; Rockman, 2011). For truly social organisms, like social insects, the colony represents an additional biologically important level of organization, expanding the complex system to be studied from the individual organism level to the colony level. Integrating molecular genetic, functional genomic, quantitative genetic/genomic and emerging evolutionary systems biology approaches will provide insight into the genetic basis and evolution of social insect traits.



5. WHY SHOULD SOCIAL INSECT RESEARCHERS CONSIDER THE IGE FRAMEWORK?

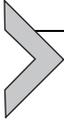
1. In theory, IGEs can strongly affect both the magnitude and direction of evolutionary responses to selection as well as expected patterns of

sequence variation within and between lineages (Linksvayer and Wade, 2009; McGlothlin et al., 2010; Moore et al., 1997; Wolf and Moore, 2010; Wolf et al., 1998). In practice, IGEs have often been found to be as important as direct genetic effects in a wide range of organisms (Bleakley et al., 2010; Wolf and Moore, 2010). As discussed throughout this chapter, IGEs are expected to be especially important in social insects as a result of long evolutionary history of being truly social (Linksvayer and Wade, 2005). In order to properly account for the contribution of socially expressed genes to trait variation and trait evolution, formal evolutionary genetic models must be used. The IGE framework is a natural extension of well-established quantitative genetic models (McGlothlin et al., 2010; Moore et al., 1997; Wolf and Moore, 2010). Correct estimation of IGE parameters and incorporation into evolutionary models is especially tricky in complex social systems such as the eusocial insects, where IGEs can originate simultaneously from multiple sources, including the queen, different functional categories of workers and brood (see Linksvayer, 2006). Furthermore, the contribution of IGEs to trait variation and the evolutionary process remains hidden to conventional genetic approaches that do not explicitly account for genetic components arising from social interactions (Wolf, 2003).

2. IGEs are also expected to make up a large proportion of the full network of genes affecting social insect trait expression (Linksvayer et al., 2009, 2012). Indeed, as described above, all of the mechanisms of social communication (pheromones, exchange of food, physical interactions, etc.) that are apparently so important to the functioning of social insect colonies provide straightforward mechanisms for IGEs originating from various functional categories of nestmates to affect trait expression. The contribution of these social regulatory mechanisms to the molecular genetic basis of trait expression is opaque to conventional approaches and has so far, remained largely hidden. Unless research programmes seeking to describe the molecular mechanisms underlying social insect trait expression explicitly consider IGEs, they will often simply overlook functionally important socially acting mechanisms—the very mechanisms that characterize eusocial colonies (Hölldobler and Wilson, 2009; Seeley, 1997). For example, as discussed in detail above, caste development across social insect lineages is well understood to depend on the socially regulated nutritional environment. While a large number of studies have sought to describe the molecular mechanisms of caste development (e.g. Barchuk et al., 2007; Evans and Wheeler, 1999; Foret et al., 2012; Mutti et al., 2011; Wang et al., 2013; Wheeler

et al., 2014), the vast majority of these studies have only considered genes that are differentially expressed in developing larvae in response to the nutritional environment, but have not considered the genes expressed in care-giving nurses that produce alternate nutritional environments, and thus have IGEs on caste (but see Huang et al., 2012; Kamakura, 2011; Vojvodic et al., 2014). An explicit IGE framework ensures that these molecular components that contribute to social regulation are actively studied (Linksvayer et al., 2009).

3. A major roadblock to the increasing number of transcriptomic and genomic studies of social insects is to characterize the function of genes identified as playing important roles in social insect trait expression or evolution. Gene function is typically inferred by trying to identify functionally annotated orthologs from model systems such as *Drosophila*. Notwithstanding the fact that the function of orthologs in *Drosophila* and social insects may differ, a number of recent transcriptomic and genomic studies in social insects have emphasized the large number of taxonomically restricted genes (Feldmeyer et al., 2014; Ferreira et al., 2013; Harpur et al., 2014; Jasper et al., 2014; Johnson and Tsustui, 2011; Simola et al., 2013; Sumner, 2014), which by definition do not have identifiable orthologs, so usually have completely unknown function. Such novel genes and genes with novel functions may be expected to be especially important in the evolution of the elaborate social communication and regulatory mechanisms that characterize insect societies (Johnson and Linksvayer, 2010). Indeed, a recent honey bee study found that the transcriptomic profiles of tissues with novel social function were dominated by a small number of taxonomically restricted genes, indicating that novel genes play important roles in traits associated with social communication and regulation (Jasper et al., 2014). As the IGE framework explicitly focuses on genes that act through these social mechanisms, this approach can help to elucidate the function of novel genes that may often otherwise be overlooked.
4. Finally, social evolution theory is frequently invoked to motivate studies of the genetic basis and evolution of insect societies (Abbot et al., 2011; Bourke and Franks, 1995; Queller and Strassmann, 1998). Social evolution theory pre-supposes the existence of socially acting genes (Hamilton, 1964). The IGE/interacting phenotypes framework provides approaches specifically designed to detect these genes with social effects on trait expression and fitness.



6. CONCLUSIONS

Maternal effects in mammals are well understood to be a biological fact that must be considered by any genetic analysis of mammalian traits (McAdam and Boutin, 2004; Wade, 1998; Wade et al., 2008). Similarly, IGEs are a biological fact in social insects and should be explicitly considered in any genetic analysis of social insect trait expression or trait evolution. This is not only true for quantitative genetic studies but also includes sociogenomic studies focused on the molecular mechanisms underpinning trait expression. The social communication and regulatory systems that characterize eusocial insect colonies guarantee an important role of IGEs in the molecular basis of traits.

I have argued that IGEs are ubiquitous, affecting trait expression for most or all social insect traits. It is reasonable to ask if there is likely any gene in the genome of social insects that does not have indirect effects on some trait. Given the functional integration of individuals within insect societies, it seems likely that a majority of genes may have both direct and indirect effects on trait expression and fitness, perhaps acting through diverse and circuitous social routes. These precise mechanisms are what we need to describe to understand the functional significance of specific genes in social insect genomes. Describing these mechanisms is indeed a daunting task—seemingly much more so than in solitary organisms where there is necessarily only a one-to-one mapping of an individual's genes to its own traits, and as a result perhaps much less pleiotropy than in highly social organisms (Mullen and Thompson, “Understanding Honey Bee Worker Self-Sacrifice: A Conceptual–Empirical Framework”; Thompson et al., 2013). On the other hand, this added social complexity is precisely the characteristic that compels both social insect researchers and casual observers to marvel at insect societies—and is the reason social insects are established as models for social evolution, collective behaviour and the genetic basis of behaviour.

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