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Review

Sensory genes and mate choice: Evidence that duplications, mutations, and adaptive evolution alter variation in mating cue genes and their receptors

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Abstract

Fascinating new data, revealed through gene sequencing, comparative genomics, and genetic engineering, precisely establish which genes are involved in mate choice and mating activity—behaviors that are surprisingly understudied from a genetic perspective. Discussed here are some of the recently identified visual and chemosensory genes that are involved in mate choice and mating behavior. These genes' products are involved in the production, transmission, and receipt of crucial sensory mate-choice cues that affect fitness. This review exposes newfound evidence that alternative splicing, gene-expression pattern changes, and molecular genetic variation in sensory genes are crucial for both intra- and interspecific mate choice and mating success. Many sensory genes have arisen through gene duplications, and data amassed from studies conducted at scales ranging from individual genes to genomic comparisons show that strong, positive Darwinian selection acts on several mating-related genes and that these genes evolve rapidly.
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Keywords: Mating behavior; Mate choice; Pheromone; Opsin; Ultraviolet; Vision; Gene; Genome; Selection; Duplication

Contents

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A major challenge posed to sexually reproducing individuals is selecting an optimal mate from a wide variety of potential mates. Mate choice involves sensory cues that provide information allowing for the evaluation of the quality of prospective mates. Despite a copious literature addressing mating *behavior* there has been a surprisingly depauperate literature regarding the *genetical* control of mating-related behaviors, such as mate choice, until recently. Theoretical [1–4] and empirical studies justifying mate choice abound [5–7] and have been extensively reviewed [8,9]. These works demonstrate the fitness advantages of choosing a good mate, such as more-fit genotypes contribute better genes, and/or produce more (or higher quality) offspring, and/or provide more resources than alternative prospective partners do. Under the assumption of good genes' benefits for offspring from high-quality mates, even costly mate choice can evolve readily and subsequently result in the coevolution of exaggerated secondary sexual traits [10]. The comprehensive background demonstrating the benefits to mate choice, and substantiating the coevolution of preference and secondary sex traits, creates an excellent launch-point for this review. Thus, in this work, I draw a clear association between sensory genes (primarily visual and chemosensory) and mate choice (or mating behavior) and review the genetic basis underlying sensory mate choice, while highlighting some of the surprising, recent comparative genomic and molecular genetic data regarding mating-related genes. These studies, combined with studies of genetic engineering, clearly associate mate choice (or mating behavior) with molecular genetic variation in specific sensory genes. I show that traits involved in mating behavior often arise from genes that have undergone duplication, typically multiple duplications, historically and recently, indicating the importance of gene duplication for providing the genetic variation in sensory genes that is co-opted for use in mate choice. I also summarize the type and strength of selection acting on mating behavior (when known) and show that traits associated with mating are often under strong selection and evolve rapidly. It is noteworthy that the majority of visual studies to date have been conducted primarily in birds and fishes, in part because these taxa are particularly colorful (and visual)—hence the emphasis on them in the visual section of my review. In contrast, other taxa (e.g., mammals and invertebrates) are the primary focus of chemosensory work, since they have a highly developed sense of smell and/or chemical communication, and are highlighted disproportionately in the olfactory section of this review. While we now realize that visual, auditory, and chemosensory cues may all be a part of an individual's mate choice, there is a vastly depauperate literature addressing the effects of the interaction of multiple mate-choice cue-types on the genetic inheritance of individual cues. Perhaps this is because we are only just beginning to identify the association between the genes involved in mate choice, and individual sensory signals, which will now be discussed.

Visual signals and mate choice

Opsin gene duplications and color vision

The brilliant, sexually selected blue and chestnut coloration of bluebirds (*Sialia sialia*) and the deep-red hues found on the otherwise drab male house finch (*Carpodacus mexicanus*) are honest signals of quality that can be assessed by prospective mates [11–15]. Here, bold coloration signals increased relative survival and mate provisioning [11,14,15]. Many species transmit such heritable, visual mate choice cues [16–19]. However, for these cues to be valuable (e.g., [20]) cue recipients must possess the appropriate visual pigments that absorb the precise light wavelengths of the cues. Opsin genes produce the visual pigments found in retinal cones. These pigments work in combination with light-absorbing chromophores to provide color vision [21]. The vertebrate classes of opsins providing color vision vary among taxa somewhat, but basically include the following (A) short-wavelength sensitive (SWS1 and/or UV) opsins, which have a λ_{max} (or light wavelength absorbance maximum) of 360–430 nm. In birds, fish, and mammals, SWS1 is blue-violet and/or ultraviolet sensitive [22]. (B) Another class of opsins that is also short-wavelength sensitive (SWS2; λ_{max}=440–460 nm) is blue-sensitive in birds [24]; blue- (SWS2-A) and violet-sensitive (SWS2-B) in fish [25]; and has not been found in mammalian genomes [23]. (C and D) Long- to middle-wavelength sensitive (LWS/MWS; λ_{max}=510–560 nm) opsins are red/green-sensitive in birds, fish, and some mammals [27]. RH2 are also MWS (λ_{max}=470–510 nm) opsins which have not been found in mammalian genomes [23] but are green sensitive in fish [28,29] (Fig. 1A) [21,22]. In addition, oil droplets with different carotenoid contents occur in bird cones and contribute to determining spectral sensitivity [30].

In general, gene duplication has allowed for a wide-range of color detection in many taxa. Consider that the vertebrate ancestor had only one LWS pigment [31]. However, Old World monkey species' comparisons indicate that the X-linked LWS/MWS genes, found in tandem and flanked by a single locus control region, are a result of gene duplication ~40 million years ago [32,33]. In fact, most diurnal primates, as well as many fishes, birds, reptiles, and other mammals, have trichromatic (LWS/MWS/SWS red/green/blue) vision [34], and howler monkeys are the only New World monkey species with trichromacy (others have only one X-linked opsin), which is also a result of duplication [35]. In fish, multiple duplications have occurred independently in different lineages, providing, zebrafish for example, with eight opsins that are found in two gene clusters (SWS1, LWS1, and LWS2 in tandem and RH2-1, RH2-2, RH2-3, and RH2-4 in tandem [25]). For vertebrates in general, genomic sequence comparisons indicate that four of five paralogous opsin genes have actually arisen through independent duplication events [29,36]. When functional duplications diverge, they allow for a wider array of color detection, thus having ramifications for sexual selection and mate choice, particularly in very colorful taxa.

Molecular evolution in cichlid opsins

Like zebrafish mentioned above, the colorful rock-dwelling African cichlid species of Lakes Victoria and Malawi also have eight opsin genes that resulted from multiple, rapid duplication events [21,27,37,38] (Fig. 1B). Each opsin codes for a distinct, visual pigment [38]. Positive selection occurs on all but two

(SWS1 and SWS2-B) opsins, and visual selective pressures differ between clear- and turbid-water cichlid lineages [28,39]. Rapid radiation of the hundreds of colorful lake species has occurred, and evidence for adaptive evolution is seen in the LWS (red-sensitive) opsin in Lake Victoria (and satellite Lake Nabugabo). This is a turbid lake, and as such, transmits reds better than other colors. Directional, sexual selection has been demonstrated for female mate choice on the red nuptial coloration in male *Pundamilia nyererei* (see Fig. 3B) [40]. The LWS opsin shows very high molecular genetic variability (e.g., 14 alleles) compared to SWS2-B and other nuclear genes (maximum 2 alleles) in species from this lake, and nucleotide variation occurs at a much higher rate in exons than in introns, in which there are also more nonsynonymous than synonymous changes, several of which are predicted to shift absorption sensitivity [21]. Parallel, divergent selection of LWS opsins occurs in four species from this lake, in more- versus less-turbid environments, in which male nuptial coloration and LWS allele-type are positively associated (more males with red-shifted LWS alleles in more turbid environments) [41]). In contrast, LWS genes displays relatively little genetic variability in fish from Lake Malawi, a clear-water lake, where more colors can be transmitted in the water column [21]. As well, body coloration is broadly similar among the lakes for several species. However, consistent with an adaptive scenario that addresses the importance of the association between environment and mate choice, yellow markings in Lake Malawi fish are often red in Lake Victoria fish, where they might not be visible if yellow, in Lake Victoria's turbid water [21].

Recent genomic analyses of over 2000 cichlid amplified restriction fragment length polymorphisms (AFLP; from 59 genomes) have allowed for the construction of a phylogeny that demonstrates evidence for divergent selection during speciation, as displayed in the repeated, parallel evolution of male cichlid color patterns (e.g., [42]). SWS1 has recently been proposed as a generally useful marker for constructing vertebrate phylogenies (based upon substitution characteristics and sequence evolution) [22]. Constructing an SWS1 phylogeny to determine whether this gene shows evidence of divergent selection in the rock-dwelling cichlids would be quite instructive and might reinforce the AFLP results. While molecular evidence of selection on LWS opsins exists, many colors are used in mate choice in cichlids and additional types of associations between male coloration, gene expression, and mate choice have been identified.

Empirical demonstrations associate opsin variation, mate choice, and body color patterns

Males from sympatric rock-dwelling African cichlid species generally display dramatically different body-color patterns [43] that cannot be explained by factors like habitat matching [44]. Males display at leks where females select mates based on their bright, nuptial colors [28]. Mate choice is argued to maintain reproductive isolation in many cichlid species [45]. Hybrids can be found in nature—sometimes where visual signals are obfuscated by low water clarity [43,46], once again indicating the impact of ecological parameters on the visual cues used for mate choice. In empirical studies, when male color-pattern differences are muted via monochromatic light, females do not display mating preferences [47]. Several demonstrations of the association between opsins best suited to particular color

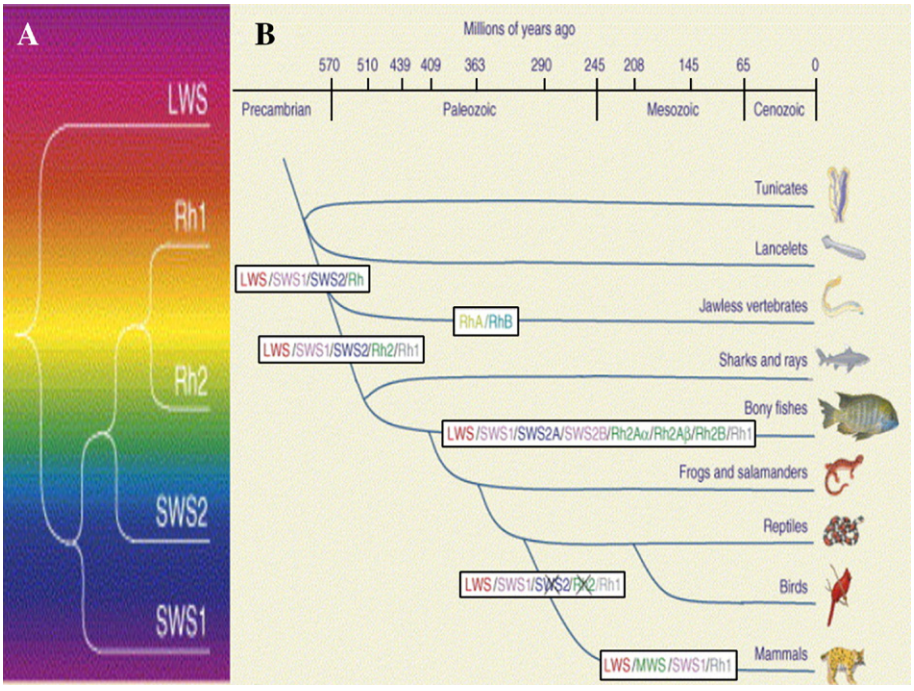

Fig. 1. (A) Basic relationship between opsin gene lineages depicted atop colors for which each protein is maximally sensitive. Reprinted from [27], Cell Press (2005), with permission from Elsevier. (B) Phylogenetic association depicting multiple duplications of the opsin genes within lineages over evolutionary time. Reproduced from [27], Cell Press (2005), with permission from Elsevier.

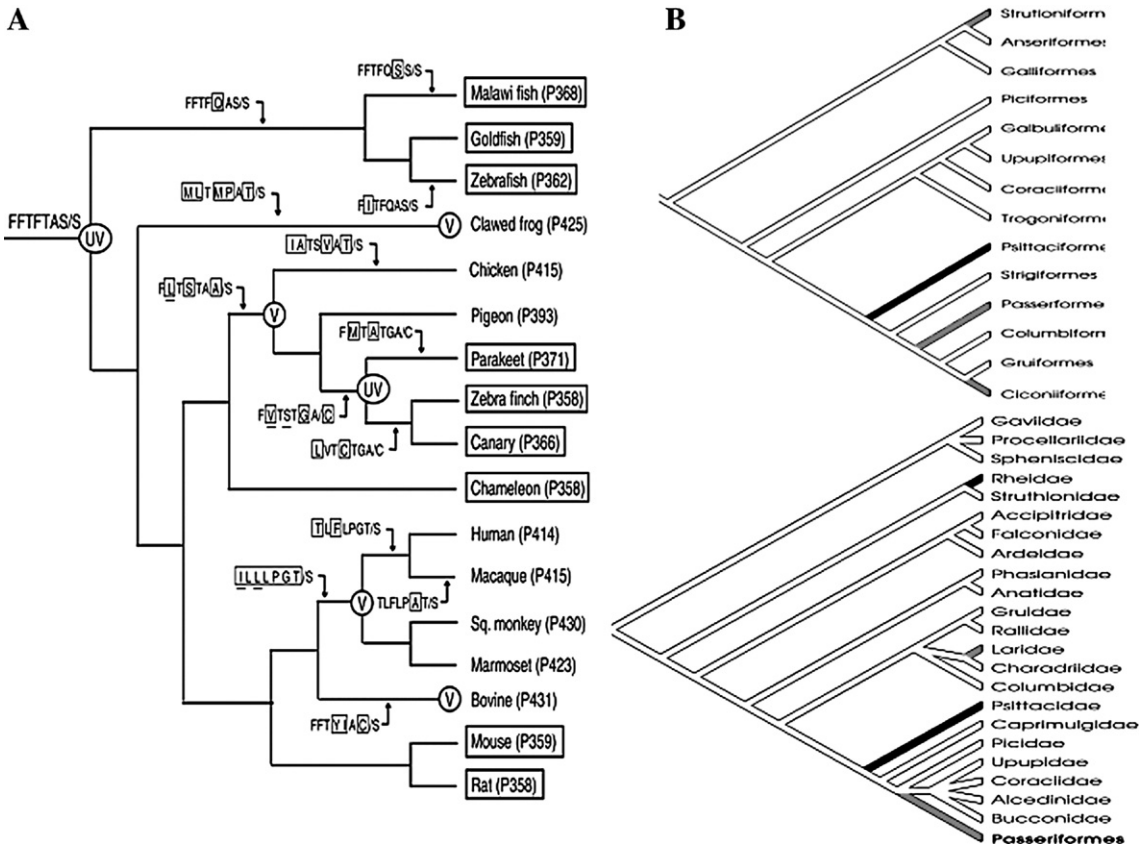

Fig. 2. (A) Phylogenetic tree of vertebrate SWS pigments and ancestral amino acids. UV pigments are in open boxes. Ancestral amino acids are underlined. First seven amino acids shown are at sites 46, 49, 52, 86, 93, 114, and 118 and amino acid after slash is site 90. Taxa in boxes have undergone amino acid replacements. V and UV refer to violet and ultraviolet sensitivity. Reproduced directly from [192] Copyright (2001) National Academy of Sciences, U.S.A. (B) Phylogenetic perspective of the evolution of ultraviolet- and violet-sensitive vision in bird orders. Phylogeny based on [212].White branches indicate violet-sensitive pigments, black indicate UV-sensitive pigments, and gray indicate taxa including both systems. The evolution of UV-sensitive pigments multiple, independent times in birds is depicted. Reproduced directly from [24] Copyright (2003) Society Molecular Biology and Evolution, Oxford University Press.

detection and the presence of these colors as mate-choice cues have now been made [21,37,48,49]. For example, Lake Malawi is a clear-water lake and as such, blue and red are high-contrast mating signals. Here, the frequency of different opsin types differs among species that have different body colors. Two species with vibrant blue coloration, *Metriaclima zebra* and *Labeotropheus fuellerborni* (Figs. 3C and 3D, respectively) have a higher frequency of RH2 and SWS2-B opsins, than they do other cone opsins [50]. Blue markings can also be UV reflective, and UV-sensitive cones (λ_{max}=368 nm) have now been identified in *M. zebra* [37]. In contrast to the blue-colored species, *Dimidiochromis compressiceps* (which lacks blue coloration) (Fig. 3E) expresses primarily RH2, secondarily LWS, and a small amount of SWS2-A. Further, LWS and SWS2-A are spectrally shifted (where LWS λ_{max}=569 nm, which is nearer to yellow than deep red, and where SWS1-A λ_{max}=440 nm, which is nearer to indigo than lighter blue). Similarly, the drab, ancestral species *Oreochhromis niloticus* (Fig. 3A) displays maximum expression for LWS, followed by RH2 [50], which is again quite unlike the opsin expression pattern of the brilliant blue-colored species. Several additional species (*Pseudotropheus acei*, *Melanochromis vermivorus*, and *Tramitichromis intermedius*) with unique coloration also express different dominant opsins, though the selective force driving these particular patterns remains, as yet, unexplained [26].

Like African cichlids, courtship by guppy (*Poecilia reticulata*) males involves the display of bright, heritable, color patterns to females [51–53]. Females tend to prefer conspicuous males, with orange-spot coloration being one notably strong preference (see [52]). However, particular preferences vary among individual females and among populations [54]. Artificial selection experiments for increased sensitivity to red and blue light demonstrate heritable responses within just a few generations, indicating the potential for rapid evolution in female preference [55]. Highly differentiated LWS isoforms (and variation in LWS λ_{max}) exist in individual guppies [56]. Multiple isoforms may occur within individuals. Thus, females may perceive orange and red coloration differently from one another, which may affect mate choice and male mating success [56]. Diversifying sexual selection and high LWS genetic variability are thought to drive the coevolution of opsin diversity and male coloration (see [28]).

High-contrast visual cues are used to the advantage of many species. Male sticklebacks (*Gasterosteus spp*.) also use red nuptial coloration in clear water, where it is the preferred coloration of females [57,58]. LWS gene expression actually

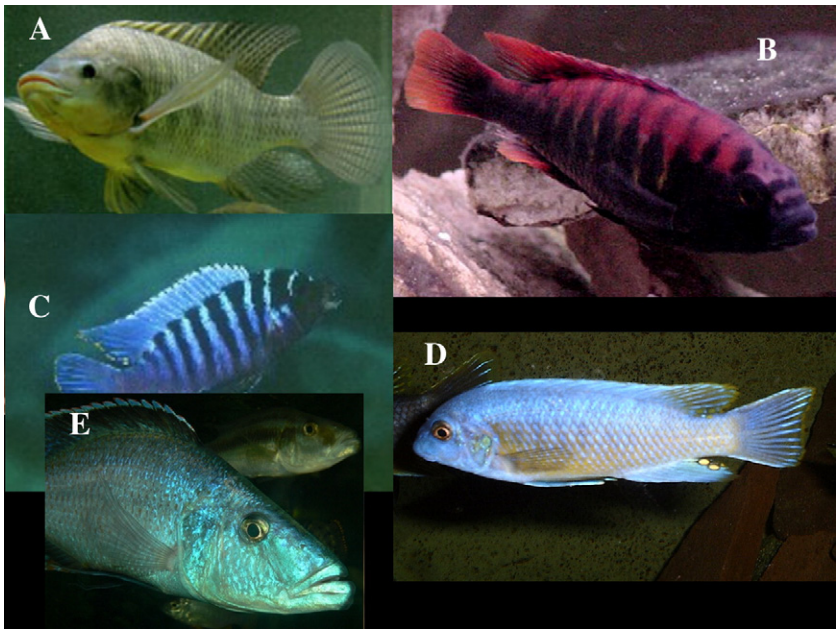

Fig. 3. Five of the many African cichlid species. (A) The ancestral species, *O. niloticus*. Photo: World Fish Center, Penang Malaysia (www.fishbase.org). (B) *P. nyererei*, demonstrating evidence of adaptive red coloration. Photo courtesy of K. Bauman. (C) *Metriaclina zebra*. Photo courtesy Irv Kornfield. (D) *L. fullerborni*. Photo courtesy S. Robson. (E) *Dimidiochromis compressiceps*. Photo courtesy S. Robson. Coloration is important to mate choice in *M. zebra* and *L. fullerborni*, which have short-wave (blue) shifted (and in *M. zebra*, UV opsin gene expression as well), whereas *D. compressiceps* does not show the same short-wave-shifted visual gene expression pattern of *M. zebra*.

changes temporally in this species, increasing during the breeding season when male belly color turns red [59].

In stark contrast to opsin variation among individuals, for deep-water species like the Cormoan coelacanth (*Latimeria chalumnae*), living at 200 m where sunlight penetration is very reduced, there is a 20-nm shift toward blue in RH1 and RH2, and only a narrow band of perceptible light (~480 nm, blue) [28]. Thus one might predict that sensory bias could be important for organisms adapted to such unique conditions. Similarly, in the Cottoid fishes of Lake Baikal, the RH1 λ_{max}=516 nm in shallow-water species, but is blue shifted to 484 nm in deeper water species [60]. Deep-water species are predicted to have a blue shift in SWS2, as well [28,61]. Finally, in Antarctic Notothenioids, there is no functional LWS opsin, consistent with the fact that red light does not penetrate their deep-sea environment. This opsin is lost in other deep-water species, as well [62]. Thus, very deep water species would not benefit from red mating coloration since it appears basically black, if visible at all at great depths, and since some species have no LWS-sensitive photopigments to absorb red-colored cues. Further, deep-water species may have a preexisting sensory bias for blue/UV coloration, particularly if they use this visual ability for other purposes such as foraging, reinforcing the idea that environment can play a profound role in the evolution of mate choice cues. Thus, the relationship between photic environment, preexisting sensory bias, and mate choice is an engaging topic of discussion (e.g., [39,63]).

Evolving ultraviolet vision from color vision

Molecular changes in opsin genes can allow for previously unseen cues to become visible, as occurs with the shift to UV vision from a SWS gene. What is remarkable about this evolutionary change is that it occurs in so many taxa, despite the dire potential for retinal damage due to UV light absorption [64]. When UVS cones ($\lambda_{max} \approx 360$ nm [65]) evolve, UV cues provide stark, visual contrast, which is frequently used during mate choice by many species [55,66]. Since so many species evolve UV vision despite its cost, from an evolutionary perspective we can ask, "How do species acquire UV vision?" The common vertebrate ancestor likely had a functional opsin gene that produced UVS pigments. In time, this opsin became a pseudogene in many taxa. UV vision has since reevolved multiple times in vertebrates (Fig. 2A). Phylogenetic analyses of multiple opsin genes for nine vertebrate species indicate that the budgerigar UV gene is more closely related to the chicken violet opsin gene than to the goldfish UV opsin [67], suggestive of multiple, independent evolutionary origins of the UV opsin for vertebrates. Regarding birds, their common ancestor evolved a SWS opsin gene from a UV-sensitive one, via four combined mutations (F49V, F86S, V116L, S118A) that produce violet-sensitive pigments (390–440 nm; λ_{max}=393). Four bird Orders have since independently reevolved UVS pigments. Sequence comparisons of birds with (budgerigars) and without (penguins and pigeons) UV vision have identified five amino acids that differ among these two groups [68]. The same two point mutations have been shown to be important for UV absorption in zebrafinches, canaries, and parakeets [69] (see Fig. 2B). More precisely, the replacement of serine by cysteine at site 90 (S90C) produces the required 35-nm shift in SW absorption that creates an absorbance spectrum consistent with UV vision in multiple species [65,70]. That the same amino acid change [24,71] occurs independently in multiple bird lineages reevolving UV vision is

indicative of the adaptive functionality of this trait. As well, invertebrate UV vision has evolved independent of vertebrate UV vision (e.g., [72]). In butterflies, S90C provides for the shift from blue–green to UV absorbance [73].

Empirical demonstrations associate a UV opsin with UV use in mate choice

Mate choice studies demonstrate that in some fish species (e.g. guppies and sticklebacks) females prefer males viewed under simulated natural skylight to males viewed in light exclusive of UV wavelengths [74,75]. In contrast, male guppies appear to prefer females housed under light exclusive of UV, which may create divergent selective pressures and maintain a sexual dimorphism [74]. Underwater, UV signals are useful over short distances only (<5 m) due to light scatter [76]. Short-range signals may therefore allow males to signal to nearby potential mates while not stimulating distant predators. In the case of guppies, a major predator (*Crenicichla alta*) has poor SWS vision, due to the absence of the appropriate cone opsin, leaving only potential mates to visualize UV signals [67].

Recently, the predacious dip and diving bird species were hypothesized to use UV signals from prey fish, but of five dipping and diving species investigated, only gulls had UV vision, indicating that this visual ability is used for some other purpose [77]. The white feathers of herring gulls are highly reflective in the visible and UV range [196], though to my knowledge sexual selection on UV cues in gulls has not yet been investigated. UV trait preferences and coloration differences appear to be involved in maintaining sexual dimorphism in several bird (e.g., bluetits, *Parus caeruleus*) and butterfly species (e.g., *Lycaena* sp.) [78]. In fact, many bird species, particularly passerines (e.g., blue tits and bluethroats, *Luscinia s. svecica*), use UV in mate choice [79,80,40]. As was true for color-rich cues, UV signals have been demonstrated to be honest indicators of fitness in species such as eastern bluebirds [11]. Zebra finch (*Taeniopygia guttata*) females prefer UV-reflecting males [81] and starling (*Sturnus vulgaris*) females rank males differently in the presence (versus absence) of UV cues [82]. Canaries in general have UV-absorbing plumage, which emits wavelengths longer than UV and produces fluorescent markings. Thus, during mate choice in budgerigars (*Melopsittacus undulatus*) both UV reflectance and UV absorbance are stimulating, particularly when juxtaposed [68,83,84].

Many butterflies (e.g., *Polyommatus icarus* [85] and *Bicyclus anynana* [86]), and lizards [87] also use UV in mate choice. In the common blue butterfly (e.g., *P. icarus*) flavinoids from the diet determine UV wing patterns, and males prefer UV-absorbing female models [85]. Interestingly, in addition to understanding butterfly genes used to view cues, male cue (color pattern) genes, as well as female preference genes, have also been identified (see below).

Mate-choice cue genes and expression patterns

Equally important as the genes involved in the *receipt* of visual mate-choice cues are the genes responsible for the *production* of these visual cues. Linkage in coloration and mate preference has been identified in butterflies. *Heliconius cydno* are black with white wing patterning and *H. pachinus* are black with yellow patterning. *H. cydno* prefer butterfly models that have white over yellow coloration, even if the wing pattern is that of *H. pachinus*. A fitness difference is associated with this preference; when *H. cydno* males are given the choice between altered white *H. pachinus* and natural, yellow *H. pachinus* females, they choose white over yellow [88]. One autosomal locus, *K*, controls forewing coloration (where white is dominant and yellow, recessive). A separate locus controls hindwing coloration [89,90]. Hybrid (and backcross) males appear to demonstrate a preference intermediate to (or with a bias toward the pure species in the backcross) their parents in their mate choice, suggestive of an additive, genetic effect. The estimated (Castle–Wright) effective number of loci for male preference is 1.35 ± 0.46. Quantitative trait loci and interval mapping demonstrate wing color and mate preference to be both associated with the wing-pattern candidate gene, *wg*. *H. pachinus* were homozygous for a "yellow" forewing allele, while *H. cydno* were heterozygous or homozygous for a "white" *wg allele*.

In fish, gene manipulation has also identified some important differences in mating-cue genes. Insertional mutagenesis of the zebrafish *hagoromo* (*hag*) gene recently demonstrated a pigment pattern mutant [91]. Zebrafish express only one *hag* mRNA, but cichlids express nine unique mRNAs (all in the skin [92]). The nine isoforms result from alternative splicing, which appears to be important for interspecific mate choice [92] since a positive association exists between morphological diversity in the African rock-dwelling cichlids and the rapid rate of amino acid substitutions in the regulatory domain of *hag* [91]. An association between rapid speciation and the *complexity* of alternative splicing also occurs: a greater number of splicing variants persist in the adaptively radiating cichlids, compared to riverine species [92].

As well as alternative splicing, point mutations in pigmentation genes affect mate-choice cues. One of the melanocortin receptor genes, *Mc1r*, plays a role in vertebrate pigmentation. *Mc1r* is one of five melanocortin genes that duplicated early in vertebrate evolution [93] and currently perform a variety of adaptive functions [94]. The expression of *Mc1r*, when bound by melanocyte-stimulating hormone, results in melanin (black-brown) pigment production in birds and mammals [95]. Simple, nonsynonymous point mutations in *Mc1r* are associated with drastic body-color changes in many species [19,96–98], including lesser snow geese (*Anser c. caerulescens*) and arctic skuas (*Sterocorarius parasiticus*). Snow geese display clinal variation (east-to-west) in body color (blue to blue/white to white, respectively) and mate assortatively by color [99–101]. Blue coloration is associated with methionine replacing valine at amino acid position 85 (V85M) in *Mc1r*. M85 homozygotes are completely, or nearly completely, blue; heterozygotes typically express blue and white coloration, and V85 homozygotes are white [19]. Similarly, in the Arctic skua cline (more northerly to less northerly) the frequency of three color morphs (light, intermediate, and dark) varies with latitude [100]. Light-

colored birds are arginine (R230), intermediate colored birds are R/H (histidine) heterozygotes, and dark birds are primarily H230 [19].

The cells that contain the melanin regulated by *Mc1r* are called melanophores. Disruption of melanophores often results in blotchy or spotted coloration, as is true in *M. zebra* and other species. In *M. zebra*, melanophores in males and most females typically form dark, vertical bars on a blue to brown background. Female mutants display blotchy black spots on orange coloration, and these color differences are associated with mate choice [102]. The frequency of orange blotch (OB) is higher in areas with relatively clear water [103], and there is evidence that OB mothers produce sons that choose OB mates [103]. Quantitative trait locus scans and comparative genomic mapping (with *Fugu* and humans) have identified a linkage between the OB color pattern in *M. zebra* females and the *c-ski1* gene [102]. As well, three cone opsins, including the LWS opsin, appear in close proximity to OB in the cichlid genome.

Often, visual cues are combined with other sensory cues during mate choice, as is true for some birds, including house finches and European Starlings (*Sturnus vulgaris*), who use visual as well as auditory cues for mate choice [82].

Auditory signals, gene expression, and mate choice: male song reflects mate quality and affects female brain gene expression patterns

Many songbird species learn to recognize individual, conspecific songs [104], though the genetic control of song production and recognition is not yet well understood. House finch and European starling songs are believed to reflect male quality and are one of several cues used by females to select mates. Female house finches prefer longer, faster male songs [105], and song length is also important to female starlings. Neurons in a few, precise auditory forebrain regions respond to conspecific song [106] and song increases expression of specific genes, including *egr1* (aka *zenk*) [106,107]. Recent song exposure appears to play a large role in female starling male song choice. Females exposed to long-bout songs have increased *egr1* transcription in the auditory triencephalon of the brain [107]. After exposure to long-bout songs, females prefer novel long-bout songs over novel short-bout songs and show increased *egr1* expression only in response to novel long-bout songs [107]. In contrast, females initially exposed to short-bout songs and then exposed to novel short- versus long-bout songs, have increased expression of the *fos* gene when listening to novel long songs [107]. *Egr1* expression in is also positively associated with sexual receptivity to song type in mountain white-crowned sparrows [108]. Sequence comparisons of birds demonstrate that the coding region of *zenk* is highly conserved across avian taxa, as is some of the 3′ untranslated region, which is, therefore, predicted to play a role in gene expression [109]. Many species, such as house finches and starlings, use a combination of sensory cues for mate choice. However, while some taxa have highly adapted visual and auditory senses, other organisms tend to rely more on olfactory cues for mate choice.

Olfactory signals and mate choice

Sex pheromones and mate choice genes in invertebrates and fungi

Sex pheromones are broadly considered chemical signals that modulate social and reproductive behavior, including mate choice and conspecific aggression [110]. They are widely used among animal taxa, especially by invertebrates and rodents. Both male and female fruit flies (*Drosophila melanogaster*) exhibit mate choice, which involves a combination of song, dance, and pheromones. Males evaluate female sex pheromones (cuticular hydrocarbons, or CH) to distinguish among fly strains because they prefer to mate with same-strain females [111,112]. In African and Caribbean populations of *D. melanogaster,* the wild-type *desat2* ($ds2^Z$) allele is found at high frequency. The predominant CH produced by females with $ds2^Z$ (and some modifiers) is 5,9-heptacosadiene (5,9-HD) [113]. *D. melanogaster* elsewhere in the world (i.e., Cosmopolitan *D. melanogaster*) have a 16 bp loss-of-function deletion in the promoter of the *desat2* gene ($ds2^M$) [113] that may minimize *desat2* gene expression. $ds2^M$ females produce high quantities of the isomer 7,11-heptacosadiene (7,11-HD) and induce mating by Cosmopolitan males more than 5,9-HD females. Adaptive selection was thought to contribute to the spread of the Cosmopolitan mutation, possibly through pleiotropic tolerance to harsh environmental conditions [111,114]. However, when cold and starvation stress experiments were repeated with transgenic fly lines, climatic adaptation results were not replicable, and the role of hydrocarbons in this experiment appeared somewhat ambiguous [115]. Similar to nature, a deficiency of unlike-line matings was seen, though this resulted from female rejection of males, not the male preference as expected [115]. Thus, we have found a link between a gene, a promoter, and a pheromone; however, additional details remain to be uncovered regarding mate choice, even in model systems such as fruit flies.

In contrast, clear, detailed associations between pheromone genes, receptors, pheromone transport, and mating success have been demonstrated in fungi. In *Candida albicans*, while there is no cognitive mate choice per se, two cell mating types, **a** and α, are required for mating. The *MF*α gene drives pheromone production in α-cells. Microarray data demonstrate that *MF*α is up-regulated after α-pheromone treatment (this also occurs in *Saccharomyces cerevisiae*) [116]. In contrast, the *STE2* gene encodes the pheromone receptor (required for **a**-cells to mate) [117]. **a**-cells respond to pheromone by up-regulating 62 genes.

Similarly, in *S. cerevisiae*, the *MAT* locus controls mating specificity. Here, the two cell types (α, **a**) produce different transcriptional regulators [118]. Mature pheromones exit cells via a transporter and *Ste6* encodes the **a**-factor transporter [118]. *Ste6* deletion mutants—created through gene disruption—show reduced mating ability, resulting from reduced filament formation [118]. Similarly, in *Sordaria macrospora*, a fungal ascomycete, the Δ*Smta-1* (deletion) mutant cannot produce fruiting bodies or spores, despite the fact that it can self-fertilize. Using a *Neurospora crassa* microarray, the pheromone

precursor gene (*ppg2*) was found to be 500-fold down-regulated in the Δ*Smta-1* mutant [119]. Pheromone (*ppg1* and *ppg2*) and pheromone receptor (*pre*1 and *pre2*) genes are thought to pair (*ppg1/pre2; ppg2/pre1*). Double knockout strains (Δ*pre2/*Δ*ppg2,* Δ*pre1/*Δ*ppg1*) and double pheromone gene knockouts (Δ*ppg1/*Δ*ppg2*) produce fewer fruiting bodies and spores than normal. Double receptor gene (Δ*pre1/*Δ*pre2*) knockouts produce no fruiting bodies or spores [120]. Clearly, pheromones and receptor genes are important to fitness in primitive species, even those capable of self-fertilization. Pheromones are equally important in mate choice in sexual species.

Chemosensory receptors and other mating-behavior genes used by nonhuman mammals

The mammalian olfactory system is comprised of two parts, the main olfactory system and the vomeronasal system [121]. Nonvolatile sex pheromones are processed by the vomeronasal organ (VNO) [122]. Vomeronasal receptor neurons project to the accessory olfactory bulb, which in turn projects to brain regions that modulate social and reproductive behavior (Fig. 4) [121]. Sex pheromones are sometimes bound to transporter proteins that shuttle pheromones and may affect sensory responses in the opposite sex [123,124].

Two candidate superfamilies of genetically variable vomeronasal receptors (V1R, V2R) appear to innervate the mammalian VNO and serve as pheromone receptors [125] that detect the odors used in mating behavior and mate choice [126–128]. At least 400 pheromones used in mate choice in nonmouse mammals [129,130] stimulate neurons in the mouse VNO [122]. Several receptors have recently been implicated in mate selection. Of 239 known mouse *V1r* sequences, 137 have uninterrupted open reading frames and are putative, functional coding genes [125]. Ninety-five putative, functional *V1r* genes have also just been reported for rats [131]. Comparisons between rat and mouse (Fig. 5) show that *V1r* gene changes are exceptionally rapid between these species and that every gene in some *V1r* gene families has likely either been duplicated or become a pseudogene since the time of divergence for these taxa [131]. Noteworthy is a similar finding in fish, in which V2Rs undergo rapid gene turnover as well [132]. Fish V2Rs are expressed in the olfactory epithelium (fish are not thought to

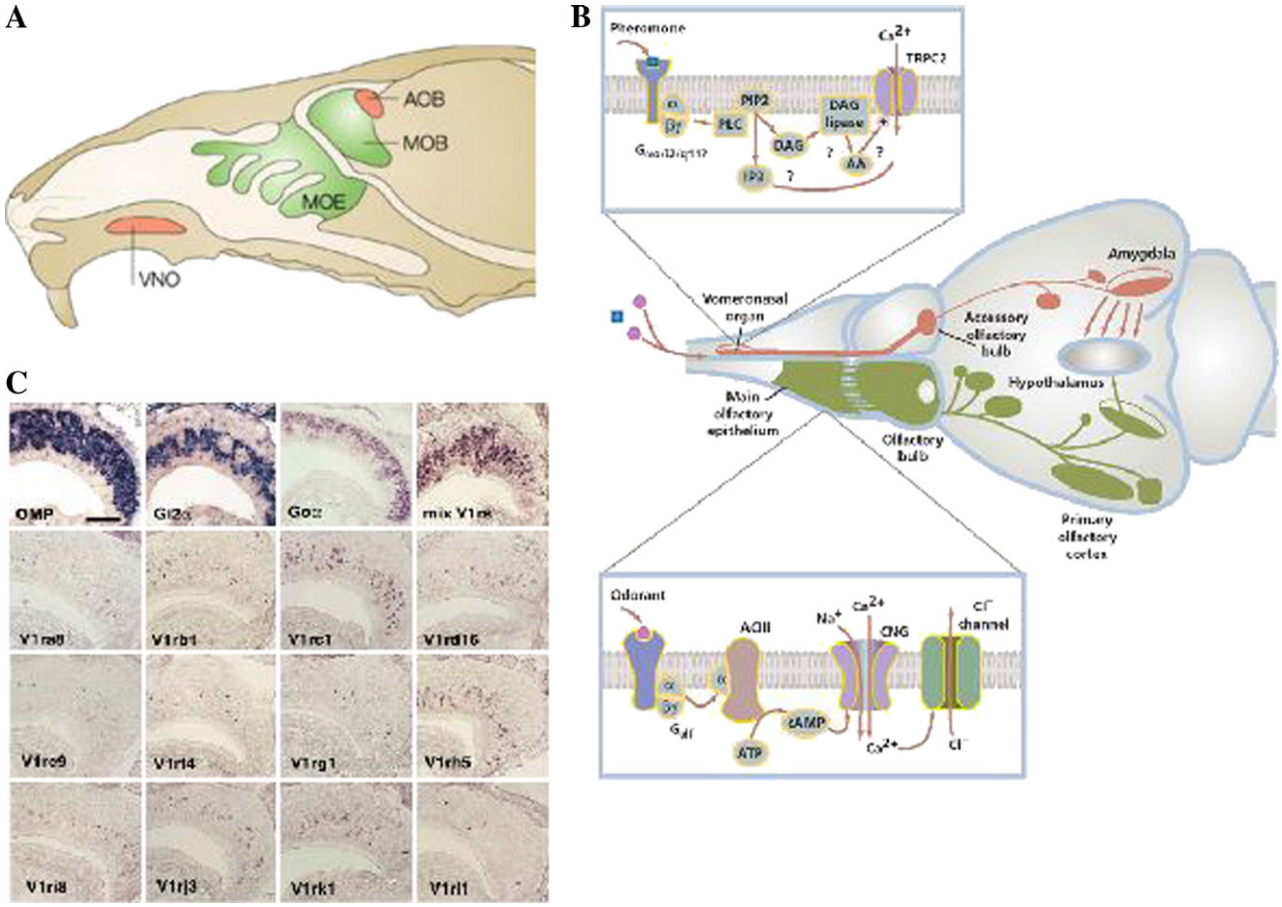

Fig. 4. (A) Locations of vomeronasal organ (VNO), main olfactory bulb (MOB), main olfactory epithelium (MOE), and accessory olfactory bulb (AOB) in a side view of a rodent's head. Reprinted by permission from Macmillan Publishers Ltd: Nat. Rev. Neurosci. [193] Copyright (2004). (B) Dorsal view of rodent head and brain (nose on left). VNO and main olfactory organ signaling cascade are shown in insets. Reprinted by permission from Macmillan Publishers Ltd: Nat. Neurosci. [194] Copyright (2003). (C) *In situ* hybridization of VNO sections using digoxigenin-labeled antisense RNA probes (black). *OPM* probe labels mature vomeronasal sensory neurons; *Gi2α* probe labels sensory neurons with cell bodies in apical layer expressing *V1rs*; *Goα* probe labels cell bodies in basal epithelium. V1r probes (families a-1) demonstrate that all V1r families are expressed in the neurons of the apical layer. Reprinted by permission from Macmillan Publishers, Nature Neuroscience [125] Copyright (2002).

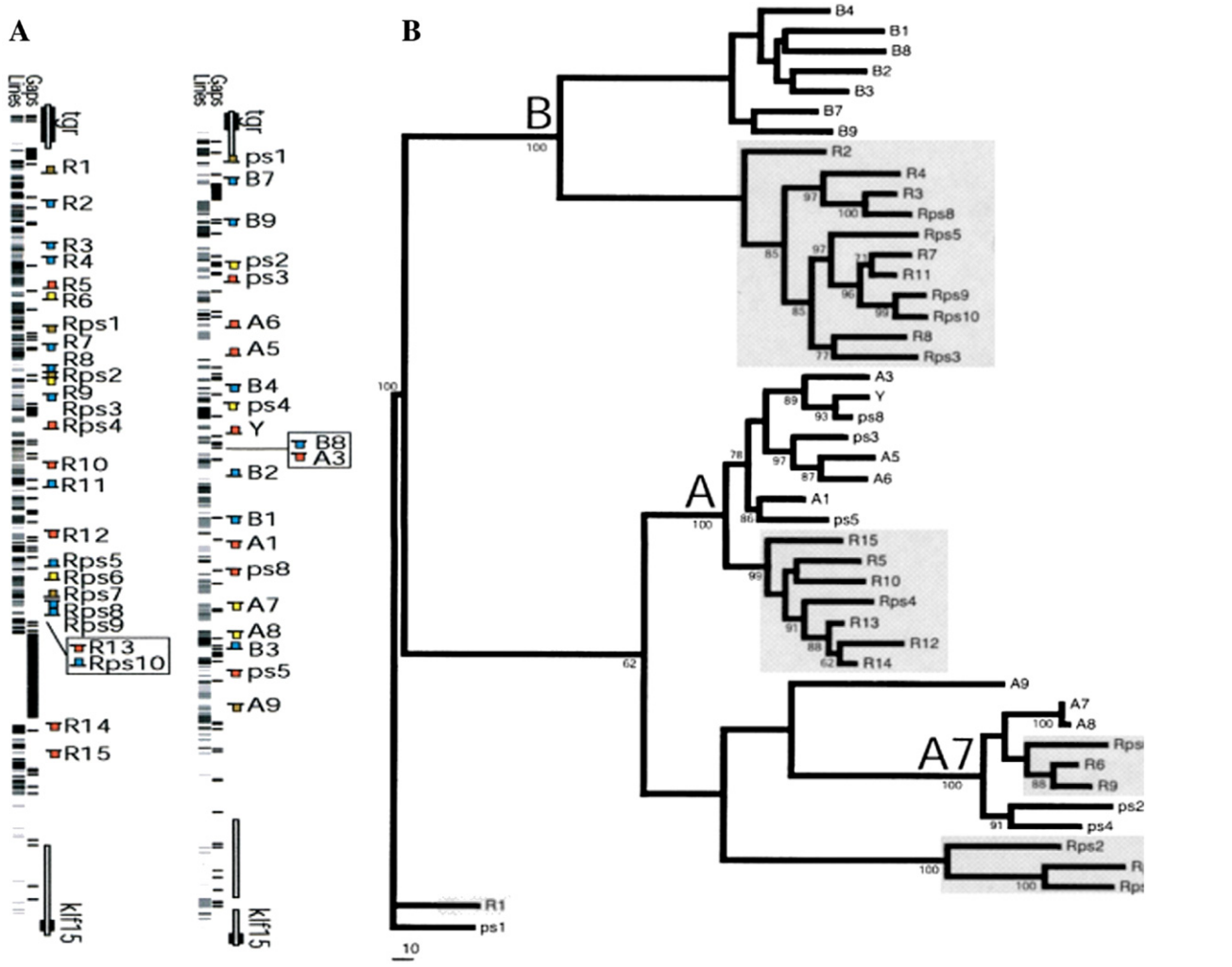

Fig. 5. (A) Synteny maps of rodent *V1r* clusters on mouse chromosome 6 and rat chromosome 4. Reproduced with permission directly from [195] Genome Research Copyright (2004). (B) Phylogram of *V1r* genes/pseudogenes from mouse chromosome 6 and rat chromosome 4. Clades diverged before the mouse/rat split but subfamilies delineate into species-specific clades, suggesting expansions occurred after the split. Reproduced with permission directly from [195] Genome Research Copyright (2004).

have a VNO) and used to identify water-soluble chemicals, which can be used in mate choice [133]. In rats and mice, 73 *V1r* genes appear to have arisen from seven ancestral genes at the time of the rat/mouse divergence [134]. Positive selection has been detected for particular *V1r* and *V2r* gene regions in rodents ([135], but see [131]), though purifying selection has been detected across entire gene sequences as well [131].

Until a recent chromosomal-engineering manipulation was performed, we had a very poor understanding of, and no functional evidence for, the role of *V1r* and *V2r* receptor genes in mammalian pheromone signaling [136]. We did know that, typically, inexperienced male mice mount (and perform pelvic thrusts on) other males until a time when they discriminate between the sexes and mount females with increasing frequency. Males homozygous for an ~600-kb genomic deletion of 16 *V1r* genes (but not any other genes) produce no *V1r* mRNA and exhibit abnormal sexual behavior. Mice with the *V1r* deletion mount fewer females (and males less often) than mice without the deletion, indicating an important role for *V1r* genes in mating-related activity [136].

Similarly, activation of VNO neurons is now also known to depend upon Trpc2 (aka TRP2), a transient receptor potential cation channel, found in the dendritic tip of VNO neurons. Unlike adult wild-type mice that engage in heterosexual matings, genetically ablated Trpc2 mutant mice (harboring deletions in critical regions of the Trpc2 protein) do not respond to pheromones, despite functionality (electrical activity) of the VNO neurons. Trpc2 mutant males also court and mount both sexes equally and do not display aggression (typically driven by pheromone) toward intruder males [137], indicating the role of Trpc2 in sex discrimination, which is essential to mate choice.

Mating behavior in rodents is also affected by arginine vasopressin (AVP) receptors in the brain, whose spatial distribution varies largely between monogamous and polygynous species (see [138]). In voles, AVP affects sexual behavior and pair bonding, and the expression pattern of vasopressin receptors is greater in the ventral pallidum of the brain in monogamous voles (*Microtus ochrogaster* and *M. pinetorum*) than in promiscuous voles (*M. pennsylvanicus* and *M. montanus*). Injection of AVP—which is stimulated naturally

in the monogamous male vole when cohabiting or mating with a female—into the brains of promiscuous voles resulted in increased olfactory investigation of, and grooming behavior toward, females. Transgenic mice carrying prairie vole receptor genes expressed a heritable receptor binding pattern similar to that of natural prairie voles and demonstrated increased affiliative behavior after AVP injections [137]. Thus, *V1ar* expression clearly affects mating behavior. Gene sequence comparisons show that monogamous vole species have similar 5′ flanking sequences and vasopressin receptor (*V1ar*) expression patterns similar to those of other monogamous voles, whereas promiscuous species have *V1ar* gene expression patterns similar to those of other promiscuous voles, and promiscuous species do not display similarity to monogamous species in the 5′ flanking sequence [138]. Of late, much has been learned about the roles of particular genes and pheromones in mate choice in mammals (see Table 1). In some gene complexes, such as the major histocompatibility complex (MHC), simple allelic differences affect mate choice dramatically.

MHC-driven mate choice and disease in nonhuman mammals

The MHC is a group of immune system genes that produce peptides on nucleated cells' surfaces that identify self/non-self antigens (Class I) and present foreign particles to T lymphocytes, initiating an immune response (Class II) [139]. MHC peptides are extremely diverse, as are the MHC-mediated odors known to be used in mate choice in humans, fish, and mice [133]. Individual rodents recognize one another through chemosensory signals that are altered by MHC peptides [140] and/or major urinary proteins (MUP) [141–143]. MUPs are the most abundant proteins in urine.

MHC peptides are extremely polymorphic in many taxa. Comparisons between mouse and human gene sequences show that MHC antigen recognition-site codons evolve rapidly. Heterozygote advantage appears to maintain the high degree of MHC polymorphism and to provide for the evolutionary persistence of many alleles ([145] for dominance; [146]). Disassortative mating may contribute to this process and/or operate on the genetic variation arising from it. Since MHC and MUP are both under strong, positive selection and evolve rapidly [144,145,135], a great diversity of odor signals exists.

Mice distinguish single-gene differences in MHC through MHC-mediated odor types. In fact, they can even distinguish single-amino-acid differences in the peptide-binding region of Class I peptides [147]. Mice mate disassortatively, preferring mates with MHC genotypes different from their own [147–149]. MHC odor type-mediated mate choice may have several benefits—including selection of disease-free mates and production of genetically variable offspring with both decreased inbreeding and increased disease resistance [146,150,151]. Many rodents use MHC-mediated odor types [152] to determine whether potential mates are infected with viruses, parasites, or nematodes [153] and several examples of preference exist. Mouse mammary tumor virus (MMTV) alters mouse body and urine odors [153]. Uninfected mice discriminate against MMTV-infected ones as mates, possibly through the use of MHC odor types [152]. Even more striking, when individuals are infected with mouse hepatitis virus, nonrandom fertilization occurs. Infected parents produce more MHC-heterozygous embryos than uninfected parents do [154].

Somewhat similarly, female mice that are oxytocin wild type display preferences for the urine odors of males not infected with the nematode *Heligimosomoides polygyrus* over those of infected males. This is true—unless a female is paired with the diseased male that is presented to the test female. The odor of the pair appears to override the aversion of the test female to the infected male (presumably due to information gleaned by the test female regarding mate choice of the paired female). However, females with oxytocin gene knockouts do not discriminate between (or respond to odors of) uninfected and infected males and do not discriminate between a lone infected male and an

Table 1
Some of the genes involved in chemosensory mate choice and mate recognition

Chemosensory gene	Gene function	Effect of mutation	Organism	Ref.
desaturase2	Hydrocarbon production	Decreases pheromone production	Fruit fly, *Drosophila melanogaster*	[197,198]
Δ14 desaturase	Sex pheromone	Produces novel hydrocarbon	Moth, *Ostrinia funacalis*	[199]
desaturase1	Sets double bonds	Reduces pheromone	*D. melanogaster*	[200]
BmOR-1, *Bombyx mori* olfactory receptor	Putative sex pheromone receptor	N/A	*Silkmoth,* B. mori	[201]
Gr68a receptor	Chemosensory neuron used in courtship	Inactivates/decreases singing, licking, courtship	D. melanogaster	[202]
Seducin	Sex pheromone	Alters male pheromone ratios	Cockroach, *Nauphoeta cinerea*	[203]
GPA1	Sex pheromone responses	Decreases pheromone response	Yeast, *Saccharomyces cerevisiae*	[204]
V1ra1/Avpr2	Pheromone receptors	Mating behavior deficits	Laboratory mice	[205]
Bβ2 mating type locus (cluster of genes)	1 pheromone, 8 receptors	Gain/loss of function	Fungus, *Schizophyllum commune*	[206]
B6 gene cluster	9 genes, 3 receptors, 6 pheromone precursors	Precludes pheromone from activating mutant receptor	Mushroom, *Coprinus cinereus*	[207]
Trpc2	Ion channel in pheromone transduction pathway	(a) Males mount males and females (b) Pseudogenes	(a) Mice (b) Old World monkeys	[208,209]
MFα, STE2	Encodes mating pheromone, receptor	N/A	Fungus, *Candida albicans*	[210]
MHC	Affects body odor/mate choice	N/A	Many mammals; fish, *Salmo salar*	[211]

infected paired male—indicating that the oxytocin gene is important for female choice of male partners, as well as for female assessment of other females' choices [144].

While assessing mate choice in rodents can be complex, perhaps the most contention revolves around determining which factors drive human mate choice.

Odorant detection and pheromone receptors in humans

Human pheromone studies evoke controversy [155]. Women detect and prefer particular male pheromone profiles, yet the vestigial VNO in humans—in combination with many human pheromone receptor pseudogenes (that do code for receptor proteins in the mouse VNO) [156]—suggests to some that human mate choice is driven primarily by alternative cues [157]. Indeed, the *Trpc2* ion channel and some *V1* pheromone receptors have been functionally impaired since the phylogenetic separation of Old World monkeys and hominoids [137,157]. Humans can, however, detect single MHC-locus differences in mice (the same differences that mice detect) [158] and women demonstrate preferences for particular male odors over others. As well, women indicate a feeling of relaxation and display increases in the rate of onset of pulses of the reproductive hormone that peaks just prior to ovulation (luteinizing hormone) after smelling men's sweat [159]. Notably, mice can actually continue to detect MHC differences even after surgical removal of the VNO, indicating that other sensory structures may be involved in pheromone detection in mammals. While random inactivation of pheromone receptor genes is an ongoing process in humans, positive selection does occur on some human odorant receptor genes [160] and in primates on a putative pheromone gene (*VN1R* aka *V1RL*) [157]. Interestingly, this gene is not expressed in the primate VNO [161].

Human leukocyte antigens (HLA) and mate choice

HLA genes are human MHC genes. They are the most variable genes in the human genome [162]. There are at least 82 HLA genes [163] and over 1000 HLA alleles, which are expressed at multiple loci—including at least 243 alleles at the A locus, 499 at the B locus, 35 at the C locus, 69 at DPB, 29 at DQB, and 321 at DRB [162,164,165]. HLA alleles affect body odor and influence individual recognition and mate preference [165]. Women detect single differences in HLA alleles between men ([166], but see [167]) and (if not taking oral contraceptives) prefer the smell of T-shirts worn by men with HLA alleles different from their own [168]. Women also prefer HLA alleles like their fathers', but not their mothers' ([166], see [167]), and report these as smelling like their current partners (e.g., boyfriends) [168], suggesting similar HLA odor choices in their private lives [166]. HLA matching is known to affect fitness in some human populations (see below). HLA variation appears to be maintained by disassortative mating [164] (see Box 1, maternal–fetal interactions [169,170] (in which higher fitness is accrued from mating with partners that have different MHC from self, due to less averse maternal–fetal effects), and/or parasite attack (e.g., [171]). These forces are not necessarily exclusive with respect to mate selection. At the molecular level, nonsynonymous amino acid replacements occur at a greater rate than synonymous in the peptide-interacting regions of two HLA loci (A and B) [172]. Positive selection and heterozygote advantage act at these loci [173,174] and allele frequencies display more rare, and fewer common, combinations than chance expectations would predict, reflecting the maintenance of rare alleles.

Box 1. Disassortative mating in humans: a case study addressing the South Dakota (USA) Hutterites

Hutterites, a religious sect, migrated from Europe to North America. The South Dakota Hutterite population exceeds 35,000 and is descended from fewer than 100 related founders [179]. In 852 adults studied, several serological HLA haplotypes were more frequent than expected by chance [180], and all loci showed homozygote deficiencies [181]—contrary to expectations for an inbred population. Strong negative selection against HLA-haplotype homozygotes exists. Decreased fecundity and increased fetal loss occur when partners have matching HLA haplotypes [174,178,180]. Recent data indicate that Hutterites mate disassortatively by HLA type or by genes in linkage disequilibrium with HLA [174,182].

Conclusions and future directions

A major theme emerging from this review is that many genes involved in mate selection evolve rapidly. At the molecular level, there is enormous diversity in mate-choice cues and strong natural selection on these cues (see Box 2). The question remains, why are rapidly evolving genes used in mate choice, or alternatively, why are mate-choice genes evolving rapidly? Highly variable traits (e.g., MHC, HLA) allow for individual identification and assessment of relative value. The use of particular genetic systems involved in mate choice may simply result from their purpose—if high variability means better survival in the face of parasites, then mate selection for high variability is beneficial. Vomeronasal receptor gene turnover (e.g., *V1Rs*) may ultimately be indicative of pheromonal cue changes among species—but why are these changes rapid? Pheromone profiles are complex. Very subtle differences in these chemical profiles can drive mate choice. In some cases, single chemosensory substances serve as sex pheromones and provide for mate recognition, but in others, relative amounts of particular chemosensory compounds are crucial [111–113]. Perhaps rapid turnover of receptors reflects subtle changes in pheromonal chemical composition among populations, strains, or species. Alternatively (or additionally), selection may generally act on sex pheromones indirectly, through, for example, pleiotropic relationships with other rapidly evolving

Box 2. Comparison of different genetic scales indicating that strong selection and rapid evolution act on many genes and traits broadly involved in mating-related activity

Broad-scope reviews indicate that directional sexual selection is stronger than viability selection [183,184]. While such studies do not assess specific mate-choice genes, sexual phenotypes are associated with differential mating success. In a few studies, rates of evolution have now been addressed. For example, rapid evolution was recently detected for white tail coloration, a sexually selected trait in dark-eyed juncos (*Junco hyemalis*) [185]. From a purely genetic perspective, comparisons of 51 nuclear gene sequences in fruit flies (*Drosophila*) and worms (*Caenorhabditis*) also show that sex-related genes have undergone directional selection and rapid evolution [186]. The fertilization protein lysin has undergone strong positive selection in abalone (*Haliotis*). The sperm protein TMPA has undergone strong selection and rapid divergence among marine snails (*Tegula* sp.) [187]. Orthologous human–rodent gene comparisons also indicate that reproductive protein genes evolve rapidly [188]. Isochores display marked guanine and cytosine (G + C) content variation across very large genome regions [189]. MHC Classes II and III show consistent (G + C) composition, but Class I demonstrates high (G + C) variability. Though isochore function is not yet well understood, identifying whether this type of Class I variability plays a role in mate choice is an exciting area of future research. Genomic mutational hot spots [190] exhibit a gene bias toward extracellular communication genes, which include cell-surface receptors (pheromone receptors), cell-adhesion genes (sexual conjugation and mating-type genes), and immune response genes, suggesting that particular types of genes in hot spots may allow for (or are found in genomic regions of) rapid evolution. Similarly, a positive correlation exists between mutation rate at minisattelite loci and extra-pair paternity, and an increased mutation rate is demonstrated in species with more intense sexual selection [191].

traits. In any case, traits with substantial genetic variation that is associated with fitness are the most informative regarding the relative value of prospective mates. This does not imply that traits under strong directional, sexual selection are not informative. However, in a directional selection scenario, a "best" mate prevails, and variation is eroded. In cases in which disassortative mating is the optimal mating strategy (e.g., HLA, Box 1), variation may sustain a diversity of mates, which benefits a diverse population, in which different individuals have different optimal mates.

This review also reveals that many sensory-related mate-choice genes arise through gene duplication. Some duplications (e.g., expansion of opsins in fish) allow for the perception of a wider range of mate-choice cues, while others result in distinct differences among taxa as (e.g., consider rodents, in which only 19% of rat *V1r* genes have a one-to-one correspondence with mouse orthologs) [131]. Whether species retain particular duplications (e.g., opsins), because of adaptation to habitat or because of sexual selection, continues to remain a scintillating question. Genomic comparisons demonstrate that in some species (e.g., pufferfish), anciently duplicated opsins (e.g., green-sensitive RH2-2) have recently been lost, despite apparent purifying selection until this loss [175]. Thus, whatever the reason for the loss, changes such as this will dramatically alter the usefulness of a particular cue (here, green coloration) for mate choice. In some cases of gene duplication (e.g., the melanocortin receptors), the mate-choice cue (here, body color) is not lost, but additional functions are gained through adaptive duplications (here, fat storage and behavioral controls) that may also be important for mate choice [93].

We are at the tip of the iceberg in understanding mate-choice genetics. There is an interesting disparity in the data collected on the genes involved in mating cues and in cue receipt. For example, regarding vision: UV opsins have been sequenced for several species, but there is a depauperate set of data addressing the *genetic* control (if any) of UV reflectance in plumage. Yet variation in plumage coloration affects fitness dramatically. Further, most of the work on opsin molecular evolution as it relates to mate preference has been conducted in birds and fishes, leaving the challenge of data collection in this area to be met for a broader range of organisms, as well. Regarding olfaction, since olfactory tissue comprises a small region of the brain in many birds, smell was historically discounted as a mode of communication. However, recent work demonstrates that olfaction is involved in mate identification in seabirds (Antarctic prions, *Pachiptila desolata*) [176]. The genetic control and neural processing involved in this behavior are not yet understood, but may have major implications for understanding mate choice in other seabirds and possibly even avian systems in general. On a broader scale, the link between mate choice and disease (MHC/HLA) [151–154] has been touched upon here, but further understanding of this association (e.g., is a pleiotropic relationship between disease resistance and mate choice prevalent?) remains to be had. Consider spiny lobsters, in which the olfactory ability to detect and avoid disease in conspecifics has just been identified; however, absolutely nothing is known about the genetic control of this phenomenon or whether it affects mate choice in this marine invertebrate [177]. We might also ask, is the positive selection that occurs on some mate choice genes due to mate choice or simply a by-product of selection on disease defense (or other traits)? Regarding selection, Wolfe and Li [178] recently reviewed the genes and proteins under positive selection, dividing them into a few

major categories—which in a broad sense appear somewhat associated with mate choice. One category of genes included only viral/bacterial and phage genes, but two other categories included reproductive genes and immune-system-related genes, and a final category swept up all remaining genes. Many more male than female reproductive genes undergo positive selection, and whether female mate choice drives and/or affects this bias remains to be investigated.

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