SOCIOGENOMICS: SOCIAL LIFE IN MOLECULAR TERMS

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Abstract | Spectacular progress in molecular biology, genome-sequencing projects and genomics makes this an appropriate time to attempt a comprehensive understanding of the molecular basis of social life. Promising results have already been obtained in identifying genes that influence animal social behaviour and genes that are implicated in social evolution. These findings — derived from an eclectic mix of species that show varying levels of sociality — provide the foundation for the integration of molecular biology, genomics, neuroscience, behavioural biology and evolutionary biology that is necessary for this endeavour.

SOCIETY
A group of organisms from the same species that live in the same area and engage in repeated interactions with each other, both cooperative and competitive. The more extensive the cooperation, the more developed the society.

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Published online: 10 march 2005, doi:10.1038/nrg1575

Life on Earth has undergone several transitions during its history, from the evolution of cells, to multicellular organisms, and then to the organization of these organisms into SOCIETIES[1]. There has been notable progress in elucidating the molecular basis of cellular function and development, and there is now a burgeoning interest in doing the same for social life ('sociogenomics'). The goal of sociogenomics is to achieve a comprehensive understanding of social life in molecular terms: how it evolved, how it is governed and how it influences all aspects of genome structure, genome activity and organismal function[2–4]. Which genes and pathways regulate those aspects of development, physiology and behaviour that influence sociality, and how are they themselves influenced by social life and social evolution? Significant progress in molecular biology and genomics, and the output of many genome-sequencing projects makes this an opportune time for this programme of research.

Sociogenomics is predicated on two of the most important insights in biology to emerge from the latter half of the twentieth century. First, as elegantly argued by Edward O. Wilson in *Sociobiology*[5], social life has a biological basis and is therefore influenced to some extent by genes and the forces of evolution. The second insight is the realization that the molecular functions of many genes are highly conserved across species, even for COMPLEX TRAITS.

The conceptual foundation of sociobiology is Darwinian theory. In particular, the emphasis on models that describe group life in terms of MUTUALISM, KIN SELECTION and RECIPROCAL ALTRUISM. The empirical foundation lies in Wilson's identification of similar patterns of social organization across taxa and his assertion that these similarities are readily ascribed to social evolution. Analysing social behaviour at the molecular level can help us to understand how complex and highly derived patterns of social behaviour have evolved from simpler ancestral behaviour, and explain the evolutionary relationships of apparently similar behaviours across distantly related taxa. Analysing social behaviour at the molecular level can also help to integrate mechanistic and evolutionary analyses, which at present are largely fragmented (FIG. 1).

Understanding the molecular basis of sociality involves a broad agenda. We focus our review on the area in which the most progress has been made: the identification of genes that influence animal social behaviour. Both solitary and social animals must accomplish many activities during the course of their lives for survival and reproduction[6]. They must find food, which for non-sessile creatures requires foraging. Many species create a nest or shelter to rear young or retreat to in times of unfavourable conditions. To do so, individuals need to identify a suitable location, construct the structure and defend it from intruders. Most animals must mate to reproduce and this again requires a complex repertoire of behaviours: mate recognition (location and selection), courtship and mating. Many animal species then engage in parental care to successfully rear their offspring.

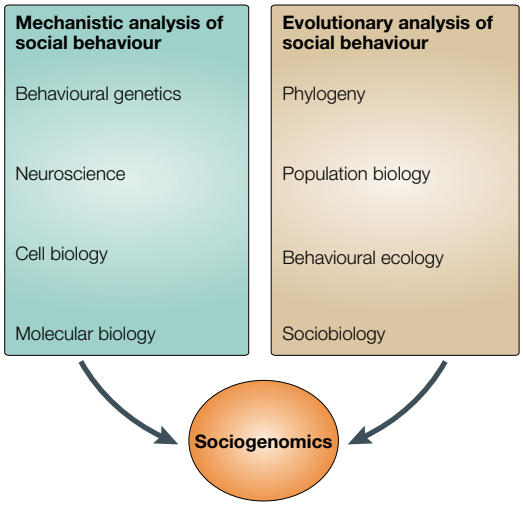

Figure 1 | **Sociogenomics as an integrative discipline in behavioural biology.** In 1975, Edward O. Wilson accurately predicted that a split would occur over the following 25 years between mechanistic (the disciplines that are depicted on the left) and evolutionary analyses of behaviour (the disciplines that are depicted on the right)[5]. Today, sociogenomics can contribute to a more integrative approach to the study of social behaviour. Information on genes provides neuroscientists and behavioural ecologists with a 'common language'. Behavioural ecologists study adaptations, which ultimately are the product of natural selection that functions on genes. Neuroscientists study neuroanatomical, neurochemical, neurodevelopmental, neuroendocrinological, neuroethological and neurophysiological mechanisms of behaviour, built by proteins that are encoded by genes. This synthesis requires using genomics to integrate mechanistic and evolutionary perspectives. It should also include phylogenetic analysis, especially because of the broad array of taxa that must be used to study the molecular basis of social life.

Social animals often accomplish these activities cooperatively, and cooperation requires coordination. Various mechanisms are used to achieve this coordination, including communication among individuals and forms of social organization that involve dominance hierarchies and DIVISION OF LABOUR. Life in society is often highly structured, with nearly all activities influenced by interactions with other society members. Social regulation influences when, how often, how intensely and with whom these activities are carried out. As will be discussed in this article, social regulation is now understood to involve changes in gene expression in the brain in response to specific social stimuli, which in turn affect behaviour (BOX 1).

This view of life is reflected in our overview of progress in this field. Beginning with examples from feeding, we move on to mate recognition, parental care, dominance hierarchies and insect societies, with their especially well-developed systems of division of labour. (Topics relevant to this review that are not covered owing to lack of space are included in TABLE 1.) Emphasis is given to topics that provide general insights, and we highlight species that are used as 'model behavioural systems'[7], especially model social species, rather than the more established model genetic systems (BOX 2). Findings so far reveal two emerging themes. First, genes involved in solitary behaviour are also used for social behaviour, indicating that molecular insights from simple behaviour can be used to generate candidate genes for more highly derived patterns of social behaviour. Second, the genome is highly sensitive to social influence — the social regulation of gene expression is a potent influence on behaviour. We end with a discussion of the prospects and challenges for this field.

COMPLEX TRAIT
A measured phenotype, such as disease status or a quantitative character, which is influenced by many environmental and genetic factors, and potentially by interactions in and between them.

MUTUALISM
Social interactions in which both parties benefit.

KIN SELECTION
William D. Hamilton's theory to explain the evolution of the hallmark of social life: altruistic cooperation (carrying out functions that are costly to the individual but that benefit others). By helping a relative, an individual increases its fitness by increasing the number of copies of its genes in the population.

RECIPROCAL ALTRUISM
Robert L. Trivers' theory to explain altruism, according to which altruism occurs when the individual is likely to later be the recipient of similar altruistic acts.

DIVISION OF LABOUR
A key characteristic of the most structured societies — those with the highest levels of cooperation — in which individuals specialize in specific occupations. In insect societies, queens reproduce while workers engage in all tasks that are related to colony growth and development; young workers tend to work in the nest, whereas older individuals forage outside.

CANDIDATE GENE
A gene that is thought to be more likely to be involved in the control of a trait in one species compared with a random gene from the genome, based on known functions in another species.

TRANSCRIPTOMICS
A global way of looking at gene-expression patterns. This can involve measurements of thousands of genes simultaneously with microarrays or measurements of small numbers of genes that are facilitated by global sequence information from EST or genome-sequencing projects.

Box 1 | **Transcriptomics and social behaviour**

Genome-sequencing projects, ESTs, microarrays and other genomic resources are now making it possible to productively use a diverse array of social animals for sociogenomic research (BOX 2). Sequence information from EST collections and other sources eliminates the need to tediously clone genes one at a time before experimentation with CANDIDATE GENES can even begin. Microarrays allow unbiased, open-ended, gene discovery in species that, unlike model genetic organisms, cannot be used efficiently for traditional forward-genetic approaches[93]. For the first time, it is possible to select organisms on the basis of their compelling social biology and develop powerful and efficient programmes of molecular analysis.

Two traditional forward-genetic models are used to discover genes that influence behaviour[96]. Seymour Benzer pioneered the approach that involves creating single-gene mutations, screening for specific behavioural abnormalities and identifying the mutated gene. Jerry Hirsch championed the approach that involves identifying behavioural variants from natural and artificially selected populations and then using them to find the underlying genetic variation. Limitations in our ability to efficiently breed many model social species preclude generation and maintenance of large numbers of mutant lines, but the second approach is being used effectively in various ways (see the section on foraging in the main text and the example of vasopressin receptor 1a in BOX 3).

Studies of social behaviour are increasingly making use of a new approach that is based on TRANSCRIPTOMICS: measuring changes in the expression of genes that correlate with changes in behaviour. Gene expression is measured in the brains of individuals that have different behaviours or different forms of the behaviour of interest. The premise of this approach, that differences in transcript abundance reflect a mechanistic link between gene and behaviour, is well supported in this review and elsewhere[9,82,83]. However, transcript abundance is not always predictive of protein abundance. Some differences in gene expression are a consequence, not a cause, of a behavioural change. It is therefore important to go beyond gene expression–behaviour correlations to manipulate transcript abundance or protein activity through transgenesis, RNAi[84], viral vectors[85] or pharmacology. The transcriptomics-based approach is a powerful entrée towards gene discovery for model social species.

Table 1 | **Examples of social behaviours studied from a molecular perspective**

Behaviour	Organism	Gene	Molecular function	Reference
Foraging				
Rover versus sitter phenotype	*Drosophila melanogaster*	*foraging*	Protein kinase G	8
Roamer versus dweller phenotype	*Caenorhabditis elegans*	*egl-4* (*egg-laying defective 4*)	Protein kinase G	15
Division of labour: onset age of foraging	*Apis mellifera*	*foraging*	Protein kinase G	10
Division of labour: onset age of foraging	*A. mellifera*	*malvolio*	Manganese transporter	18
Division of labour: foraging related?	*A. mellifera*	*period*	Transcription cofactor	69
Division of labour: foraging related?	*A. mellifera*	*ace* (*acetylcholine esterase*)	Acetylcholine esterase	70
Division of labour: foraging related?	*A. mellifera*	*IP(3)K* (*inositol 1,3,5 triphosphate kinase*)	Inositol signalling	71
Division of labour: exocrine gland function	*A. mellifera*	*Royal jelly protein*	Secreted nutritive protein	72,73
Foraging specialization: nectar versus pollen	*A. mellifera*	*Protein kinase C*	Protein kinase C	124
Social feeding	*D. melanogaster*	*npf* (*neuropeptide F*)	Neuropeptide Y (NPY) homologue	20
Social feeding (aggregation)	*C. elegans*	*npr-1* (*neuropeptide receptor family 1*)	Receptor for NPY	21,22
Mate recognition and courtship				
Vocal learning, vocalization	*Taeniopygia guttata*; *Homo sapiens*	*FOXP2* (winged helix/forkhead protein)	Transcription factor	26–29
Vocal learning, song recognition	*T. guttata*	*zenk* (*Zif269/Egr1/NGFIA/Krox24*); others	Transcription factor; other functions	30–34,125
Pheromone-mediated communication	*Mus musculus domesticus*	*V1R, V2R* (vomeronasal receptor, families 1 and 2)	G-protein receptors	35
Pheromone-mediated communication	*D. melanogaster*	*Gr68a* (*Gustatory receptor 68a*)	G-protein receptor	126
Pheromone-mediated communication	*Bombyx mori*	*BmOR1* (*olfactory receptor 1*)	G-protein receptor	127
Male courtship	*D. melanogaster*	*fruitless;* others	Transcription factor; other functions	116; other genes in 8
Male courtship; timing of mating	*D. melanogaster*	*period*	Transcription cofactor	128,129
Female receptiveness (lordosis)	Rodents	Oestrogen responsive genes	Various functions	115,130
Post-mating behaviour				
Refractoriness to mate, ovipositioning, decreased longevity	*D. melanogaster*	Genes for seminal proteins	Various functions	131
Monogamy, parental care	Rodents	*V1aR, OTR* (vasopression receptor 1A; oxytocin receptor)	Vasopressin and oxytocin receptors	85,121,123
Maternal care	*Rattus norvegicus*	*GR* (glucocorticoid receptor)	Glucocorticoid receptor	36,37
Attachment to mother	*M. m. domesticus*	*Orpm* (opioid receptor-μ)	Opioid receptor	122
Maternal care, pup retrieval	*M. m. domesticus*	*Dbh* (dopamine β-hydroxylase)	Biosynthesis of norepinephrine and epinephrine	132
Social hierarchies				
Territorial versus non-territorial males	*Haplochromis burtoni*	*GnRH1 (gonadotropin releasing hormone 1)*	Gonadotropin-releasing hormone	45–48
Dominant versus subordinate males	*Procambarus clarkii*	*5HTR1, -2 (serotonin receptor type 1 and 2)*	Serotonin receptors	51
Dominance interactions				
Aggression	*M. m. domesticus*	*Maoa* (monoamine oxidase A)	Monoamine oxidase	53
Aggression	*Macaca mulatta*	*5HTT* (serotonin transporter)	Serotonin transporter	38
Subordinate behaviour	*M. m. domesticus*	*Dvl1* (dishevelled)	Wnt-receptor signalling pathway	133,134

*This list highlights studies in which specific genes have been identified.

Foraging: solitary to social with the same genes

The* foraging *(for) gene. Studies of cyclic GMP (cGMP) signalling pathways have revealed strong conservation in the molecular underpinnings of feeding-related behaviours (FIG. 2). Sokolowski and colleagues showed in *Drosophila melanogaster* that the *foraging* gene (*for*) encodes a cGMP-dependent protein kinase (PKG), and that naturally occurring allelic variation in this gene results in two genotypes, 'sitters' and 'rovers'[8] (FIG. 2a). Although *D. melanogaster* lives most of its life in a solitary way, the behavioural variation associated with these allelic differences indicates a parallel to the feeding-related behaviour of the highly social honeybee, *Apis mellifera* (FIG. 2b). Honeybees stay in the hive when they are young and then rove far and wide outside in search of food when they get

Box 2 | **To be or not to be social**

One property that distinguishes sociogenomics from allied molecularly and genetically orientated fields such as neurogenomics, behavioural neuroscience and behavioural genetics is a special interest in species that live in a society. Of particular interest are species that can be studied under natural or naturalistic conditions. These species, which include birds, bees, crustaceans, fish, primates and voles, offer a rich set of behaviours for analysis that should contribute to the development of general principles. Studies done under ecologically relevant conditions make it easier to interpret molecular data within a broad framework that integrates mechanistic and evolutionary perspectives, a goal that is shared with another nascent line of study — 'evolutionary and ecological functional genomics'[97]. Studies done under ecologically relevant conditions also address a practical concern: laboratory conditions can sometimes obscure natural patterns of social behaviour[98].

Organisms that live in a society engage in repeated interactions with each other — both cooperative and competitive — in various contexts that are related to survival and reproduction. A defining feature of animal society is 'reciprocal communication of a cooperative nature'[5]. In the most structured societies, these kinds of interactions influence most aspects of life. In other societies, individuals might be less communicative or cooperative except for activities related to reproduction, but they show many related behaviours, including attraction, aggression, affiliation, attachment and dominance.

Many species do not live in societies at all but they sometimes aggregate and show behaviour — such as mating (BOX 5) — that is relevant to the study of sociality. We advocate the inclusion of these behaviours in this programme of research, for both logistical and conceptual reasons. They are readily studied in the model genetic organisms *Drosophila melanogaster, Caenorhabditis elegans* and *Mus musculus*, so they can be analysed with all the powerful molecular techniques that are available. In addition, sociality probably evolved through modifying the molecular and neural mechanisms that are associated with the perception and processing of environmental stimuli by solitary organisms. Analyses of certain behaviours that are shown by solitary animals can enhance our understanding of social life.

older. However, foragers collect food to fulfil the needs of the colony, and not to satisfy personal hunger, as flies do. In addition, the onset age of foraging is socially regulated in bees, in that it is based on the needs of the colony. For example, precocious foraging occurs when young bees sense a lack of foragers, with a process that is PHEROMONE-mediated[9]. The fly–bee behavioural comparison motivated Ben-Shahar and colleagues to use *for* as a candidate gene to study the regulation of social foraging[10]. They found that *For* (*Amfor*), an orthologue of the *D. melanogaster for* gene, is involved in the regulation of onset age of foraging in honeybees. Levels of *For* mRNA in the brain are higher in foragers than in bees working in the hive, and experimentally activating PKG causes precocious foraging. Foraging is socially regulated in honeybees;

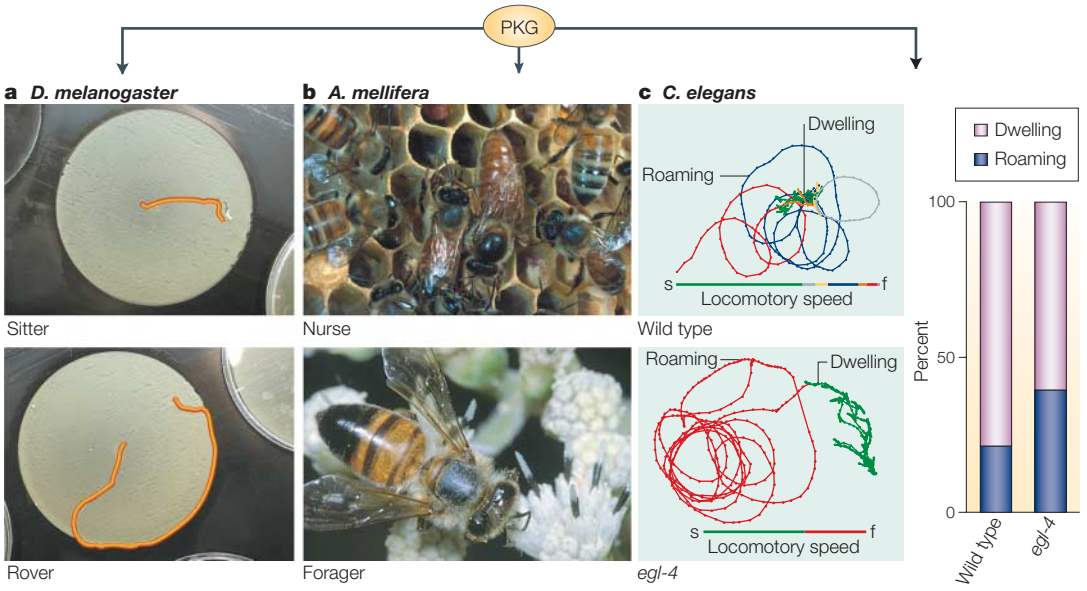

Figure 2 | **cGMP signalling pathways show strong conservation in the regulation of feeding-related behaviours.** Variation in the cyclic GMP pathway is associated with variation in the feeding-related behaviour of *Drosophila melanogaster* 'sitters' and 'rovers'[8] (larvae are shown in **a**); honeybee (*Apis mellifera*) 'nurses' and 'foragers'[10] (**b**); and *Caenorhabditis elegans egl-4* (*egg-laying defective 4*) mutant 'dwellers' and wild-type 'roamers'[15] (**c**). *egl-4* mutants spend more time in the higher-speed roaming state relative to wild-type mutants; this difference is quantified in the histogram to the right of the locomotor tracings. For *D. melanogaster* and *C. elegans*, the variation is genotypic, involving different alleles. For *A. mellifera* it is developmental, involving age-related changes in gene expression in the brain. f, fast; PKG, cGMP-dependent protein kinase; s, slow. Parts **a** and **b** are modified, with permission, from *Nature* REF. 24 © (2002) Macmillan Magazines Ltd. Part **c** is modified, with permission, from REF. 15 © (2002) Elsevier Science.

PHEROMONE
A chemical released by members of a species that influences the behaviour of other members of that species.

brain levels of *For* mRNA are also high in precocious foragers. The *foraging* gene therefore supports the idea that changes in gene regulation are associated with behavioural evolution[11]. (Other genes that are implicated in social evolution in various contexts are presented in BOXES 3,4.)

It has also been suggested that *For* is one of several QUANTITATIVE TRAIT LOCI (QTLs) that affect the tendency of a honeybee to collect either pollen or nectar[12] — another aspect of foraging that is influenced by social factors[13]. Strains that are selected for their tendency to gather either high or low levels of pollen differ in several other aspects of behaviour: responsiveness to sucrose and tactile stimuli, and onset age of foraging[12]. These findings raise fascinating questions about the GENETIC ARCHITECTURE of the various molecular pathways that underlie these behavioural phenotypes. QTL analysis in honeybees is enhanced by this organism's haplodiploid genetics, extraordinarily high rates of recombination[14], and forthcoming information from the honeybee genome sequence (see BeeBase in the Online links box).

cGMP signalling also affects feeding-associated behaviour in other species. For example, in *Caenorhabditis elegans* genotypic differences in the *for* orthologue *egl-4* (*egg-laying defective 4*) are implicated in variations in food-dependent locomotion. Allelic variants of the *egl-4* gene affect the proportion of time that the animals spend 'roaming' or 'dwelling' (FIG. 2c), owing to effects on sensory neurons that are involved in locomotion and olfaction[15]. Mutations that decrease PKG

QUANTITATIVE TRAIT LOCI (QTLs). Loci that control quantitative (that is, continuous) traits. QTLs are identified by showing a statistical association between genetic markers and measurable phenotypes.

GENETIC ARCHITECTURE
Broadly describes the distribution of gene effects that produce a given phenotype. It includes a description of the number of genes that influence the trait, their relative position and magnitude of the effects, and the nature of the interactions between them.

COMPLEMENTARY SEX DETERMINATION
Unfertilized eggs produce males and fertilized eggs produce females. This results in certain asymmetries in relatedness, including sisters being more closely related to each other than mothers and daughters. Recognition of this in the Hymenoptera (ants, bees, wasps) led Hamilton to propose kin selection as a principal force in the evolution of eusociality.

GREEN BEARD GENE
A type of gene predicted by Richard Dawkins that shows the following three effects: production of a recognizable trait (for example, a green beard), recognition of that trait in others and preferential treatment of those with the trait.

MONOGYNY
In this context, an insect society that is headed by a single female (the queen).

POLYGYNY
In this context, an insect society that is headed by many females (queens).

GENOMIC IMPRINTING
Expression of only one of two alleles of a gene owing to differential methylation of either the maternal or paternal copy.

SEXUAL SELECTION THEORY
Derived from sex-specific differences in gamete size that led to predictions of sex-specific differences in mating strategies, parental investment and genomic imprinting.

Box 3 | Population genetics meets molecular genetics in social evolution

Scientists have long been interested in the evolution of social life, especially altruism[5,99]. Advances in molecular biology and genomics now make it possible to identify genes and pathways that are involved in social evolution. Some of the most prominent findings from animals are highlighted below; microorganisms are covered in BOX 4.

Complementary sex determination (csd)

csd encodes a protein that regulates COMPLEMENTARY SEX DETERMINATION in the honeybee[85], which gives rise to haplodiploidy. Haplodiploid-induced asymmetries in relatedness between offspring and sisters in social insects have been crucial in the development of one of the most prominent theories of social evolution: kin selection[5,99]. *csd* is a novel gene, but its encoded arginine–serine (RS) domains indicate that it is related to *transformer*, which is important in *Drosophila melanogaster* (X0) sex determination. *csd* was identified by positional cloning, which was aided immensely by the very high recombination rate of the honeybee[100], especially in the region of *csd*. RNAi was used to demonstrate its function.

General protein 9 (Gp9)

This gene is involved in the regulation of queen number in colonies of the fire ant *Solenopsis invicta*[101]. The *b* allele, possibly in conjunction with alleles at genetically linked loci, mediates a GREEN BEARD GENE effect. Workers (non-reproductive) with a *b* allele (*Bb*; *b* is a recessive lethal) favour queens that also carry this allele, whereas *BB* workers favour *BB* queens. Because *Gp9* encodes a putative odorant-binding protein, its alleles might have a differential effect on the production and perception of pheromones. *Gp9* sequence analysis indicates that MONOGYNY preceded POLYGYNY in the *Solenopsis* genus. This is one of the few studies so far that has used phylogenetic approaches to infer evolutionary processes at both molecular and behavioural levels.

The major histocompatibility complex (MHC)

The MHC is a family of ~50 genes that are known in mammals for their inter-individual variability. In addition to their role in cell–cell recognition, genes in the MHC are involved in systems of behavioural recognition that have a bearing on social evolution[102,103].

Mesoderm-specific transcript (*Mest*)

Mest is regulated by GENOMIC IMPRINTING and is expressed in mice only from the paternal allele[104]. Heterozygote knockout mice that inherit a mutant allele from the paternal germline are smaller than the wild type, which is consistent with an evolutionary theory of imprinting[105] that is based on the competing interests of the two parents predicted by SEXUAL SELECTION THEORY.

Vasopressin receptor 1a (*V1aR*)

This gene encodes a receptor for vasopressin, a neuropeptide that is involved in reproductive behaviour in vertebrates. Monogamy is extremely rare in mammals and monogamous vole species have a different distribution of this gene in the brain from polygamous species, owing to variation in the V1a promoter (FIG. 4). *V1aR* gene transfer from the monogamous prairie vole (*Microtus ochrogaster*) increases the monogamous habits of the otherwise non-monogamous meadow vole (*Microtus pennsylvanicus*)[85]. Although this manipulation undoubtedly affects the expression of other genes in the brain, these results indicate that changes in the regulation of even a single gene can drive the rapid evolution of a social behaviour[85].

Vitellogenin (*Vg*)

The Vg lipoprotein is used as a yolk protein in invertebrate and some vertebrate lineages. Worker honeybees, although mostly sterile, produce vitellogenin. Expression of both mRNA and protein is highest in 'nurse' bees that use it to produce brood food rather than eggs. These findings indicate that genetic regulatory pathways for reproduction in solitary insects have been used in the evolution of insect societies[10,18,106,107] (see the section on foraging in the main text for a discussion of a similar theme).

Box 4 | **Social microbes**

Managing a social life is complicated — a consideration that has been incorporated into one prominent theory of human brain evolution[108]. But the core elements of sociality — altruism and division of labour — are possible without a brain at all, as seen in some species of microorganisms. Social microbes, with their short generation times and tractability in the laboratory, are proving especially useful for identifying genes that are implicated in social evolution, as indicated below.

Contact site (*csA*)
This gene encodes a homophilic cell-adhesion molecule and, as predicted by Haig[109], seems to function like a green beard gene. When food is scarce, the slime mould *Dictyostelium discoideum* shows reproductive division of labour: free-living individual cells aggregate into a slug, with reproductive spore cells positioned on top of non-reproductive (altruistic) stalk cells[110]. Wild-type cells are more likely to form stalk cells (that is, are more altruistic) than *csA*-knockout cells, and also preferentially allow wild-type, rather than *csA*-knockout, cells to form spore cells[111].

***dif* insensitive mutant (*dimA*)**
The transcription factor that is encoded by this gene illustrates that pleiotropy can promote altruism. *dimA* is required by *D. discoideum* to receive the DIF1 extracellular signal that causes cells to enter the pre-stalk (non-reproductive) stage. *dimA*-knockout cells ignore the DIF1 signal, evading the altruistic fate of stalk formation. They should presumably have a reproductive advantage over wild-type cells. However, in the presence of wild-type cells, *dimA*-knockout cells are excluded from the spore group, so negating any advantage they might gain by evading the stalk fate. Cheating by *dimA* loss of function is prevented because both altruism and reproduction require *dimA* function[112].

Group A signal (*asgB*)
The DNA binding protein that is encoded by *asgB* is involved in growth and development in the bacterium *Myxococcus xanthus*, which forms multicellular aggregations such as slime moulds in response to starvation. Strains that have a mutation in this gene 'cheat' and produce a higher proportion of spore cells relative to their representation in an aggregating population[113]. The maintenance of reproductive division of labour in *M. xanthus* indicates that cheating is kept in check by the effects of other to-be-discovered genes, as in *D. discoideum*. Alternatively, the persistence of cheaters could reflect the balance of population dynamic forces[114].

signalling lead to an increase in roaming, indicating that this behaviour is PKG-dependent, but with a different method of regulation from flies and bees. A similar connection between lower PKG signalling and roaming is seen in colonies of the harvester ant *Pogonomyrmex barbatus*. Foragers have lower levels of *for* expression in the brain than individuals that work inside the nest do[16].

These findings indicate the existence of pathways that are highly conserved but evolutionarily labile enough to be connected with different manifestations of the same general behaviour across diverse species. *for* might be part of such a pathway for feeding-related behaviour. Indeed, phylogenetic analysis supports the link between variation in *for* and variation in feeding-related behaviour in eukaryotes[17].

The possible existence of such pathways is of special significance because it indicates that molecular insights from simpler (for example, solitary) forms of behaviour can be used to generate candidate genes for more highly derived patterns of social behaviour. This idea is supported by studies of *malvolio* (*Mvl*), which encodes a manganese transporter. A mutation at this locus in *D. melanogaster* causes a loss of responsiveness to sucrose, and this deficit is eliminated by treatment with manganese. In honeybees, the situation resembles what is seen for the *foraging* gene; brain levels of *Mvl* (*AmMvl*) mRNA are higher in foragers than in bees working in the hive, and manganese treatment not only increases sucrose responsiveness, but also causes an earlier onset of foraging[18]. These results indicate that some genes that influence feeding behaviour in *D. melanogaster* have also been used in social evolution to regulate division of labour in insect societies.

SUBTRACTIVE HYBRIDIZATION
A technique used to identify differentially expressed genes. The DNA species present in one sample are specifically enriched by hybridizing with nucleic acids from another sample and removing the associated double-stranded molecules.

Neuropeptide Y (NPY). NPY is another molecule that seems to be involved in a well-conserved pathway for feeding-related behaviours. This neuropeptide has been studied extensively in the vertebrate hypothalamus for its involvement in regulating appetite[19]. In *D. melanogaster,* neuropeptide F, an orthologue of NPY, influences several feeding-related behaviours, including food aversion, hypermobility and cooperative burrowing[20]. In *C. elegans*, de Bono and Bargman showed that naturally occurring variation in *npr-1*, a gene that encodes a putative receptor for an NPY-like molecule, causes variation in feeding behaviour[21]. The behavioural differences are caused by a single amino-acid difference in NPR-1. Some strains of nematodes feed alone on bacterial 'lawns', whereas others aggregate while feeding.

Aggregated feeding in *C. elegans* can be induced by stressful conditions such as crowding and high concentrations of oxygen[22], but is inhibited by high NPY-like signalling in several neural circuits. In addition, nociceptive (pain-receptive) pathways promote *Caenorhabditis elegans* aggregation[23]. This result is consistent with an insight from behavioural ecology studies that show that group formation is often triggered by adverse conditions[24]. *Caenorhabditis elegans* can therefore be used to further explore the relationships between pain, stress and sociality. It is not clear whether *C. elegans* worms engage in the kinds of cooperative interactions that typically characterize social feeding[6], but to aggregate they must be able to tolerate having members of the same species in close proximity. Plasticity in this type of affinity for members of the same species might therefore be a prerequisite for more extensive social interaction. These are good examples of

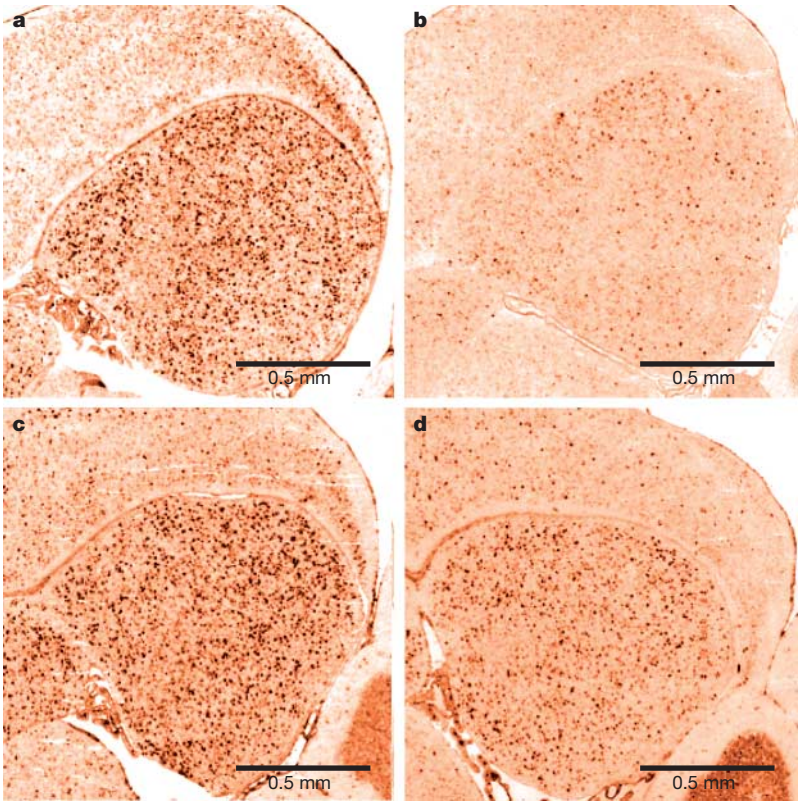

Figure 3 | **Expression of the immediate early gene *zenk* in the brain of the zebra finch (*Taeniopygia guttata*) in response to song.** The four panels show a cross section through the auditory telencephalon (caudomedial nidopallium; NCM) of the zebra finch (parasagittal plane near the midline; rostral left, dorsal up). Expression of *zenk* mRNA is visualized by *in situ* hybridization using a digoxigenin-labelled RNA probe. **a** | *zenk* expression is activated in NCM when a conspecific song is first heard; mRNA levels are especially high in response to new songs. **b** | *zenk* response habituates with stimulus repetition, apparently because songs become 'familiar'. **c**,**d** | The strength of the *zenk* response is a sensitive indicator of not only familiarity, but also stimulus context. mRNA levels increase again if a familiar song is presented from a new position (**c**) in space or (**d**) at reduced volume. The scale bar indicates 0.5 mm. Modified, with permission, from REF. 32 © (2004) Elsevier Science.

IMMEDIATE EARLY GENES
The first genes expressed in response to cell stimulation that then lead to cascades of expression of other genes.

GENOMIC ACTION POTENTIAL
David F. Clayton invoked the classical neuronal action potential to describe by analogy how gene expression, beginning with activation of immediate early genes, increases the responsiveness of neurons to key environmental stimuli.

EPIGENETIC
Modifications of chromatin or DNA (for example, histone deacetylation and cytosine methylation) that can be stably transmitted through many cell divisions, but can also be reset (unlike changes in DNA sequence).

the kind of provocative insights into social behaviour that can be obtained with a 'non-social' animal (BOX 2).

Mate recognition: genes and social signals

Gene activation is important in mediating various forms of mate recognition. In many species of bird, males attract and court females through song. In territorial species, males also use songs to recognize neighbours and potential intruders. These discrimination abilities have a significant effect on mating success, as males that are able to establish and maintain territories enjoy greater reproductive success[6].

Song production and perception has both innate and learned components. In a pioneering effort, Nottebohm, Konishi and their associates identified brain regions and neural circuits that show marked sexual dimorphism and are involved in song communication[25]. Similarities between human speech and bird song have long been noted, so it is particularly intriguing that one gene expressed in brain regions that are specialized for song perception is *FOXP2* (forkhead box P2)[26,27]. An orthologue of this gene has been implicated in the regulation of human speech by both genetic association studies[28] and evolutionary analyses involving other primate species[29]. Bird song therefore provides an excellent system in which to study socially mediated plasticity and remodelling in the adult brain, which could also lead to the identification of novel mechanisms and genes that are involved in learning and memory.

Clayton and colleagues used SUBTRACTIVE HYBRIDIZATION of cDNA libraries to show that song presentation induces gene expression in the forebrain of the male zebra finch (*Taeniopygia guttata*)[30], thereby launching a line of study on how song perception triggers activation of neural circuits through gene activation. *zenk*, an IMMEDIATE EARLY GENE that is well known in other learning and memory contexts[31], has figured prominently in molecular songbird research. *zenk* expression is activated in regions of the zebra finch brain that process auditory information when a conspecific song is heard, and *zenk* mRNA levels are especially high in response to new songs[32] (FIG. 3). Even songs that are heard for only a few minutes induce a *zenk* response, and songs heard repeatedly over the course of 2.5 hours become 'familiar' and distinguishable from other songs on the basis of the strength of the *zenk* GENOMIC ACTION POTENTIAL[31].

What is the neural circuitry that endows *zenk*, deep in the nuclei of forebrain neurons, with this extreme sensitivity, which is so necessary to respond adaptively to the nuances of social life? It is expected that insights into this question can be gained by using microarrays and other genomic resources to study the molecular pathways involved in song learning and discrimination in regions of the bird brain that are specialized for these functions[33,34]. Similar questions are being pursued with mice, which rely on pheromone-based gene activation for mate recognition[35]. Molecular analysis of mating behaviour itself also has been instructive (BOX 5; FIG. 4).

Parental care: epigenetic regulation

It goes without saying that the parent–offspring dyad is a particularly intense example of a social relationship. Parents face a 'choice' of evolutionary significance: invest time and energy in the nurturing of current offspring or initiate the next round of reproduction[6]. In many species, including humans, offspring require extended parental care to survive, leading to complex behavioural interactions between parent and offspring. Parental care shows how social interactions can influence behaviour through EPIGENETIC effects.

Epigenetic inheritance of behaviour in rats. Rat mothers (*Rattus norvegicus*) differ strikingly in how they care for their offspring. Those that lick, groom and nurse their pups extensively endow them with two important attributes: better tolerance of stress and good mothering skills when they themselves get old enough to reproduce[36]. This is because frequent contact of this type increases the expression of the gene that encodes a glucocortocoid receptor in the hippocampus, and greater hippocampal density of these receptors enables the animals to better regulate their

Box 5 | **Sex education**

Mating involves sophisticated, although often ephemeral, interactions between conspecifics. An animal obtains information about a specific aspect of its social environment — potential mates — and then adjusts its behaviour accordingly. To reproduce successfully, it must be able to discriminate between conspecific and heterospecific individuals, recognize a member of the opposite sex from one of the same sex, assess whether a potential partner is receptive to mating and discriminate between potential mates of different quality. Animals also modulate their own responses to a sexual advance in accordance with their internal condition. Errors in any of these five components of mating can be costly.

Mating is one of the best studied behaviours in molecular genetic terms for two reasons. First, mating can be studied in the laboratory; copulation and egg fertilization provide unequivocal measures of performance, that are not affected by laboratory conditions. Second, mating can be readily studied in the highly tractable genetic model animals, *Caenorhabtitis elegans*, *Drosophila melanogaster* and *Mus musculus*. Genes have been identified that affect four of the five mating components listed above: species recognition, gender recognition, assessment of sexual receptivity and modulation of receptivity in response to variation in internal physiological state. The findings and their implications, described below and reviewed extensively elsewhere[8,82,83], provide important insights that are relevant to the study of genes and social behaviour.

Many genes controlling one behaviour

The control of mating in rodents by steroid hormones is the best understood system in behavioural neuroendocrinology. Pfaff and colleagues have established LORDOSIS BEHAVIOUR as a classical system for studies on the hormonal, neural and molecular bases of behaviour[115]. This knowledge has been used to show that many genes involved in steroid hormone pathways are involved in modulating neural circuits that control rodent mating. We expect that many genes will be implicated in the control of many, if not all, social behaviours.

One gene controlling many behaviours

Pleiotropy is rampant for genes that influence mating in flies. CLOCK GENES and 'learning' genes are also 'mating' genes, so highlighting the fallacy of naming genes in this way. Pleiotropy is probably the rule rather than the exception for behaviour[8]. This is especially the case for social behaviour, which is typically a product of many sensory, integrative, motivational and motor processes.

Activational and organizational roles of genes in behaviour

Some genes, such as those involved in determining the onset age of foraging in honeybees, seem to modulate neural circuits to cause ACTIVATIONAL EFFECTS on behaviour. The *fruitless* gene (*fru*) in *D. melanogaster* affects courtship behaviour through an ORGANIZATIONAL EFFECT[116]. The male-specific isoform of FRU, a BTB-ZF transcription factor (which is a zinc-finger protein of the BTB, or POX domain, family), functions during pupal development to generate neural circuits that are required during adulthood for courtship. This is analogous to the organizational effects that are mediated by sex hormones in vertebrates[115].

LORDOSIS BEHAVIOUR
The posture of a female rodent when receptive to mating; includes raised tail and hind quarters, and an arched back.

CLOCK GENES
Genes that are involved in the production and regulation of circadian (intrinsic daily) rhythms.

ACTIVATIONAL EFFECT
In behavioural endocrinology, relatively rapid behavioural effects that are caused by actions of a hormone increase or decrease on established neural systems. This concept can also be usefully applied to describe similar effects that are caused by gene products.

ORGANIZATIONAL EFFECT
In behavioural endocrinology, hormone effects that occur early in development and result in permanent changes in adult neural systems, and so behaviour. This concept can also be usefully applied to describe similar effects that are caused by gene products.

SEROTONIN
A biogenic amine that can function as a neurotransmitter, neuromodulator or neurohormone, and controls many physiological and behavioural processes.

GENOTYPE X ENVIRONMENT INTERACTION
The influence of specific combinations of genetic and environmental factors on a trait that goes beyond the additive action of these factors. This can refer to genes that control sensitivity to the environment or environmental factors that influence gene expression.

AMYGDALA
Region of the vertebrate brain that is involved with emotions, including anger and fear.

response to stress hormones. Pups that receive less care grow up with fewer glucocortocoid receptors in the hippocampus, larger fluxes of stress hormones, increased fearfulness and they bestow less care on their offspring.

Meaney and colleagues[37] have shown that the effects of high levels of maternal care involve histone acetylation and DNA demethylation in the promoter region of the glucocortocoid-receptor gene, specifically of a response element for nerve growth factor inducible protein A (NGFIA, also known as EGR1). These epigenetic changes increase the ability of NGFIA to upregulate the expression of the glucocortocoid-receptor gene. Individuals from litters that experienced poor maternal care and were treated with an inhibitor of histone deacetylation showed the high levels of stress tolerance and glucortocoid-receptor gene expression typically seen after a more attentive upbringing. It will be exciting to learn in the future just how variation in maternal care manages to leave different 'etchings' on the genome.

Epigenetic inheritance of behaviour might have an adaptive significance by enabling rat mothers to produce offspring with temperaments that are appropriate for prevailing environmental conditions[38]. For example, if rats in nature responded to harsh conditions by reducing maternal care, the resulting fearful and cautious offspring might themselves fare better under such conditions.

Epigenetic inheritance of behaviour in primates. Maternal effects that are similar to those observed in the rat have been detected in rhesus macaques (*Macaca mulatta*). Stressful rearing conditions cause changes in adult behaviour, but epigenetic mechanisms have not yet been reported. The strength of the maternal effects in the rhesus macaque varies with genotype at the locus encoding a SEROTONIN transporter (5HTT)[38], providing an excellent example of how interaction between the genotype and the social environment can influence behaviour, in this case for an identified gene. Suomi speculates that genotypic variation for the impact of early experiences on adult behaviour might also be adaptive for macaques in certain environments[38]. Another GENOTYPE X ENVIRONMENT INTERACTION that involves the *5HTT* gene has been reported for 'resilience' in humans[39]. Functional magnetic resonance imaging analyses revealed that people with the 'short' allele for this gene show increased neuronal activity in the AMYGDALA when exposed to social stress, which might explain the association of this allele with increased fearfulness[40].

Genes that are responsive to social status

Dominance hierarchies. For some animals, social interactions are fleeting or limited to only certain aspects of life. For animals that live in a society, nearly all activities are influenced by interactions with other society members, and in most cases, dominance hierarchies structure these interactions. Dominance hierarchies govern access to necessary resources and determine who reproduces and how often[5]. Animals show astounding abilities to assess their position in a hierarchy and respond accordingly[41,42].

Social status has a profound influence on the physiology of society members. In vertebrates, this is mediated primarily by circulating stress hormones such as cortisol and their effects on immune and brain systems[43], including neurogenesis[44]. In some cases, such as the African TELEOST *Haplochromis* (*Astatotilapia*) *burtoni*, the hierarchy is dynamic, and genes are involved in orchestrating changes in behaviour that enable an individual to respond adaptively to its current social status. In other societies, such as those formed by social insects, the hierarchy is even more structured.

***Dominance-related interactions in* Haplochromis burtoni.** The regulation of dominance hierarchies in *H. burtoni* provides another example of a gene that, similar to *for*, is involved in a non-social behaviour but has been used in social evolution. *Haplochromis burtoni* has two forms of males. Dominant males are aggressively territorial, brightly coloured, have high levels of circulating testosterone and enjoy high levels of reproductive success. Subordinate males lack all these attributes and their derived reproductive advantages. Fernald, Hoffmann and colleagues[45,46] showed that dominant males have larger hypothalamic neurons that contain the neuropeptide gonadotropin-releasing hormone (GnRH) than subordinate males. This neurohormone has a crucial function in the HYPOTHALAMIC PITUITARY AXIS, which controls physiological and behavioural aspects of reproductive maturation in vertebrates. The larger size of these neurosecretory cells indicates the capacity for increased neurohormone release[47]. Larger cells also reflect increased expression of the *GnRH* gene.

GnRH expression in *H. burtoni* is sensitive to changes in social context[45]. Dominance hierarchies are fluid, with a great deal of turnover of the territories used by males to attract females. Non-territorial males that move up in social rank and acquire a territory rapidly show an increase in *GnRH* gene expression and acquire the suite of characteristics that is associated with dominance. This social reponsiveness seems to be due to just one of the three *GnRH* genes in the *H. burtoni* genome, indicating the involvement of gene duplication and specialization in social regulation[11,48]. As is the case for songbirds, new genomic tools and resources such as EST databases and expression microarrays are being developed for *H. burtoni* and other fish[49] (see Stanford Genome Evolution Center in the Online links box) to further understand the genomic responses that enable the social environment to sculpt brain and behaviour.

Dominance-related interactions in other animals. In many animal societies, dominance-related interactions begin with threatening behaviours before developing into fully fledged aggression, and often this posturing is sufficient to decide the outcome and produce a winner and loser. In the dominance hierarchies of crayfish (*Procambarus clarkii*) and other animals, winners are more likely to dominate in future encounters, whereas losers are more likely to retreat[50]. The effects of this previous social experience in crayfish are mediated, in part, by social regulation of two serotonin-receptor subtypes, 5HT1 and 5HT2, but it is not yet known whether these socially mediated changes are due to transcriptional or post-transcriptional mechanisms. 5HT1 and 5HT2 receptors affect the excitability of peripheral lateral giant (LG) neurons that influence dominance behaviour[51]. Dominant individuals have more excitable LG neurons, possibly owing to an increase in 5HT2-mediated signalling, and they are less likely to retreat during an

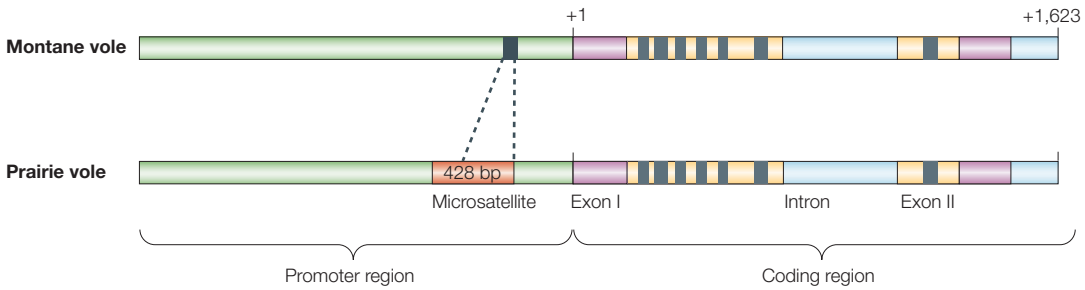

Figure 4 | **The vasopressin receptor 1a gene and monogamy in voles.** The diagram shows a schematic of the promoter of the vasopressin receptor 1a (*V1aR*) gene. Monogamous and polygamous species of vole show different spatial patterns of expression of this gene in the brain. Viral vector-mediated gene transfer demonstrated that species differences in both spatial expression of the *V1aR* gene and mating habits are due to variation in the V1a promoter. A 428-bp insert, present in the monogamous prairie vole, is absent in the polygamous montane vole. This insert is also present in another monogamous species (*Microtus pinetorum*) and absent in another polygamous species, *Microtus pennsylvanicus* (not shown here). Variation in the V1a promoter might also contribute to inter-individual differences in behaviour in prairie voles[123]. Modified, with permission, from *Nature Reviews Neuroscience* REF. 121 © (2001) Macmillan Magazines Ltd.

TELEOST
A group of bony fish that includes nearly all the important food and game fish, and many aquarium fish.

HYPOTHALAMIC PITUITARY AXIS
Endocrine and neuroendocrine tissues that together control physiological and behavioural aspects of reproductive maturation in vertebrates. Gonadotropin-releasing hormone (GnRH), made in the hypothalamus, causes the pituitary to release gonadotropins, which leads to the release of gonadal steroid hormones.

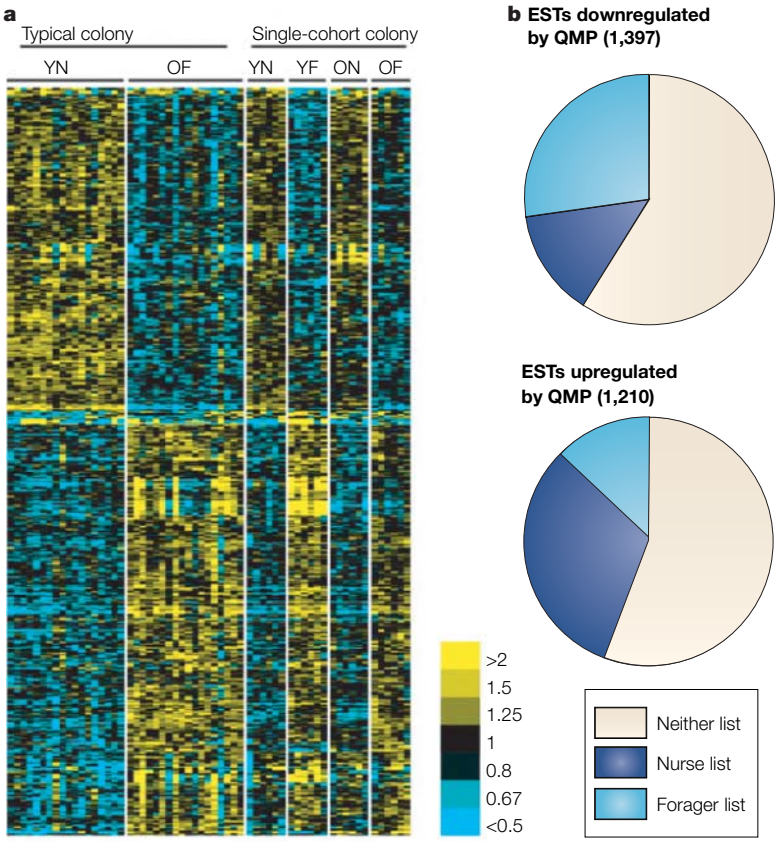

Figure 5 | **Brain gene-expression profiles are associated with division of labour in honeybees. a** | Gene-expression levels are indicated by a colour scale for each of the 60 individual bee brains (columns) that were profiled with cDNA microarrays[76]. Sample groups from typical colonies were used to obtain young nurses (YN) and old foragers (OF). Single-cohort colonies (composed of bees of the same age) were used to uncouple age and behaviour and obtain YN and young foragers (YF) and OF and old nurses (ON). Only the 548 cDNAs that have >1.25-fold (see colour key) mean difference between nurses and foragers are shown for graphical purposes (cDNAs are arranged on the Y axis by hierarchical clustering; tree not shown). Overall, about 40% of the ~5,500 genes that were analysed showed differential expression between nurses and foragers. Modified, with permission, from REF. 76 © (2003) the American Association for the Advancement of Science. **b** | Many of the differentially expressed genes in panel **a** are also influenced by exposure to physiological factors that are known to affect honeybee division of labour, such as juvenile hormone[77] and queen mandibular pheromone (QMP)[78]. Exposure to QMP delays the onset age of foraging and, as this panel shows, it also downregulates hundreds of genes, many of which are upregulated in the brains of forager bees. Genes with patterns of regulation in the brain that are consistent across multiple experiments such as these are the most attractive candidates for functional analysis.

EUSOCIAL
Social species that show three features: an extreme dominance hierarchy — with some individuals reproducing a great deal and others little or not at all — overlapping generations of adults in the nest and cooperative care of offspring.

CASTE
In insect societies, a group of individuals that specialize in carrying out particular tasks. This behavioural specialization is often associated with differences in age, anatomy and morphology.

encounter. Subordinate individuals show an inhibited LG neuron response and an increase in 5HT1-mediated signalling, and they are more likely to retreat. Therefore, these serotonin receptors are involved in a reciprocal network in which the modulatory effects of serotonin on dominance behaviour are in turn influenced by the animal's social status. The role of serotonin in aggression seems to be widely conserved in arthropods and vertebrates[38]. The *MAOA* (monoamine oxidase A) gene, which encodes an enzyme that is involved in the metabolism of serotonin and other biogenic amines, has been implicated in aggression on the basis of human linkage analyses[52] and experiments with transgenic mice[53], but pleiotropic effects of this gene can lead to differences in interpretation[54].

Insect societies: coordinated gene expression

Social insects — ants, bees, wasps and termites — are the best-known EUSOCIAL species[55–58], and they live in the most structured animal societies on Earth. Eusociality is rare, but highly successful. In some tropical habitats, ants and termites are the dominant life forms on a biomass basis, despite their tiny individual size[59]. In addition, other than humans, only eusocial insects are known to possess symbolic language (honeybees), agriculture (fungus-growing ants and termites), tournament-based warfare (honeypot ants) and a high-density lifestyle with colony populations of hundreds of thousands or even millions of individuals. Eusocial species have a CASTE system featuring queens, who are mainly responsible for reproducing the colony, and workers, who carry out all the tasks required for colony development and growth. In 'advanced' eusocial species, the fate of an individual — queen or worker — is determined long before adulthood, and there is far less dominance-related aggression among individuals than in other animal societies. This sets the stage for COLONY-LEVEL SELECTION to create systems of division of labour among groups of highly specialized workers and intricate forms of communication to integrate their activities. Early indications from microarray studies are that castes and division of labour depend on the coordinated expression of many genes.

Division of labour: environmental and genetic influences. Caste determination in many insect societies is environmentally mediated, with nutrition and endocrine signalling functioning as proximate factors — better-fed individuals develop into queens[60]. In advanced eusocial species, queens and workers differ strikingly in morphology and behaviour. Workers are generally smaller than queens, and, in ants, are wingless. RNA DIFFERENTIAL DISPLAY and cDNA array analysis has revealed extensive differences. For example, queen-destined larvae have higher expression of respiration-related genes, which could be related to their increased growth rate and body size[61–63]. To study the molecular basis of wing loss in ant workers, Abouheif and Wray[64] measured the expression of wing-development genes that function in a hierarchical network (genes such as *ultrabithorax, extradenticle, engrailed, wingless, scalloped* and *spalt*) and are highly conserved in *D. melanogaster* and other insects. To their surprise, winglessness was not associated with a break at the same node of the network in all ant species examined — different species showed inactivation at different points. These findings provide a good example of how different genomes can achieve the same end in different ways, although the genes that are involved are similar.

Recent findings indicate that caste determination in some ants is also influenced by genotypic variation[65], contrary to the long-held idea that only environmental variables are involved in determining which larvae develop into queens[55]. Genes associated with caste determination in aphids and termites have also been identified[66,67]. Further molecular studies of caste determination in social insects can contribute significantly to our understanding of how hereditary and environmental information affect the genome to orchestrate development.

Division of labour: age-related influences. In many insect societies, there is a further division of labour among workers on the basis of behavioural specializations that are associated with age[55]. Using the candidate-gene approach, several genes that are involved in neural plasticity (*period*, *acetylcholinesterase* and *inositol 1,4,5-triphosphate 3 kinase*) have been found to be differentially expressed in the brain between honeybees that are engaged in brood care ('nurses') and foragers[68–71]. Unlike for *For*[10] and *Mvl*[18] (see earlier section on foraging), it is not yet known whether these expression changes are causally related to the transition from hive work to foraging or a consequence of foraging. There is also differential expression of other genes in exocrine glands that produce substances used for various occupations such as nursing, foraging and defence[72,73].

Age-related division of labour in honeybees has also begun to be studied with microarrays[74–79]. Whitfield *et al.*[76] reported that nurses and foragers show differences in brain mRNA abundance in about 40% of the ~5,500 genes analysed (out of an estimated 14,000 genes in the bee genome). Studies of 'precocious foragers' (see earlier section on foraging) indicate that the expression of many of these genes is socially regulated. The nurse–forager differences were so robust that mRNA profiles from individuals correctly predicted the behaviour of 57 out of 60 bees, although whole brains were profiled (FIG. 5). Molecular analyses of other behavioural specializations are also underway[79,80]. Results from microarray experiments indicate that many molecular pathways are involved in regulating the behavioural maturation of honeybees. Rather than forming one central mechanism, perhaps they form a network of interlinked pathways, which might provide robust and flexible regulation in the face of ever-changing environmental and social conditions[68].

Future prospects and challenges

Exciting progress has already been made in identifying genes that influence social behaviour and in explaining some of the ways in which social behaviour influences genome function. These findings, together with the equally important discoveries of genes that are implicated in the evolution of social behaviour, will help to attain the goal of a comprehensive molecular understanding of social life.

Achieving this goal presents a considerable challenge. Social phenotypes, especially behavioural phenotypes, are especially difficult to study. Many social behaviours are sensitive to context and must be studied under natural conditions. This means that behavioural analysis must be approached with creativity, in both the field and the laboratory. An eclectic mix of species is required to capture the broad range of phenomena that is encompassed by sociality. One way to enhance the possibilities with this mix is to cluster model social species around other species with the best genetic and genomic resources; for example, voles and mouse, bee and fly, songbirds and chicken, and cichlids and zebrafish. There also must be strong efforts to further enhance the value of model social species by developing genomic resources such as EST collections, microarrays, and a wide variety of freely available cDNA and genomic libraries. For the most compelling species, strong efforts should also be made to obtain full genome sequences, which at present is the best resource for analysing genes and genomes.

A truly rigorous molecular analysis of sociality requires the ability to establish causal relationships between the effects of genes on social behaviour, and vice versa. This means increasing or decreasing the expression of specific genes in specific tissues or brain regions at specific points in the life of an animal (however, gene targeting also has some limitations, especially for

COLONY-LEVEL SELECTION
A special form of group selection, first described by Charles Darwin, to explain the evolution of altruistic (sterile) workers in insect societies.

RNA DIFFERENTIAL DISPLAY
A technique for detecting those genes that are expressed only under specific conditions. It involves isolation and comparison of mRNA from two or more populations, PCR amplification of mRNA and resolution on a DNA-sequencing gel.

ENDOPHENOTYPE
A component of a complex behavioural phenotype that can facilitate the identification of relevant genes and elucidate their function. An endophenotype can involve a simpler behaviour or an underlying endocrine or neural mechanism.

MUSHROOM BODIES
A region of the insect brain that is involved in multimodal sensory integration, learning and memory.

Box 6 | Behavioural dissection to understand how genes influence social behaviour

It is much harder to work out how a gene influences the expression of a social behaviour than to determine whether it does so in the first place. There is a long and winding road that extends from gene products to molecular pathways to neural circuits in the brain. Dissecting a complex behaviour into component modules[18,117] or ENDOPHENOTYPES[118] can help, as the following examples demonstrate.

Upregulation of the *foraging* gene in the bee brain affects the onset age of foraging (see the foraging section in the main text). One effect is a PKG-induced increase in positive phototaxis[119]. *For* is preferentially expressed in the optic lobe and in a subset of intrinsic neurons in the MUSHROOM BODIES that process visual information[10]. Bees live in a dark hive, and an increase in positive phototaxis positions them closer to the hive entrance. There they seem to be stimulated to forage by exposure to other stimuli, such as successful foragers communicating by means of the dance language[120].

Differences in the distribution of the vasopressin receptor 1a (*V1aR*) gene in the brain cause monogamy or polygamy in voles (BOX 3; FIG. 4). Insel and Young[121] suggested that monogamy might be a form of 'addiction'. They note that monogamous (prairie) voles have more V1a receptors in regions of the brain that form the mesolimbic 'reward' system than polygamous species, and the surge of vasopressin that occurs on mating stimulates dopaminergic reward circuits in these regions. This might help form the lifelong bonds that characterize the prairie vole lifestyle. Similarly, pups from a line of knockout mice that lack the opioid receptor-μ gene show a deficit in attachment behaviour to their mothers, perhaps because maternal stimuli can no longer be perceived as highly rewarding or pleasurable[122]. Neurobiological models of addiction can therefore be used to help explain how these genes influence social behaviour, and vice versa. Dissection into component behavioural modules should lead to a better understanding of how genes influence social behaviour.

CHRONOBIOLOGY
The study of how organisms keep time, from circadian rhythms to seasonal changes, at all levels of biological organization.

NANOVECTOR
A nanoparticle that can be used to deliver nucleic acids and drugs.

HOMEOBOX GENES
Genes that contain a 180-base-pair sequence involved in the regulation of animal and plant development. This sequence encodes a DNA-binding helix–turn–helix motif, indicating that homeobox-containing gene products function as transcription factors.

behavioural experiments[81]). Gene targeting is done routinely in model genetic organisms, notably in studies of learning and memory and CHRONOBIOLOGY[8,82,83]. Sociogenomics will undoubtedly benefit from intense interest by the pharmaceutical industry in developing new therapeutics that affect the genome, using techniques such as RNAi[84], viral vectors[85] and NANOVECTORS[86]. RNAi already is being used to test hypotheses of gene function in animal species that are favourable for studies of sociality but lack advanced genetic (breeding) resources[84,87].

New developments in genomics also hold great promise for this enterprise. There are efforts to develop 'universal arrays'[88], which would allow extensive gene-expression profiling for all species, and not just those for which extensive sequence information is already available. There is also great interest in developing innovative methods to radically shrink sequencing costs; the US National Institutes of Health have released a request for applications for the '$1,000 human genome', that is, techniques to resequence the genome of individuals for both research and diagnostic purposes[89]. If this goal is achieved, the cost of sequencing new genomes could also drop precipitously, so increasing the number of species that can be studied with genome-enabled resources. Advances in proteomics[90] and systems biology[91] also promise to contribute greatly.

This programme of research requires using genomics to integrate molecular biology, neuroscience, behavioural biology and evolutionary biology. One important challenge is to understand the manner in which molecular pathways affect brain circuits to influence behaviour. Dissecting complex social behaviours into simpler behavioural modules can help to understand these relationships (BOX 6).

Another important challenge is to learn more about the molecular basis of social evolution. This can be done by emulating the field of developmental biology, which has been successful in discovering molecular mechanisms that underlie the development of certain morphological traits and then using that information as a foundation to study evolutionary questions that are related to that trait. One of the best examples of this approach concerns the role of HOMEOBOX GENES in both wing development and the evolution of variation in wing number in several insect species[92]. The 'evo-devo' approach promises to achieve advances in our understanding of social evolution that are of comparable importance. The first insights of this type can be seen in the study of PKG and GnRH signalling (see the earlier sections on foraging and genes that are responsive to social status, and the vitellogenin example in BOX 3). Studies in this field benefit from knowledge of behavioural evolution gained from behavioural ecology studies[4,93]. Finally, new informatics approaches are required to derive maximum benefit from this broad synthesis (see the BeeSpace web site in the Online links box).

Conclusions

This review highlights two emerging themes that relate to the connection between genes and social behaviour. First, genes involved in solitary behaviour are also used for social behaviour. The possible existence of evolutionarily labile pathways indicates that molecular insights from simple behaviour can be used to generate candidate genes for more highly derived patterns of social behaviour.

The second is that the genome is highly sensitive to social influence. Social regulation of gene expression has a powerful influence on behaviour. As gene regulation becomes better understood[94], it will be important to determine the extent to which sociality involves unique forms of transcriptional regulatory codes, as well as novel genes[11].

Socially induced changes in gene-expression profiles, currently captured most easily by microarray analysis, are themselves a new type of social phenotype. Brain gene-expression profiles represent the first manifestation of the interaction between hereditary and environmental information[95]. Transcriptomes, especially for social behaviour, are highly dynamic, in contrast to earlier genetically based models of behaviour that tended to be rigid and deterministic. Our new-found appreciation for the responsiveness of the genome to social influence provides a biological basis for what observers of animal and human societies have long known: that flexibility is the hallmark of behaviour.

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Acknowledgements

We thank H.A. Hoffman and R.E. Lenski for helpful advice. We also thank A.B. Barron, Y. Ben-Shahar, G. Bloch, S.E. Fahrbach, A.L. Toth, B. Schatz, M.B. Sokolowski and three anonymous reviewers for comments that improved the manuscript. Research by the authors was supported by grants from the US National Institutes of Health, US National Science Foundation, US Department of Agriculture and the Burroughs Wellcome Trust (G.E.R.), a University of Illinois-Beckman Postdoctoral Fellowship (C.M.G.), and a US National Science Foundation Postdoctoral Fellowship in Bioinformatics (C.W.W.).

Competing interests statement

The authors declare no competing financial interests.

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http://www.life.uiuc.edu/robinson/
http://www.cals.ncsu.edu:8050/entomology/grozinger/
http://www.life.uiuc.edu/cwwhitfield/

Online Summary

- Studying the molecular basis of social life (sociogenomics) requires an integration of molecular biology, genomics, neuroscience, behavioural biology, evolutionary biology and new forms of bioinformatics.
- An eclectic mix of species that show varying levels of sociality is being used to study the molecular basis of social life, especially social behaviour.
- Sociogenomics is predicated on two of the most significant insights in biology to emerge from the later half of the twentieth century. First, social life has a biological basis and is therefore influenced to some extent by genes and the forces of evolution. Second, the molecular functions of many genes are highly conserved across species, even for complex traits such as behaviour.
- Genes have been identified that both regulate social behaviour and that are implicated in the evolution of social behaviour.
- One emerging theme that relates to the relationship between genes and social behaviour is that genes involved in solitary behaviour are also used for social behaviour.
- A second theme is that the genome is highly sensitive to social influence, through social regulation of gene expression in the brain.
- A transcriptomics-based approach is the method of gene discovery most easily used for model social species.

Online links

Entrez

egl-4
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=176991

EGR1
http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=6681285

for
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=44817

For
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=406092

FOXP2
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=93986

Mvl
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=42490

BeeBase:
http://racerx00.tamu.edu/PHP/bee_search.php

BeeSpace:
http://www.igb.uiuc.edu/beespace/

Charles Whitfield's web page
http://www.life.uiuc.edu/cwwhitfield

Christina Grozinger's web page:
http://www.cals.ncsu.edu:8050/entomology/grozinger

Stanford Genome Evolution Center:
http://cegs.stanford.edu/index.jsp

The Robinson Laboratory:
http://www.life.uiuc.edu/robinson