

# Chapter 1

## Female Mate Choice in Rodents

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### 1.1 Introduction

Sexual selection theory (Darwin 1871) predicts that in each species members of the two sexes employ different mating tactics – depending on the constraints each sex has on reproduction (Clutton-Brock 1989) – to maximize reproductive success (i.e., Darwinian fitness). These tactics are applied within the mating system of a given species (i.e., monogamy, polyandry, polygyny, promiscuity). This “conflict between the sexes” (reviewed in Chapman et al. 2003) arises because the amount of resources each sex invests in future progeny may differ significantly, depending on the species investigated (Alonzo and Warner 2000). Among mammals, it is usually the female that is the choosier one due to the higher amount of resources allocated to the production of gametes and to the raising of offspring (see Chap. 3). In recent years interest has grown to decipher the way and the reasons how and why the two sexes choose their mates the way they do. As a result, the paradigm on mate choice has shifted from the active (more or less aggressive) male and a passive (more or less coy) female view to a view where both sexes are actively choosing their mating partner from a pool of potential candidates.

Several excellent reviews have been written covering particular topics of reproduction, such as mating systems, mate choice, genetic compatibility, sexual conflict, sperm competition, behavioral genetics, cooperative game theory and sexual selection, and others (Clutton-Brock 1989; Anderson and Iwasa 1996; Zeh and Zeh 1996; Birkhead 2000; Tregenza and Wedell 2000; Paul 2002; Chapman et al. 2003; Stockley 2003; Dall et al. 2006; Roughgarden et al. 2006; Solomon and Keane 2007; Wolff and Sherman 2007; Greenspan 2008). These reviews cover a broad array of issues and provide detailed insights into, and theoretical background of their particular topic. For readers particularly interested in such topics, these reviews

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provide an excellent body of knowledge (more reviews are mentioned in the text). This and the fact that growing interest in these topics has led to a large and continuously growing number of newly published studies in recent years led us to focus on only certain aspects of rodent behavior (those to which genes could be linked) and in particular female mate choice.

In the near future, the application of genomic information retrieved from whole genomes (e.g., mouse and rat; <http://www.ncbi.nlm.nih.gov/sites/genome>) and techniques such as detailed brain receptor mapping will hopefully help us to gain new insights into genes and pathways involved in the development of behavior (e.g., by knockout genes/animals).

## 1.2 Mate Choice by Males (Short)

Because sexual selection theory also predicts that the more abundant sex competes for access to the less available sex, research in the past has focused on the mating strategies of males. Their “maximizing of progeny” is embraced between the two extremes of (1) copulation with the largest possible number of females and no parental care and (2) copulation with a single female and securing offspring survival by providing parental care (Clutton-Brock 1989). Successful mating for males requires access to receptive females whose spatial distribution may vary over time on one hand and who may be socially organized in many different ways on the other (e.g., solitary, dispersed, clustered, and matrilinear groups). However, even the presence of receptive females is no guarantee for males to reproduce successfully because other factors, such as environmental ones (e.g., competition with other males, habitat structure), and/or female selective behavior (see below), might compromise the access to females. Thus, males may have to employ a broad array of strategies to gain that access, including defeat of competitors in open fights, competitive mate searching, coercion of females, mate guarding, scent marking, adjustments to ejaculate volume, and sperm competition (Thornhill 1983; Schwagmeyer and Wootner 1986; Schwagmeyer 1990; DelBarco-Trillo and Ferkin 2004; Dean et al. 2006; reviewed in Waterman 2007; Firman and Simmons 2010). Further aspects, in particular with respect to sperm competition, are discussed below in response to female mate choice mechanisms.

## 1.3 Mate Choice by Females

Female mate choice (or, better, the choice of which potential candidate fertilizes the egg) may be exerted at various stages: before and/or during copulation, after copulation but before fertilization, after fertilization (Birkhead and Møller 1993). Females also use a broad array of traits in mate choice (reviewed in

Solomon and Keane 2007). One of the criteria females apply to their selection approach is the apparent provision of beneficial services by a male (e.g., provision of food, shelter, defense against harassment by other males, or even parental care). The latter, however, is rare in rodents, because most species are polygynous and promiscuous (Solomon and Keane 2007). Two of those rare examples are the California mouse (*Peromyscus californicus*) and the Djungarian hamster (*Phodopus campbelli*). Females of both species need male support for the successful upbringing of their progeny (Wynne-Edwards 1987; Gubernick and Teferi 2000). It is unknown, however, if females apply a “parental care” criterion in their preference for a certain male. Another choice criterion may be the male’s genetic background because mating with a particular male may confer greater fitness on the offspring of the choosy female (increased viability, higher mating success, higher fecundity). This is due to the fact that selection acts on the variation in heritable traits; thus, a new combination of genes may increase the fitness of the offspring (Møller and Alatalo 1999). Other criteria employed are the following: mating status, because multiple-mating males tend to have reduced sperm counts and lower fertility in later ejaculates (Austin and Dewsbury 1986); infection status (Klein et al. 1999); dominance status (Shapiro and Dewsbury 1986) (see Chap. 3); body size (Solomon 1993); spatial ability, such as orientation and ability to locate mates or nests (Okasanen et al. 1999; Spritzer et al. 2005); relatedness (Keane 1990); and familiarity (reviewed in Anderson 1994). The latter criterion, for instance, is used by the highly inbred naked mole rat (*Heterocephalus glaber*), where reproductively active females prefer to associate with unfamiliar males, a mechanism that is interpreted as inbreeding avoidance (Clarke and Faulkes 1999) or at least to keep inbreeding below a critical threshold. Even if females are not very selective about their mating partners, they may still have postmating selection mechanisms implemented that allow them to choose between the sperm of several donors and/or to differentiate in their energy allocation toward offspring sired by different mates (Thornhill 1983; Eberhard 1996; Ben-Ari 2000).

However, either way of female choice (before/after mating) based on heritable traits bears a theoretical dilemma. The preference of females for a particular trait (i.e., directional selection) causes genetic variability in this trait to diminish quickly until it becomes fixed (Anderson 1994). This, in turn, reduces choice until it ceases to exist because there is no variability left in the trait. Unfortunately, a heterozygote (fitness) advantage (Brown 1995; Falconer and Mackay 1995) does not provide a remedy to that dilemma because after a population has reached homozygote/heterozygote equilibrium, females cannot increase their offspring’s fitness any further by solely mating with a heterozygous male (Partridge 1983; Tregenza and Wedell 2000). However, during the last few decades, evidence has accumulated suggesting that heritability can be extended from fitness-related traits to life-history traits (Mousseau and Roff 1987; reviewed in Roff 1997). Furthermore, as is pointed out later in the chapter, in nature females base their choice on the weighting of multiple traits.

## 1.4 Polyandry, Fitness, and Genetic Compatibility in Rodents

As mentioned above, in mammals it is usually the female that is the choosier sex because females bear much higher costs in offspring production and upbringing due to the production of larger gametes and higher parental investment. Thus, one would expect that females increase their reproductive success by choosing and mating with one “high-quality” male, whereby only as many copulations should be performed as are needed to fertilize the egg to reduce the costs of mating. In contrast to these expectations, however, polyandry – the mating with more than one male during a single reproduction cycle – appears to be a common reproductive strategy among females of many species (Birkhead and Møller 1998). The intraspecific frequency of such multiple-male matings, however, varies greatly among rodent species. In red squirrels (*Sciurus vulgaris*) the frequency is only ~12% (Wauters et al. 1990), whereas in meadow voles (*Microtus pennsylvanicus*) it may reach 79% (Berteaux et al. 1999). In addition, the percentage of multiple paternities also varies greatly among rodents. Whereas in Columbian ground squirrels (*Spermophilus columbianus*) the proportion of litters sired by more than one male is ~16% (Murie 1995), in a promiscuous wild guinea pig (the yellow-toothed cavy, or *Galea musteloides*) it may go up to 90% (Hohoff et al. 2003). However, these numbers can vary in the same population across different years as shown for the 13-line ground squirrel (*Spermophilus tridecemlineatus*), where the proportion of multiple paternities found in litters ranged from 0 to 50% in different years (Schwagmeyer and Brown 1983). In addition to these varying percentages in multiple-male matings and multiple paternities across rodent species, there is also no clear picture regarding the effects of multi-male mating on the likelihood of conception and producing a litter. Whereas that probability was increased in Gunnison’s prairie dog (*Cynomys gunnisoni*) (Hoogland 1998), it appeared to be reduced in the Djungarian hamster (*P. campbelli*) and the deermouse (*Peromyscus maniculatus*) (Dewsbury 1982; Wynne-Edwards and Lisk 1984). In some species, there were no differences in conception and the birth rates between monoandrously and polyandrously behaving females: e.g., black-tailed prairie dogs (*Cynomys ludovicianus*) (Hoogland 1995), Columbian ground squirrels (*Spermophilus columbianus*) (Murie 1995), prairie voles (*Microtus ochrogaster*) (Wolff and Dunlap 2002), and 13-lined ground squirrels (*Spermophilus tridecemlineatus*) (Schwagmeyer 1986, reviewed in Solomon and Keane 2007).

### 1.4.1 Polyandry Versus Monoandry

A simple and convincing test for whether polyandry is indeed an advantageous reproduction strategy for females to gain genetic benefits is to compare reproductive success of polyandrous versus monoandrous (mated more than once with the same male) females. A study on female bank voles (*Clethrionomys glareolus*) demonstrated

that offspring of polyandrous females performed significantly better at reproduction than those of monoandrous females, although other fitness parameters (e.g., offspring body mass or winter survival) showed no differences between the two offspring groups (Klemme et al. 2008). Interestingly, there was a sex bias in offspring reproduction performance because the better performance was mainly due to sons of polyandrous females producing more offspring than those of monoandrous females (Klemme et al. 2008). Similar results were obtained in a promiscuous South American rodent, the common yellow-toothed cavy (*Galea musteloides*). Polyandrous females that mated successfully with four males weaned more surviving offspring than monoandrous females, although the litter sizes did not differ between the two groups (Keil and Sachser 1998). Similar results were found in a semelparous (dies after reproduction) marsupial, the brown Antechinus (*Antechinus stuartii*, also called Stuart's Antechinus or Macleay's marsupial mouse, not a rodent but occupying a rodent-like niche), where polyandry greatly increased offspring survival (Fisher et al. 2006). When female house mice (*Mus musculus domesticus*) were experimentally bred with a sibling and a nonsibling, microsatellite data revealed that paternity was biased toward nonsiblings (Firman and Simmons 2008a, b). These data support the hypothesis that polyandrous females copulate with several males to induce sperm competition and/or to enforce cryptic female choice, thereby facilitating postcopulatory inbreeding avoidance and increasing the viability of their offspring (Yasui 1997; Keil and Sachser 1998; Firman and Simmons 2008a).

The question then arises regarding the requirements for a male to be designated "high-quality". Does it have to be a good provider of material resources (e.g., *Mus musculus* females mate more frequently with males that defend high-quality territories) (Wolff 1985), a good provider of genetic resources (see below), or both? It is easily comprehensible that multiple matings require higher fitness costs than do single matings; thus, material benefits may be a good compensation for these additional costs (Hosken and Stokley 2003; Klemme 2006). However, such obvious material benefits appear to be absent in many polyandrous species; thus, the alternative explanation is that polyandrous behavior is driven by genetic benefits (reviewed in Jennions and Petri 2000).

Monoandrous females also have to consider that if they mate with a male that has already mated multiple times in succession, his sperm count and sperm fertility may be reduced (Austin and Dewsbury 1986), temporarily limiting his fertilizing capacity. Therefore, monogamous females should mate with males that have not yet mated with other females (Salo and Dewsbury 1995). Among the socially monogamous prairie voles (*Microtus ochrogaster*), females indeed tend to choose unmated males (Pierce and Dewsbury 1991). Moreover, females of species that mate multiply, such as rats (*Rattus norvegicus*) and golden hamsters (*Mesocricetus auratus*), prefer to mate with previously unmated males (Krames and Mastromatteo 1973; Huck et al. 1986). However, this is not a general rule, as two multiple-mating species of voles, montane voles (*Microtus montanus*) and meadow voles (*M. pennsylvanicus*), do not display preferences for unmated males (Pierce and Dewsbury 1991; Salo and Dewsbury 1995). Unfortunately, the fitness consequences of these preferences (litter sizes, offspring viability) have not yet been explored, nor have studies investigated

if males of these various species have evolutionarily different responses (in terms of sperm production) to the various female choice strategies. Such an evolutionary response of males to monoandrous or polyandrous females, however, was shown in an experiment with house mice (Firman and Simmons 2010). A population of mice that had been held for a long time under enforced monogamy was divided into two groups to create a polygamous line (strong selection for sperm competition among males) and a monogamous line (continuing relaxed selection). It took only eight generations of selection for the epididymal sperm count and sperm motility to be significantly increased in the polygamous line compared with that of the monogamous line still under relaxed selection (Firman and Simmons 2010).

A comparison of rates of early reproductive failure and litter size variation among promiscuous, monogamous, and polygynous (but still relatively monoandrous) mammals found (after controlling for phylogeny) that promiscuous species had significantly lower rates of early reproductive failure (measured as ova produced but wasted between ovulation and early postnatal development) than monogamous and polygynous species (Stockley 2003). The pairwise comparisons included, besides other mammals, 15 high-multiple-mating rodent species and 7 low-multiple-mating rodent species. Monoandrous females compensated for higher early reproductive failure with increased ova production and thus produced average litter sizes similar to those of the average litter sizes produced by more promiscuous females. The results are consistent with predictions of the genetic incompatibility avoidance hypothesis (see below), although alternative explanations may apply as well (e.g., adoption of an insurance strategy of offspring overproduction and subsequent reduction according to local resource availability) (Stockley 2003).

Another interesting aspect is the occurrence of extra-pair copulations (EPCs) and extra-pair paternity (EPP) in monogamous species (see Chap. 2). A study in the European alpine marmot (*Marmota marmota*:  $n=98$  genotyped at 12 microsatellite loci and  $n=499$  genotyped at 5 loci) revealed that females actively sought EPPs (Cohas et al. 2006). The number of occurrences increased with the number of subordinate males present (rendering it more difficult for the dominant pair-male to guard the female); and extra-pair mates were more heterozygous than within-pair mates. However, the occurrence of EPP did not depend on male heterozygosity, indicating that the closer related within-pair males were also successful sires (Cohas et al. 2006). The study concluded that female choice for genetic benefits may be a mechanism driving EPP in monogamous species (Cohas et al. 2006). Interestingly, both the number and the proportion of extra-pair young increased with both high similarity and dissimilarity between the social pair. This is best explained by the genetic compatibility hypothesis (see below), a mechanism to avoid both inbreeding and outbreeding depression (Cohas et al. 2008).

### 1.4.2 *Intrinsic Male Quality Versus Genetic Incompatibility*

The potential gain of genetic benefits by polyandrous females leads to the “intrinsic male quality hypothesis” and the “genetic incompatibility hypothesis” (Zeh and

Zeh 1996; Jennions and Petri 2000; Colegrave et al. 2002; Roberts and Gosling 2003). The first one states that “high-quality” males carry “good genes” (Møller and Alatalo 1999; Colegrave et al. 2002; Neff and Pitcher 2005), and sexual selection for them is based on the assumption that good genes (good alleles) in males are equally good for all females because that is their intrinsic virtue (Iwasa et al. 1991; Anderson 1994; Rowe and Houle 1996). A good allele is defined as an allele that increases fitness independent of the architecture of the remaining genome, which in diploid organisms includes the homologue to the particular “good allele.” Across the genome, good genes show additive genetic variation (Neff and Pitcher 2005). The genetic incompatibility hypothesis, however, states that selection for genetic compatibility (or avoidance of incompatibility) arises because interactions between male and female genotypes determine offspring viability; therefore, a male that may be a genetically suitable mating partner for one female may not be suited for another (Brown 1995; Zeh and Zeh 1996, 2001; Tregenza and Wedell 2000).

Under the good genes model, variation in genetic quality of males is of interest for females (to recognize the good alleles), but may not be directly assessable (Iwasa et al. 1991; Anderson 1994); hence, secondary but recognizable (indirect) “indicators of quality” have to be employed. Such indicators are useful for assessing quality prior to mating, thereby avoiding resource investment in low quality offspring. However, the model leads to directional selection in males because females prefer males whose indicators promise good genes (Colegrave et al. 2002). The latter become a fixed trait in the population, and choice ceases to exist. Under the genetic incompatibility hypothesis the existence of intrinsically superior alleles is not necessary because each male is assessed separately and the male’s quality is determined by each female individually. Hence, quality assessment of males by females depends on the individual genotypes of the mating partners (parental genetic compatibility) rather than on the presence of male “good for all females” alleles (Brown 1995; Zeh and Zeh 1996, 2001; Tregenza and Wedell 2000; Colegrave et al. 2002).

Thus, a working definition of a *compatible allele* is that it is an allele that increases fitness when in a specific genotype – i.e., when paired with a specific homologue (overdominance) or allele at another gene locus (epistasis). Across the genome, compatible alleles then show *nonadditive* genetic variation. Thus, when variation in fitness exists because of compatible alleles, the population does not respond to directional selection, but the mechanisms of acquiring compatible alleles (e.g., preference alleles) respond to directional selection (Neff and Pitcher 2005). The interaction of genotypes, however, can only occur after mating. Females therefore need to have cytological and/or biochemical mechanisms in place by which male quality (=suitability of the male’s genotype) can be assessed directly without the use of prior secondary indicators. Such assessment could happen in at least two ways: (1) sperm of genetically better suited males would be given a greater chance to fertilize the egg than the sperm from a less compatible competitor or (2) females could distinguish between the offspring sired by different males. In the latter case, females could allocate more resources to offspring sired by males more genetically compatible with them, potentially leading to differential



viability of offspring sired by males that differ in their degree of genetic compatibility with the particular female (Tregenza and Wedell 2000). The model's advantage lies in the fact that this process does not lead to directional selection because compatibility needs to be assessed separately and anew for any new combination of mating partners, whereby both sexes maintain polymorphisms in their genotypes (Birkhead 1998). The avoidance of inbreeding, and thus the avoidance of accumulating deleterious alleles, can therefore be seen as the most widespread behavior under the genetic incompatibility hypothesis (Tregenza and Wedell 2000; Klemme 2006; Klemme et al. 2008). Theoretical models have shown that as soon as there are costs of mating involved some form of compatibility based sperm selection is necessary for the evolution of “polyandry for compatibility” (Colegrave et al. 2002).

Another aspect, which may not immediately come to mind, is the conservation of species via freezing of gametes (Fickel et al. 2007). The usual practice of freezing only sperm or oocytes (often sperm only) does not take into account the compatibility of genotypes as an important fitness trait of a species. Thus, it should be supplemented (whenever possible) by freezing compatible gametes (wherever compatible individuals are known) to improve the chances of fertilization after thawing (Fickel et al. 2007). This practice would better serve the purpose of conservation, although its feasibility might be limited.

## 1.5 Influence of the *t*-Complex on Behavior in Mice

### 1.5.1 *Organization and Impact*

The *t*-complex in mice, detected during the first third of the last century (reviewed in Bennett 1980), is a very large chromosome segment on chromosome 17 of the mouse genome (Bennett 1975; Lenington et al. 1992) with several of its genes already annotated (*t*-complex proteins: TCP1, TCPs 10a–c) [for chromosomal localization see the National Center for Biotechnology Information (NCBI) GenBank]. It consists of a number of tightly linked loci connected by at least four inversions (Artzt et al. 1982b) that all are inherited as a single genetic unit (haplotypes) due to the suppression of genetic recombination between them (Artzt et al. 1982a, b; Delarbre et al. 1988). Loci of the *t*-complex influence embryonic development, tail length, male sperm transmission ratio (Fraser and Dudley 1999), male fertility, and other traits. Among the tightly linked loci of the *t*-complex is also the major histocompatibility complex (MHC) (Artzt et al. 1982b), and some studies indicate interactions between the latter and other regions of the complex affecting mating behavior (Lenington et al. 1988; Lenington and Egid 1989). In total, the complex comprises about 1% of the total mouse genome, and the variants found in several species of mice may have evolved from a common ancestor (Delarbre et al. 1988).



### 1.5.2 Natural Occurrence and Distribution of the *t*-Complex

Wild mice are polymorphic for a recessive mutation that occurs within the *t*-complex, and heterozygous individuals can be found in most house mice populations (*M. m. domesticus*) as well in populations of at least three other species of the genus *Mus* (*M. m. musculus*, *M. cervicolor*, *M. spretus*) (Delarbre et al. 1988). Interestingly, in heterozygotes, carrying two different *t*-haplotypes, *t*-complex recombination is not suppressed, indicating that *t*-chromosomes may be mismatched only in the combination of a *t*- and a wild-type haplotype and not in the combination of two different *t*-haplotypes, because crossing over is permitted between the latter (Silver et al. 1980; Artzt et al. 1982a). To date, more than 25 *t*-haplotypes have been characterized, most of them being lethal in respective homozygotes (Silver 1985). So far, eight lethal classes and one semi-lethal class have been classified by genetic complementation tests (Bennett 1980). Homozygotes carrying the *t*-lethal allele die prenatally, male *t*-semi-lethal homozygotes are sterile, as are males carrying two complementing *t*-lethal haplotypes (Baker 2008).

### 1.5.3 What Maintains Deleterious Genes?

Without a particular mechanism maintaining the deleterious genes, one would expect *t*-lethals and *t*-semi-lethals to be quickly eliminated by selection. However, despite a strong selection against *t*-complex haplotypes (often also called alleles), they persist (as mentioned above) in a population in proportions of up to 25% (Lenington et al. 1992). The reason for that imbalance is distorted sperm segregation in males, also called transmission ratio distortion (TRD) (Bruck 1957; Bennett and Dunn 1971; Lyttle 1991), allowing heterozygous males to pass *t*-alleles on to more than 90% of their offspring [>95% reported by Ben-Schlomo et al. (2007); 80–100% reported by Baker (2008)]. Although the number of *t*-type sperms produced by heterozygous males equals their number of wild-type (+) sperms produced, TRD causes the latter to be damaged in some way, thus reducing their ability to fertilize a female (Fraser and Dudley 1999). Despite TRD, only ~25% of mice in wild populations are heterozygous (*t*/+) (Lenington et al. 1992). This, in light of TRD's much lower than expected frequency of *t*-alleles in natural populations, cannot be explained by chance; in fact, it was demonstrated to be due to avoidance of heterozygous mates by the opposite sex (Lenington 1983, 1991). Examination of preferences of homozygous +/+ females and heterozygous +/*t* females for males of both genotypes revealed that heterozygous +/*t* females but not homozygous +/+ females had a strong preference for homozygous +/+ males (Lenington et al. 1992). Thus, heterozygous females had greater avoidance of heterozygous males than did homozygous females (Lenington 1983, 1991; Williams and Lenington 1993), a finding that was independent of the particular *t*-allele the female was carrying (Williams and Lenington 1993). The usefulness of that strategy is easily comprehensible: From the mating of a heterozygous female with

a heterozygous male, on average 25% of the offspring are homozygously lethal for the *t*-allele, whereas the offspring from the mating of a homozygous female with a heterozygous male does not contain *t*-allele homozygotes. This shows that the female's avoidance of heterozygous males is related to her own genotype, indicating that (1) genes on *t*-haplotypes function as modulators of these preferences and (2) genetic compatibility influences mate choice (Lenington et al. 1992).

#### 1.5.4 *t*-Complex and Other Female Choice Guiding Traits

Female mate preference is also affected by factors such as parental genotype (Lenington and Egid 1985) and is stronger among females in estrous than among diestrous females (Lenington et al. 1992; Williams and Lenington 1993). In addition, when heterozygous *+t* females were forced to choose between two heterozygous *+t* males (one carrying the same *t*-haplotype, the other carrying a different one), they preferred the male with the haplotype differing from their own (Lenington et al. 1992). Interestingly, female partner preference is also affected by the dominance status of the male (traits affecting dominance status are heritable) (Drickamer 1992; Horne and Ylönen 1998). In a restricted situation, female mice give priority to male dominance status over the *t*-complex genotype (Lenington et al. 1992), indicating that there might be additional forces affecting the frequency of *t*-mutations in wild mice.

In addition to female effects, males also show behavioral variation. They are more aggressive toward heterozygous *+t* females and less likely to mate with them than with homozygous wild-type females (Lenington 1991; Lenington et al. 1992). The example with the *t*-complex and dominance shows that female mate choice is not a simple choice considering a single trait but, rather, a complex behavior influenced by more than just one trait. It also illustrates that the result of a female's mate choice (i.e., which male eventually fertilizes the egg) is the outcome of a relative weighting procedure by which various traits may be weighted against each other. Dominance, for instance, may be outweighed by infection status or spatial ability. Female house mice (*M. m. domesticus*) preferred odors from nonparasitized but subordinate males over those from parasitized dominant males (Mihalcin 2002, cited in Lacey and Solomon 2003; Kavaliers and Colwell 1995). In a laboratory experiment, female meadow voles (*Microtus pennsylvanicus*) – a species that, in contrast to den-living mice, is far more outspread territorially and lives at lower densities – preferred males with good spatial ability and low dominance rank over males with poor spatial ability and high dominance rank (Spritzer 2003).

#### 1.5.5 Recognition of Heterozygotes

The question then arises, how do the sexes recognize the trait “*+t*-heterozygous” in the opposite sex? About two decades ago, it was discovered that genes within the

*t*-complex are associated with specific odors (Drickamer and Lenington 1987) and that both males and females can use these smell cues to recognize and to discriminate against the genotypes of the opposite sex (Lenington 1991).

The mouse genome is fully sequenced (for the sequence of chromosome 17 see <http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?taxid=10090&chr=17>), but to date not all of its genes have already been annotated and/or assigned to chromosomes. According to GenBank, chromosome 17 carries 1,511 genes; but the function of many of them remains to be elucidated. Because the *t*-complex is so deeply involved in mate choice, the gene(s) that influences mating preferences should be closely linked to the *t*-complex itself. Indeed, tests with female mice carrying the partial *t*-haplotype *t*(w18) indicated that the genes controlling mating preferences lie in the region of the *t*-complex distal to the MHC (Lenington 1991; Lenington et al. 1992).

## 1.6 Influence of the Major Histocompatibility Complex on Behavior

### 1.6.1 MHC Organization in Rodents

During the 1960s it was discovered that one of the important gene clusters involved in the immune response in vertebrates is the MHC, which in mice is usually referred to as the H-2 complex (McDevitt and Chinitz 1969) and in rats as the RT1 complex (Kelley et al. 2005). MHC genes are important in tissue recognition, acceptance, and rejection (Steinmetz et al. 1982) because they encode ubiquitously expressed cell-surface glycoproteins, so-called transplantation antigens, that serve as recognition structures for cytotoxic T cells (Stroynowski et al. 1987). The MHC is usually highly polymorphic (reviewed in Jordan and Bruford 1998); and, in contrast to that in birds and fish, in mammals it is inherited as a single unit (haplotype). So far, about 100 alleles have been described in mice (Klein 1975, 1986), but their number is certainly much higher. In fact, the number of potential MHC genotypes comprising two sets of MHC alleles in each diploid individual could easily exceed the size of a population of a given species (Yamazaki and Beauchamp 2005). In the mammalian model, the MHC is generally divided into regions with similar function, including classes I, II, and III (Klein 1986) and extended classes I and II (Herberg et al. 1998). The number of genes and the presence and location of each region varies among species (reviewed in Kelley et al. 2005).

The class I region is composed of classic (Ia) and nonclassic (Ib) genes. MHC Ia molecules generally present peptide antigens to CD8 cytotoxic T lymphocytes through T-cell receptors, whereas the functions of MHC Ib genes are diverse (Williams et al. 2002; Holling et al. 2004). Interestingly, Ib molecules such as M10 genes have numerous positions that are (as in Ia molecules) under positive selection (Emes et al. 2004), sparking questions as to whether they are also involved in ligand

binding (Ishii et al. 2003). Members of both categories may act as ligands for receptors on natural killer (NK) cells.

Class II molecules can present antigens to CD4 T lymphocytes (T-helper cells) (Villadangos 2001). The turnover rate of peptides of the class I region is generally higher than that of the class II region (Takahashi et al. 2000). The class III region contains a highly dense selection of diverse immune and nonimmune genes (Aguado et al. 1996; Milner and Campbell 2001; Xie et al. 2003).

### 1.6.2 Mouse MHC

The H-2 complex is located on chromosome (chr) 17 of the mouse genome (*M. musculus*,  $2n=40$ ). It is organized in a manner similar to that of human MHC, except for an additional classic class I locus (Walter et al. 2002) located centromeric to the class II region (Kumánovics et al. 2003). The number and sequences of class I loci also differ from those of humans (Trowsdale 1995), although there is some homology regarding class I gene location (Amadou 1999). Unlike primate MHCs, the H-2 lacks MIC (MHC class I chain)-related genes. However, the MIC-related MILL gene family (MHC class I-like located near the leukocyte receptor complex) is located near the leukocyte receptor complex on chr 7 (Kasahara et al. 2002). Interestingly, some mouse species deviate in their MHC organization from this general model. The African pigmy mouse (*Nannomys setulosus*), for instance, has thousands of class I genes (Delarbre et al. 1992). Intermingled in the extended class I region (close to the telomere) are also numerous loci for olfactory receptors (ORs) (Kelley et al. 2005).

In contrast to many other mammals, mouse T cells do not express class II molecules on their surface, which indicates differences in genetic regulation of these molecules in comparison to other mammals (Holling et al. 2004).

### 1.6.3 Rat MHC

The RT1 complex is located on chr 20 of the rat genome (*R. norvegicus*,  $2n=42$ ). The RT1 class I region contains eight gene clusters (HLA has only 4). One of these clusters, RT1-A, is located centromeric to the class II region, similar to H-2K in the mouse (Walter and Günther 2000; Hurt et al. 2004). Like H-2 in mice, the rat RT1 lacks MIC-related genes (Hurt et al. 2004), such as MICA and MICB, which are present in humans, and has M-like class I genes, homologous to mouse H-2M, which are absent in the human MHC. RT1 also exhibits a duplication of C4 (a gene for a complement component) and flanking genes, but these genes are not tandemly duplicated as in the mouse and humans (Walter et al. 2002; Hurt et al. 2004). The rat MHC also differs by the presence of a larger number of BTNL (butyrophilin-like) genes centromeric to RT1-Da and a second and putatively functional HLA-DRB-

related gene, RT1-Db2 (Hurt et al. 2004). As with the exceptions to the mouse H-2 model of MHC complex organization, there are also exceptions to the rat model of MHC organization. For instance, there are differences within the class II regions; the mole rat (*Spalax ehrenbergi*) completely lacks DR genes; however, the multiple  $\alpha$ -genes and  $\beta$ -genes in the DP loci assume its functions (Nizetic et al. 1987). As in the mouse H-2, there are numerous ORs in the extended (telomeric) class I region (Kelley et al. 2005).

### 1.6.4 Polymorphisms and Antigen-Binding Site

Haplotypes of the MHC are determined by the combination of alleles at either locus (Kelley et al. 2005). In addition to these loci, a number of other genes are also known to reside in the H-2 region (Steinmetz 1983; see also GenBank). Whereas MHC class I gene products are expressed in all nucleated cells and are responsible for the defense against intracellular pathogens (e.g., viruses), class II genes are usually involved in defending against extracellular pathogens (e.g., parasites, bacteria). Each of the class I and II MHC proteins is a dimer that consists of two polypeptide chains (Eggert et al. 1999) (the  $\beta_2$ -microglobulin of class I molecules is not coded by the MHC). Some genes of the MHC are among the most polymorphic loci in vertebrates (Klein 1986), whereby the so-called antigen-binding site (ABS) – a domain of the glycoprotein that binds to the antigen – forms the most variable portion of the proteins (Hughes and Hughes 1995; Hughes and Yeager 1998), resulting in the above-mentioned more than 100 alleles in mouse MHC (Klein 1975, 1986). These allele differences among individual MHC complexes provide their carriers with different degrees of (1) resistance against pathogens (Potts and Slev 1995; Fröschke and Sommer 2005) and (2) susceptibility to autoimmune diseases (reviewed in Apanius et al. 1997).

### 1.6.5 Other Functions of the MHC

In addition to its immunological function of self/nonself discrimination, MHC loci contribute to an individual's odor (Singer et al. 1997; Schaefer et al. 2001): (1) directly, because some genes encode volatile-binding peptides and soluble proteins (classes I and II in mice, only class I in rats (Eggert et al. 1999) and (2) indirectly, because they influence the composition of the intestinal bacterial flora (in rats but not in mice) (Schellinck and Brown 1992). Thus, high variability in MHC alleles may translate into high variability of odors (Yamazaki et al. 1990), thereby providing the means of individual recognition (Eggert et al. 1999) and kin recognition (Schellinck et al. 1993; reviewed in Brown and Eklund 1994). The fact that MHC genes themselves generate a characteristic type of odor, rather than dedicated odor-determining genes, was shown by point mutations in H-2K and HLA transgenic mice, which generated distinct odor profiles in olfactory assays (Bard et al. 2000). Further evidence for a

central, odor-specifying role of MHC genes themselves was given by demonstrating that mice that lacked  $\beta_2$ -microglobulin (B2m), and thus were unable to express their genomic class I MHC genes, were distinguishable by scent from otherwise identical mice that had an intact B2m gene. This odor-type disparity appeared at 9–12 days of gestational age, the period during which the MHC is first detectable in fetal cells of normal mice (Bard et al. 2000). However, even though these experiments clearly demonstrate that individuals can be distinguished based on their MHC condition, they do not provide proof that this trait is also used in mate choice.

Some nonclassic class I genes in mice and rats are expressed in the vomeronasal organ (VNO) – a region that harbors numerous ORs genes – displaying an additional function in pheromone detection (Schaefer et al. 2001; Ishii et al. 2003; Loconto et al. 2003; reviewed in Emes et al. 2004). However, a study carried out in mice to investigate the role of VNO in the recognition of MHC odor types concluded that the VNO is not involved (at least not in Y-maze tests) in MHC odor recognition because surgical removal of the VNO did not disrupt MHC odor-type discrimination (Yamazaki and Beauchamp 2005).

### 1.6.6 “Balancing Selection” Versus “Rare Allele Advantage”

So far, six models have been suggested to explain the maintenance of MHC variability (Potts and Slev 1995), of which the two most influential are explained here. In the “balancing selection model” (often misleadingly called “overdominance”) (for definitions see Takahata et al. 1992), it is assumed that heterozygous animals are able to bind more foreign peptides than are homozygous individuals (Takahata et al. 1992). However, as pointed out above, there might be a trade-off between the heterozygote advantage (Irwin and Taylor 2000) by expressing numerous alleles on the one hand and the consequentially increased chance of autoimmune disease on the other (Tregenza and Wedell 2000). The maintenance of a balance between these two effects, in the end, promotes an optimal rather than a maximal degree of heterozygosity. This has consequences for female mate choice because females should choose males with an intermediate degree (the optimal complementary set of alleles) of dissimilarity (Penn and Potts 1999; Tregenza and Wedell 2000).

The second model, the “rare allele advantage” model, assumes that the pathogens and MHC alleles are under negative frequency-dependent selection. Thus, a female should be able to increase reproductive success by mating with a male that has a different MHC genotype than that of the female (disassortative mating), thus providing the offspring with a greater variety of MHC alleles (thereby increasing offspring viability). Such MHC dissimilarity from its parents would allow the offspring MHC to recognize pathogens that have evaded the parents’ immune cell repertoire (reviewed in Apanius et al. 1997; Penn and Potts 1999). Independent from the model, in both cases the progeny have an MHC dissimilar to either of the parents, resulting in improved resistance against pathogens.

### 1.6.7 Does MHC Influence Mate Choice?

Although the question of the MHC influencing mate choice has recently been addressed in species other than the mouse (Sommer 2005; Schwensow et al. 2007, 2008), most of the work was done in laboratory mice using MHC-congenic (strains that are genetically identical except for their MHC) inbred strains. Apparent MHC-based mate preferences were observed in crosses of strains set up to produce MHC-congenic strains (Yamazaki et al. 1976). However, strain variation in the source strains generated a widespread pattern of results; mate choice was strongest in homozygotes and weak or intermediate in heterozygotes (mice studies are reviewed in Jordan and Bruford 1998). Other studies have even suggested the presence of additional postmating selection mechanisms (Wolgemuth 1983; Wedekind et al. 1996). In vitro fertilization experiments with two inbred H-2 congenic mouse strains yielded nonrandom MHC combinations in the blastocysts, which according to the authors indicated either oocyte choice for the fertilizing sperm or an influence on the outcome of the second meiotic division after the sperm had entered the egg (Wedekind et al. 1996). Another mouse study showed that both MHC dissimilarity and a good gene indicator (e.g., male investment in scent marking) have a role in determining female preference (the balance of selection pressure on each trait depends on how females weight these desirable qualities under different conditions), but that their relative influence varied depending on the degree of variability in each trait among available males (Roberts and Gosling 2003). In some house mouse strains, the scent-marking rate (an indicator of “male quality”) superseded MHC dissimilarity as a predictor of female preferences. The latter became important only when differences in the scent-marking rates among males were small. The authors concluded that such interactions between condition-dependent and disassortative mate choice criteria suggest a mechanism by which female choice can contribute to the maintenance of additive genetic variance in both the MHC and the condition-dependent traits, even under consistent directional selection (Roberts and Gosling 2003). As already noted, female mate choice in nature is a complex behavioral pattern influenced by more than just one male trait.

To corroborate the results from experiments on laboratory MHC-congenic inbred strains, mating experiments were also performed with wild mice populations. In one of those studies (Potts et al. 1991), the analysis of progeny resulted in 27% fewer MHC-homozygous individuals than expected from random mating. However, another study (Eklund 1997), also carried out on wild mice, suggested that although females did make MHC-related choices they did not necessarily prefer mates dissimilar from their own family MHC genotype. They also chose similar genotypes, showing both assortative and disassortative behavior. This contradicts results from primate studies that showed that there is a MHC similarity disadvantage: Mating of individuals who shared the same MHC haplotype resulted in increased fetal loss (Knapp et al. 1996; Ober et al. 1998).

A study on another rodent, the Malagasy giant jumping rat (*Hypogeomys anti-merina*), also did not find associations of mating patterns with the MHC genotype



(Sommer 2005). It must be noted, however, that for rodents other than mice there exists no repertoire of MHC-congenic strains, rendering analyses regarding MHC-associated mate choice difficult. In these species, usually only parts of the MHC can be (and have been) studied. Often the homologue to the HLA-DRB2 locus is used, which in mice corresponds to H2-E $\beta$ 1 and in rats to RT1-D $\beta$ 2 (Kelley et al. 2005). So, if a study in nonmouse rodents fails to detect associations of mating patterns with the MHC genotype, it may be due to the fact that either there is indeed no such association or there is just no association with the particular locus studied, although associations may exist with other loci of the MHC (HLA contains more than 260 gene loci, and similar numbers are expected for H-2 and RT1) (Kelley et al. 2005).

These and other problems in the field of mate choice and MHC have sparked considerable controversy due to (at least partially) a lack of robustness of results, failure to reproduce results, flaws in experimental design, and interpretation of results. The point at issue in this controversy is the fact that it is difficult to demonstrate that mate choice depends on MHC variability and not on genotypes of loci that are only linked to the MHC rather than being a true part of it (Hughes and Hughes 1995). In the latter case MHC allelic diversity would be unimportant and had no influence on mate choice. The presence of an association between non-MHC loci in the MHC region and mate choice in humans was indeed suggested (Weitkamp and Ober 1998). Another argument that has been brought forward is that differences in patterns of nucleotide polymorphisms between the parts of loci that code for ABSs and those that code for non-ABSs cannot be explained by sexual selection (Hughes and Nei 1989; Hughes and Hughes 1995). However, this can be argued against if it is the ABS that influences mating preference (e.g., by determining odor) (Singer et al. 1997; Zavazava and Eggert 1997; Eggert et al. 1999). In addition, selection acts on single sites rather than on entire peptides; thus, differences in nucleotide polymorphisms between ABS and non-ABS are expected because both elements may well be under different selective pressures owing to their different functions.

A possible explanation for the controversial findings regarding MHC and mate choice is that the expression of MHC genes (at least of some) depends on heterogeneity in the environment (Ewing 1979) (i.e., on the infection status of the individual studied; Wedekind et al. 1996). Thus, in a pathogenic environment increased fitness would be achieved by the presence of particular individual MHC alleles (condition-dependent trait), which in turn could explain MHC-based selection of currently (in that environment) “good genes,” whereas in the absence of such pathogenic environment other alleles may be favored. Therefore, sexual selection of condition-dependent traits during mate choice could be used to select successful MHC alleles, thereby providing offspring with a higher relative immunity in their pathogenic environment (Grob et al. 1998; see also Roberts and Gosling 2003). However, it is not the mere presence of a particular individual MHC allele combination that is of relevance but, rather, their expression. However, because of the highly polymorphic structure of MHC, expression studies are difficult and still rare. Recently developed and established techniques to measure expression levels of MHC alleles (Axtner and Sommer 2009; Weyrich et al. 2010) will render such studies possible in the near future.

An additional, yet not explored aspect is that in the arms race between pathogen and MHC the pathogen should aim at manipulating the host's odor in a way that its host becomes attractive to the opposite sex (despite being infected), which in turn would increase the pathogen's chance to infect a new host during mating. Such strategy would balance the "dissimilarity strategy" of the host species.

Another difficulty lies in the comparison of mate-choice results from laboratory strains and wild mice. It stems from the fact that wild mice employ a large repertoire of mating patterns (e.g., multiple mating, EPCs) (Manning et al. 1992) that is lost when inbred strains are mated experimentally. Such differences were seen when mice held under semi-natural conditions were allowed to establish their own mating system (Potts et al. 1991). Under these conditions, male-controlled female settlements deviated from random expectations (in respect to MHC), and ~25% of the observed MHC homozygote deficits were accounted for by within-territory matings, superficially suggesting that males had based their mate choice on MHC. However, a closer look revealed that the main cause for the MHC homozygote deficit lay in extraterritorial matings by females, where they tended to choose males that had a higher degree of MHC dissimilarity than their territorial males (Potts et al. 1991, 1992).

Despite this ongoing debate, MHC loci remain prime candidates (together with the olfactory sensory system, see below) for involvement in mate choice (Jordan and Bruford 1998) simply because the exceptionally high levels of polymorphisms at MHC loci provide the variability required for a genetically based recognition system. In addition, plausible hypotheses exist for the mechanisms by which MHC molecules might generate individual odors (Schellinck et al. 1993; Zavazava and Eggert 1997; Eggert et al. 1999). For the sake of clear argument, it might be necessary to continue to use MHC-congenic strains in future research because it appears to be the only way to demonstrate unequivocally a direct role of MHC in mate choice (Jordan and Bruford 1998).

## 1.7 Other Genes Known to Influence Mate Choice in Rodents

### 1.7.1 *Oxytocin (Oxt) in Mice*

The gene for oxytocin (*Oxt*, also called *OT*) contains three exons (378 bp total length) and is located on chromosome 2 in mice (chr 2 F1|2 73.5 cM; GenBank <http://www.ncbi.nlm.nih.gov/mapview/maps>; NC\_00068.6) and on chr 3 in rats (chr 3q36; GenBank). The mature hormone itself is a nonapeptide, derived by enzymatic cleavage from a larger precursor. It is synthesized in the hypothalamus and released into the blood from the posterior lobe of the pituitary. It is also expressed in corpora lutea (reviewed in Stormshak 2003) and testes (Bathgate and Sernia 1994; Einspanier and Ivell 1997). The hormone has been associated with various

behaviors, including social recognition, anxiety, pair bonding, and maternal behavior (reviewed in Caldwell and Young 2006).

As noted earlier, if a male's trait in which a female is interested is not assessable directly, females have to employ other, indirect indicators on which to base their assessment of male quality (Iwasa et al. 1991; Anderson 1994). However, not only genetic quality can be evaluated this way, social information can also be acquired directly or indirectly from cues inadvertently produced by individuals ("inadvertent social information"). This "public information" can be used by other individuals in the population for their behavioral response (Danchlin et al. 2004). Female rodents use odors (olfactory cues) to adjust their responses to males.

To investigate the role of oxytocin in rodents, *Oxt* gene wild-type (*Oxt*WT) mice were compared with *Oxt* gene knockout mice (*Oxt*KO) in various preference trials (Kavaliers et al. 2006). In these trials, female *Oxt*WT mice distinguished between parasitized males (subclinically infected with a gastrointestinal nematode parasite) and nonparasitized males, displaying aversive responses (analgesia, increased corticosterone) to, and avoidance of, the odors of parasitized males. The response changed when the odors of another estrous female were associated with parasitized males. The presence of the odor of another estrous female together with that of an infected male (indicative of potential mate interests by other females) attenuated the aversive responses and resulted in a choice for the odor of the infected male (independent of the sexual status of the choosing female). Thus, some cues of one *Oxt*WT female's choice influenced the mate choice by another *Oxt*WT female, even leading to decision reversal. In contrast to *Oxt*WT females, the ability of *Oxt*KO females was impaired in terms of using odor to adjust their responses to either uninfected males of differing sexual states or infected males. It appears that oxytocin is required to process inadvertent social information (Kavaliers et al. 2006).

In female prairie voles (*Microtus ochrogaster*), oxytocin concentrations were increased in the nucleus accumbens during unrestricted interactions with a male compared with the absence of a male (Ross et al. 2009). How these concentration do or do not change in a situation where females are given choices between different males remains to be seen, although, as we have seen earlier, no differences in conception and birth rates were observed between monoandrous and polyandrous female prairie voles (Wolff and Dunlap 2002); therefore, strong differences might not be expected.

A different approach was taken in another study on mice, where strains were generated carrying either a null mutation in the oxytocin receptor gene (*Oxtr*<sup>-/-</sup>) or in the oxytocin gene (*Oxt*<sup>-/-</sup>) (Takayanagi et al. 2005). *Oxtr*<sup>-/-</sup> mice were viable and had no obvious deficits in fertility or reproductive behavior. Receptor-deficient females had normal parturition but displayed defects in lactation and nurturing, whereas adult *Oxtr*<sup>-/-</sup> males were deficient in social discrimination and showed elevated aggressive behavior. *Oxt*<sup>-/-</sup> sons from *Oxt*<sup>-/-</sup> females, but not from heterozygous *Oxt*<sup>+/-</sup> females, showed similar high levels of aggression. These data show that the OXT/OXTR system is part of the mechanism that shapes aggressive behavior in adults (Takayanagi et al. 2005), which in turn may influence the dominance status of a male and thus its reproductive fitness.

In addition to the effects on reproductive behavior mentioned above, testicular oxytocin has been shown to influence reproductive fitness directly. It promotes spermiation (removal of unnecessary cytoplasm and organelles from mature spermatozoa in the seminiferous tubules) and sperm transfer in mice (Assinder et al. 2002). A comparison of oxytocin wild-type mice (*Oxt*WT) with both oxytocin knockout mice (*Oxt*KO) and an oxytocin transgenic mouse strain (bOT4.2), which overexpresses testicular oxytocin, showed that both the timing of spermiation and the appearance of epididymal sperm differed significantly among groups (bOT4.2 < *Oxt*WT < *Oxt*KO) (Assinder et al. 2002).

### ***1.7.2 Pkdrej in Mice: Polycystic Kidney Disease (Polycystin) and REJ (Sperm Receptor for Egg Jelly, Sea Urchin Homologue)-Like***

The mouse *Pkdrej* gene, which in contrast to all other *Pkd* genes is expressed in the male germ line only, is a homologue to the sea urchin receptor for egg jelly (REJ). It is located on chr 15 (chr 15 E2) and contains only a single exon (GenBank: NC\_000081.5). It is a member of the polycystin-1 gene family, a family of integral membrane proteins that includes *Pkd1* as well as *Pkd111*, *Pkd112*, *Pkd113*, and *Pkdrej*. Members of the protein family are present in fish, invertebrates, and mammals. Polycystins are composed of multiple domains and are widely expressed in various cell types. In humans, mutations in polycystin-1 (PKD1) and polycystin-2 (PKD2) have been shown to be the cause for the dominant, autosomally inherited polycystic kidney disease (Sandford et al. 1999). Because in echinoderms polycystin-1 proteins are required for the acrosome reaction (Neill and Vacquier 2004), *Pkdrej* was proposed to be a component of the egg-coating zona pellucida glycoprotein 3 (ZP3)-activated signaling pathway (Jewgenow and Fickel 1999), triggering mammalian acrosome reactions (Hamm et al 2007).

The mouse *Pkdrej* precursor is 2,126 amino acids (aa) long and contains several functional domains. In addition to the 11 transmembrane domains, the three most prominent are (1) the 116 aa long PLAT/LH2 lipase/lipogenase motif of polycystin-1-like proteins, (2) the 544 aa long REJ domain in the extracellular N-terminal region, and (3) the 431 aa long polycystin cation channel (PKD channel) (GenBank <http://www.ncbi.nlm.nih.gov/mapview/maps>).

A recent study investigated the influence *Pkdrej* has on sperm competence in mice by generating a *Pkdrej*-mutated strain via replacement of the first six transmembrane domains by an internal ribosome entry site-LacZ/neomycin-resistance cassette (Sutton et al. 2008). Fertility of male *Pkdrej*<sup>tm/tm</sup> homozygous mice were unaffected in unrestricted mating trials. However, mutant males exhibited lower reproductive success when they had to compete with either wild-type males in sequential mating trials or in artificial insemination tests with mixed (mutant + wild-type)-sperm populations (Sutton et al. 2008). The study also revealed that sperm from *Pkdrej*<sup>tm/tm</sup> mice needed more than 2 h longer to become detectable

within the egg–cumulus complex in the oviduct than those of wild-type males. Although sperm from males of both genotypes were able to capacitate in vitro, one of the component processes of capacitation, the ability to undergo a zona pellucida-evoked acrosome reaction, was decelerated in sperm from mutant males compared to sperm from wild-type males. However, no genotypic differences were observed in another component process of capacitation, the transition to hyperactivated flagellar motility. Thus, at least two processes are differentially regulated by *Pkdrej*: exocytotic competence and motility. These findings suggest that *Pkdrej* controls the timing of fertilization in vivo through effects on sperm transport and exocytotic competence. Moreover, it is a factor in sperm-competitive postcopulatory sexual selection (Sutton et al. 2008).

### 1.7.3 Olfactory Receptors

We have elaborated on examples of how olfactory cues such as body odor or urine scent marks are used by rodents to communicate mate-choice-relevant (and other) traits and how they modulate the mate preference behavior. For instance, mouse urine vapor is composed of more than 80 chemical compounds (Singer et al. 1997) coming from large chemical groups such as alcohols and aldehydes, esters and ethers, ketones, aromatics, and acids (Schaefer et al. 2001). In addition, mouse urine contains major urinary proteins (MUPs) (in the rat they are termed  $\alpha_{2u}$ -globulins) that are produced in the liver and released into urine by filtration from blood (Novotny et al. 1999). These olfactory cues, however, are only the emitting (signal) part of the system. The complementary receiving end is comprised of ORs, as signals need to be received and processed properly to induce an adequate response. ORs are clustered in two sensory systems: the main olfactory system (MOS), with its genes belonging to the largest gene family yet identified (Gaillard et al. 2004); and the accessory olfactory system (AOS).

Receptors of the MOS, called olfactory receptors, belong to the seven transmembrane (7TM) G-protein-coupled receptor superfamily (GPCR) (Emes et al. 2004; Gaillard et al. 2004) and are expressed in the olfactory epithelium, which is connected to the main olfactory bulb (MOB) via nerve axons.

The mouse genome contains 913 intact OR genes and 296 pseudogenes (Godfrey et al. 2004). Humans have ~900 ORs (of which about two-thirds are pseudogenes) divided into 17 families and 300 subfamilies (Glusman et al. 2001; Young and Trask 2002; Zhang and Firestein 2002; Quignon et al. 2005). In the rat (*R. norvegicus*) genome, 1,493 intact ORs and ~350 putative pseudogenes have been identified (Quignon et al. 2005). The genes are clustered in 56 loci (including 8 loci with pseudogenes only), which contain 1–265 genes (including pseudogenes) and are distributed across 19 chromosomes (except chr 6, 18, and Y). The largest loci are on chr 3 (218 intact ORs/47 pseudogenes/37 subfamilies), chr 1 (131/18/54), and chr 8 (109/16/8). Subfamilies vary considerably in size and contain 1–61 genes (Quignon et al. 2005). Mouse (*M. musculus*) ORs are distributed over 51 loci

(including 2 loci with pseudogenes only) across 17 chromosomes (none on chr 5, 12, 18, or Y). Loci contain 1–244 genes (including pseudogenes) that were classified in 241 gene subfamilies by sequence comparison (Godfrey et al. 2004). The largest loci are on chr 2 (189 intact ORs/55 pseudogenes/36 subfamilies), chr 7 (107/26/50), and chr 9 (91/22/10).

As in rats, gene numbers per subfamily varied extensively in mice (Godfrey et al. 2004), indicating that some ligands (odor classes) may be more easily detected or discriminated than others, given that functional diversity is associated with OR subfamilies. The latter assumption is supported by the facts that (1) 94 mouse OR gene loci encode only genes of a single subfamily (92 other loci encode only 2–4 subfamilies) and (2) most subfamilies are encoded by just one locus (Godfrey et al. 2004). For example, mouse OR73 and OR74 both recognize aromatic aldehydes (Kajiya et al. 2001) and are members of the same subfamily of five ORs, leading to the assumption that the other three ORs of this subfamily may also detect aromatic aldehydes. So far, odor ligands have been identified for 22 mouse ORs (Krautwurst et al. 1998; Zhao et al. 1998; Kajiya et al. 2001), allowing the 19 subfamilies to which they belong (containing 96 ORs in total) to be examined for hypothetical functional assignments (Godfrey et al. 2004). Thirteen subfamilies, containing 59 ORs, were predicted to recognize aliphatic odorants, and the other six subfamilies (comprising 37 ORs) most likely recognize odorants of other chemical structures. A phylogenetic tree, constructed with sequences of one OR gene from each of the 241 subfamilies together with 25 ORs whose ligands were known for assignment purposes, showed that 9 (all encoded at a single locus on chr 7) of 13 subfamilies containing receptors for *n*-aliphatic acids/alcohols were located on one distinct tree branch, an observation that had also been made by others (Glusman et al. 2001; Zhang and Firestein 2002). OR subfamilies that contained receptors for other chemical classes of odorants were scattered among the other branches (Godfrey et al. 2004).

To study the effects of different odorants on a female (e.g., body odor or scent marks of different males), the response has to be measured either at the receptors directly or in the region of the brain where the signals are processed. Odor-induced neural activity in the MOB can be detected by measuring and mapping changes in *c-fos* mRNA expression (a proto-oncogene belonging to the immediate early gene family of transcription factors) in the glomerular layer of the bulb. Female anestrus BALB/c mice (MHC haplotype H-2<sup>d</sup>) exposed to urine odor of age-matched males from either of two H-2 haplotypes (mice strains B6.AKR:H-2<sup>k</sup> and C57BL6:H-2<sup>b</sup>) could clearly differentiate between the urine odors of the two male haplotypes, as indicated by the spatially different *c-fos* expression patterns evoked in the MOB (Schaefer et al. 2001).

Receptors of the AOS, called pheromone receptors, are expressed together with some nonclassic MHC class I genes (Ib; see above) in the VNO (Dulac and Torello 2003; Emes et al. 2004), which itself is situated in the septum of the nose. AOS family members belong to two types of receptor – vomeronasal receptor type 1 (V1R) and type 2 (V2R) – whose genes are widely distributed across the genome (Table 1.1). Like ORs, both AOS receptor types belong to the 7TM GPCR, but the difference between them is that V2R belongs to the family of C GPCRs (7TM at the C-terminus)

**Table 1.1** Number and distribution of vomeronasal receptor genes in the genomes of the mouse and rat

Chromosome no.	Receptor type	No. of receptor genes <sup>a</sup> in <i>Mus musculus</i>	<i>Rattus norvegicus</i>
3	V1R/V2R	–/3	–/2
4	V1R/V2R	1/–	1/–
5	V1R/V2R	2/3	1/1
6	V1R/V2R	49/3	54/3
7	V1R/V2R	41/13	47/2
10	V1R/V2R	–/3	–/2
13	V1R/V2R	29/–	–/–
14	V1R/V2R	–/1	–/1
17	V1R/V2R	13/6	16/2
X	V1R/V2R	2/6	1/1

V1R, vomeronasal receptor type 1; V2R, vomeronasal receptor type 2

<sup>a</sup>Without pseudogenes, without duplications, and without receptor-like genes. However, there are seven mouse and two rat V1R genes and ten mouse and one rat V2R genes that are not yet assigned to a chromosome and that will likely change those numbers once assigned. The GenBank search was carried out at: <[http://www.ncbi.nlm.nih.gov/projects/mapview/map\\_search.cgi?taxid=10090&qrng=901&query=vomeronasal](http://www.ncbi.nlm.nih.gov/projects/mapview/map_search.cgi?taxid=10090&qrng=901&query=vomeronasal)>

(Matsunami and Buck 1997). In terms of their functions, it is assumed that V1Rs bind to volatile organic compounds, whereas V2Rs bind to proteins (Emes et al. 2004).

The impact of the VNO on social and reproductive behavior in rodents was demonstrated by deletion of a cluster of 16 V1R genes, which resulted in significant changes of male and female behavior. Males showed reduced libido: The percentage of males that mounted a female was significantly lower in V1R-deletion mutant mice than in the wild-type animals (Del Punta et al. 2002), which is consistent with results obtained after surgical removal of the VNO (Clancy et al. 1984). V1R-deletion mutant females showed a reduced level of maternal aggressive behavior (Del Punta et al. 2002). Results from additional tests in V1R-deletion mutant males, however, differed from results obtained after VNO removal. For instance, the emittance of ultrasound vocalizations (70 kHz) by males during the first minutes of exposure to a female was not altered by deletion of the 16 V1Rs, whereas these calls were attenuated when the VNO was removed (Wysocki et al. 1982). In addition, the percentage and degree of aggressive behavior towards other males were likewise not altered in the mutants compared to the wild-type males. The study also identified three chemical compounds (of eight tested) that mutants were not longer able to detect (Del Punta et al. 2002), supporting the view that each receptor molecule binds only to a certain variety of ligand (Krautwurst et al. 1998; Zhao et al. 1998; Kajiya et al. 2001; Godfrey et al. 2004).

Tests to determine the role of the VNO in recognition of MHC odor types in mice revealed that VNO was not involved in these processes (at least not in Y-maze tests): Surgical removal of the VNO did not disrupt MHC odor-type discrimination (Yamazaki and Beauchamp 2005). This leads to the conclusion that it is not the AOS but the MOS that functions as the primary interface for interactions with the



complexity of MHC odor types (Singer et al. 1997; Schaefer et al. 2001; Yamazaki and Beauchamp 2005).

A male-specific, nonvolatile 7-kDa peptide was identified in mice tears by Kimoto et al. (2005). It is produced in the extraorbital lacrimal gland and released in tear fluid during direct contact with a female (Kimoto et al. 2005; Touhara 2007). The peptide has been named “exocrine gland-secreting peptide 1” (ESP1) and is a member of a likewise newly identified multigene family that consists of ~40 homologous genes clustered in proximity to the MHC class I region (Kimoto et al. 2007). ESP1 stimulates the female vomeronasal V2Rp5 receptor and evokes a calcium signal in vivo. Thus, peptides of the ESP family add to the variation in the pattern of communication signals between individuals, sex, strains, or species.

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2011, XVIII, 413 p., Hardcover

ISBN: 978-4-431-53891-2