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Genetic compatibility, mate choice and patterns of parentage: Invited Review

T. TREGENZA* and N. WEDELL*†
*Ecology and Evolution Group, School of Biology, University of Leeds, LS2 9JT, UK, †Department of Zoology, University of Stockholm, S-106 91 Stockholm, Sweden

Abstract

There is growing interest in the possibility that genetic compatibility may drive mate choice, including gamete choice, particularly from the perspective of understanding why females frequently mate with more than one male. Mate choice for compatibility differs from other forms of choice for genetic benefits (such as 'good genes') because individuals are expected to differ in their mate preferences, changing the evolutionary dynamics of sexual selection. Recent experiments designed to investigate genetic benefits of polyandry suggest that mate choice on the basis of genetic compatibility may be widespread. However, in most systems the mechanisms responsible for variation in compatibility are unknown. We review potential sources of variation in genetic compatibility and whether there is any evidence for mate choice driven by these factors. Selfish genetic elements appear to have the potential to drive mate compatibility mate choice, though as yet there is only one convincing example. There is abundant evidence for assortative mating between populations in hybrid zones, but very few examples where this is clearly a result of selection against mating with genetically less compatible individuals. There are also numerous cases of inbreeding avoidance, but little evidence that mate choice or differential fertilization success driven by genetic compatibility occurs between unrelated individuals. The exceptions to this are a handful of situations where both the alleles causing incompatibility and the alleles involved in mate choice are located in a chromosome region where recombination is suppressed. As yet there are only a few potential sources of genetic compatibility which have clearly been shown to drive mate choice. This may reflect limitations in the potential for the evolution of mate choice for genetic compatibility within populations, although the most promising sources of such incompatibilities have received relatively little research.

Keywords: genetic incompatibility, polyandry, reinforcement, selfish elements, sexual selection, sperm competition

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Introduction

Mate choice may be exercised by either sex, although, because they invariably invest more in their gametes, females are generally choosier than males. Females may choose mates on the basis of material benefits such as the quality of the male's territory or the size of a food gift she receives on mating. Alternatively, males may be chosen because they have genes which will confer greater fitness (including mating success) on the female's offspring. If males differ in heritable traits, then even if females do not choose their mate before mating, polyandrous females may still have the opportunity postmating to choose between the sperm of several males (cryptic female choice-Thornhill 1983; Eberhard 1996), and may also be able to invest differentially in embryos sired by different fathers.

Regardless of whether female choice occurs before or after mating, the major theoretical difficulty in understanding mate choice on the basis of heritable traits is that if particular traits are preferred by females, genetic variability in these traits will rapidly be exhausted. On simple theoretical grounds the fitness related traits which females are generally assumed to be choosing should not remain

Correspondence: Tom Tregenza. Fax: + 44 113233 2835; E-mail: gentbt@leeds.ac.uk

heritable. This paradox cannot be overcome through a straightforward fitness advantage to heterozygosity, because such an effect will drive the population towards a genetic equilibrium, at which point females cannot increase the fitness of their offspring by simply choosing to mate with a heterozygous male (Partridge 1983; see below). Therefore, heterozygote advantage does not mean that females mating with fitter males gain advantages for their offspring — to do this requires females to mate disassortatively.

Despite theoretical questions regarding the maintenance of heritability in fitness related traits, there is evidence that life history traits (Mousseau & Roff 1987; Houle 1992) and traits affecting offspring viability (Møller & Alatalo 1999) are heritable, as are sexually selected traits (Pomiankowski & Møller 1995; but see Alatalo *et al*. 1997; Tregenza & Wedell 1997). A number of explanations have been proposed for the maintenance of variance in sexually selected traits (Hamilton & Zuk 1982; Pomiankowski & Møller 1995; Rowe & Houle 1996). These explanations are based either on a rapidly changing environment, benefits of high trait variance or large numbers of loci affecting sexually selected traits. However, there is an alternative class of explanations for female choice which do not suffer from the potential for choice to exhaust genetic variation. Rather than choosing males with intrinsically superior genes, females may choose males with whom they, as individuals, are genetically more compatible. Under this paradigm the particular combination of male and female genotypes dictates offspring fitness, so the most genetically suitable male for one female may not be the best for another. This scenario can be extended to include incompatibilities created by selfish genetic elements and intracellular symbionts.

The possibility that genetic compatibility may drive female choice and/or polyandry (Zeh & Zeh 1996, 1997) (see Box I) provides a potential explanation for these behaviours. It is also intriguing because if particular females are selected to avoid matings with particular, incompatible males, this may reinforce the incompatibilities and hence promote speciation.

Advantages of heterozygosity

The extreme examples of heterozygote advantage (defined broadly to include all benefits of heterozygosity) are revealed by homozygote disadvantage in matings between relatives (Pusey & Wolf 1996). Inbreeding, mating with an individual with whom you share genes from a common ancestor, may theoretically result in incompatibilities for two reasons: (i) Dominance — heterozygotes experience lower expression of recessive deleterious mutations; and (ii) Overdominance — certain heterozygotes are superior *per se*, perhaps because they produce a greater variety of gene products. There is still no consensus on the relative contributions of these two effects where individuals are closely related, although there is more evidence that dominance is important (Thornhill 1993).

Although a distinction tends to be drawn between the higher fitness of the offspring of unrelated parents (compared to closely related parents) and heterozygote advantage in general, this is essentially an arbitrary division (Shields 1982). All cases of reduced fitness resulting from dominance and overdominance effects can be regarded as lying on a continuum from incest to complete outbreeding. In reality, complete outbreeding does not exist — if one traces a completely outbred population backwards in time it must double in size every generation. All matings result in inbreeding to some degree and offspring are liable to suffer from the effects of homozygosity due to dominance and overdominance.

Mating between relatives

Part of the reason why avoidance of breeding with close relatives is regarded as a special case of mate choice for genetic compatibility is that the prevalence of deleterious recessives will be limited by selection, so their effects will tend to be rare except in close relatives. A second factor is that the high probability of negative effects of homozygosity in matings between close relatives means that selection may act to promote alleles which reduce incestuous matings. Such mechanisms are common in plants where the potential for self-fertilization has led to the evolution of self-incompatibility (SI) systems (Matton *et al*. 1994; Williams *et al*. 1994). SI exaggerates the effects of genetic incompatibility due to dominance and overdominance by reducing self-fertilization or aborting embryo development (Waser 1993). As well as avoiding self-fertilization, SI will create incompatibilities with other individuals who share the same incompatibility alleles, as revealed by the spatial structure of incompatibility found in the tree *Dombeya acutangula* (Gigord *et al*. 1998). It has been suggested that the major histocompatibility complex (MHC) in animals is also a mechanism to avoid inbreeding (see Box II). In general SI alleles or their animal equivalent are only effective at reducing deleterious effects due to dominance and overdominance in close relatives because recombination breaks down the association between the incompatibility loci and the loci which harbour deleterious recessives or are less advantageous as homozygotes. An exception to this, where SI leads to genetic incompatibility between distantly related individuals, is where the alleles associated with inbreeding depression are closely linked with alleles for SI, as may be the case in the MHC. Relative to plants, genetic systems which reduce matings between relatives in animals are less well understood, although there is abundant evidence that many species avoid mating with kin (Blouin & Blouin 1988; Pusey & Wolf 1996).

There is evidence that inbreeding avoidance can occur postmating. In laboratory matings between sand lizards

Box I

Genetic compatibility and polyandry

Genetic compatibility (GC) has become the focus of recent attention (Zeh & Zeh 1996, 1997; Jennions 1997) in part because of growing interest in potential genetic benefits to females of mating with more than one male. If males vary in their genetic compatibility with females, and there is some mechanism by which sperm of more compatible males is more likely to fertilize the female's eggs, or if females can invest more resources in embryos sired by more compatible males, then genetic compatibility could drive polyandry. This role for GC in driving polyandry is attractive because polyandry is extremely common and frequently unexplained. Also, the intimate association between sperm and the female reproductive tract means that differential success of more compatible genotypes might be more likely to occur after mating rather than beforehand, when information about compatibility may be scarce. Female genotype dependent variation in the relative postmating fertilization success of males has been found in the beetle *Callosobruchus maculatus* (Wilson *et al*. 1997), and between strains in *Drosophila melanogaster* (Clark *et al*. 1999) indicating the potential for differential fertilization success according to genetic compatibility. Even more persuasive is the pattern of differential fertilization success according to MHC genotype in mice (see Box II). As well as the potential for differential success of sperm, polyandry may also allow differential mortality of embryos or young before they have received maximum maternal investment (Stockley & Macdonald 1998).

Potential variation in genetic compatibility has become something of a default explanation for observations of females mating with several males having higher offspring viability where material benefits and 'good genes' explanations can be ruled out. Studies of adders (*Vipera berus*) (Madsen *et al*. 1992), sand lizards (*Lacerta agilis*) (Olsson *et al*. (1994), pseudoscorpions (*Cordylochernes scorpioides*) (Zeh 1997; Newcomer *et al*. 1999), field crickets (*Gryllus bimaculatus*) (Tregenza & Wedell 1998), cuis *Galea musteloides* (Keil & Sachser 1998) and tree swallows (*Tachycineta bicolor*) (Kempenaers *et al*. 1999) have all found that polyandry improves embryo or offspring viability. In all cases females do not appear to gain material benefits from mating and, except in the adder and sand lizard studies, there is good evidence that higher viability is not due to certain males having genes which confer high viability on embryos or offspring regardless of the female to whom they mate. Except in the reptile examples, all authors point out that their results are consistent with a genetic compatibility hypothesis for the benefits of polyandry. As yet, the sources of incompatibility in these cases are unknown, although it is striking that in both the reptile examples the populations have low genetic diversity, whilst in the crickets and cuis, experiments were carried out using long standing laboratory populations. Newcomer *et al*. (1999) suggest that this inbreeding might generate genetic benefits to polyandry. However, chronic inbreeding in a population and risk of inbreeding in any given mating are liable to have opposite implications for female choice and polyandry. Long periods of inbreeding will reduce all potential sources of genetic incompatibility — strong selection against deleterious recessives will reduce their frequency, alleles at overdominant loci will tend to be lost and coadapted gene complex diversity and selfish element diversity will be reduced, diminishing potential benefits of female choice and polyandry in inbred populations. However, if a population is small, but not yet inbred, the increased risk of inbreeding may increase selection in favour of female choice. It is possible that the tendency for inbreeding to reduce benefits of female choice is outweighed by increased risk of mating with a relative in the small populations used in most studies. For females to use polyandry to avoid closely related males fathering their offspring requires a mechanism by which sperm from more distantly related mates is more likely to fertilize their eggs. Such a mechanism appears to exist in sand lizards (Olsson *et al*. 1996; see Advantages of heterozygosity above). The possibility that similar mechanisms are widespread could be investigated using a comparative approach, looking at whether polyandry is more common in species with a population structure which exposes them to greater risks of inbreeding. Alternatively, females may use polyandry facultatively, so if they are in an environment where there is high risk of inbreeding (as distinct from being inbred) they may be more polyandrous. Somewhat paradoxically, noninbred populations are more likely to evolve mechanisms to avoid inbreeding. Therefore, the benefits of polyandry described from outbred populations of pseudoscorpions and tree swallows are more likely to be due to reduced incidence of inbred embryos than are the benefits of polyandry found in inbred populations.

An alternative role for polyandry is that it allows females to choose to fertilize their eggs using sperm with alleles which are more compatible with the environment in which the offspring will develop (rather than more compatible with the female herself). If a polyandrous female can preferentially use sperm from a particular mate according to where she lays her eggs, for which there is some evidence in dung flies (*Scathophaga stercoraria*) (Ward 1998), then this might drive polyandry although it cannot explain its initial evolution. Also, mate or sperm selection for habitat compatibility is rendered less likely by dominance effects because genes from adapted males will not produce adapted offspring unless the relevant alleles are dominant.

Box II

MHC and mate choice

The vertebrate major histocompatibility complex (MHC) is a cluster of genes primarily involved in immune response regulation (Kuby 1997; Janeway *et al*. 1999) [the MHC is also referred to as H-2 in mice and HLA (Human Leucocyte Antigen) in humans]. The MHC is inherited as a unit (haplotype) and is typically highly polymorphic and heterozygous — in the mouse there are around 100 different alleles at each locus (Klein 1986). Because of the role of the MHC in encoding proteins that present foreign peptides to T-cells, MHC differences between individuals are associated with differences in parasite resistance and susceptibility to autoimmune disease (reviewed in Apanius *et al*. 1997). The MHC plays a role in individual odour both through production of soluble proteins or proteins which bind volatile molecules and through influencing bacterial gut-flora. Coupled with the high variability of the MHC, this provides a basis for individual (Zavazava & Eggert 1997; Eggert *et al*. 1999) and kin recognition (reviewed in Brown & Eklund 1994). The origin of MHC allelic diversity may be in parasite and pathogen defence, with kin recognition as a secondary function. Alternatively, the MHC may originally have functioned as a genetic incompatibility system (recognizing self/nonself) and only later become involved in immune recognition (Burnet 1971; Monroy & Rosati 1979).

Why is the MHC a likely source of genetic compatibility variation?

The MHC is thought to be involved in genetic compatibility because of benefits associated with MHC heterozygosity inferred from the homozygote deficiency found in most studied populations. Also, females mating with a male with the same MHC haplotype suffer increased foetal loss in humans (Komlos *et al*. 1977; Schacter *et al*. 1984; Ober *et al*. 1997), and primates (Knapp *et al*. 1996), and there is some evidence for reduced hatching success in reptiles (Wittzell *et al*. 1999). Two models have been proposed for the maintenance of MHC diversity based on its role in immune defence. According to the overdominance model, heterozygotes are able to bind twice as many foreign peptides as homozygotes (Hughes 1992; Takahata *et al*. 1992), a benefit which may be balanced by costs of expressing numerous MHC alleles due to an increased chance of autoimmune disease. This trade-off promotes an optimal degree of MHC heterozygosity, leading to the expectation that females will prefer males with an intermediate level of MHC-dissimilarity (Penn & Potts 1999). The alternative model is that there is an advantage to rare alleles, such that MHC alleles are in a cyclical frequency dependent coevolutionary arms race with pathogens (Hill *et al*. 1991, 1992; Slade & McCallum 1992; Penn & Potts 1999) (cf. Hamilton & Zuk 1982). This favours MHC-disassortative mating preferences, resulting in progeny that are MHC dissimilar from their parents and therefore able to recognize parasites evading their parents' MHC (reviewed in Penn & Potts 1999). Similarly, common MHC alleles may be more vulnerable to molecular mimicry by pathogens, generating negative frequency dependent selection on MHC alleles (Apanius *et al*. 1997). Again, MHC disassortative matings results in progeny with a different immune-cell repertoire from their parents, enhancing their resistance and decreasing their risk of autoimmunity (Penn & Potts 1999).

Evidence for mate choice based on MHC compatibility

MHC differences between individuals may reflect general genetic dissimilarity (Brown & Eklund 1994). Therefore, studies which cannot explicitly demonstrate MHC specific effects, may simply reflect genetic incom-patibility due to relatedness. Also, most studies of MHC mate preferences cannot distinguish between loci within the MHC region and closely linked loci as the target of mate choice (Jordan & Bruford 1998).

There is now substantial evidence for MHC-based mate choice between unrelated individuals in several mammals (for recent reviews see Grob *et al*. 1998; Jordan & Bruford 1998; Ober 1999; Penn & Potts 1999). MHC-correlated mate preferences have been demonstrated in mice (e.g. Yamazaki *et al*. 1976, 1978, 1988; Egid & Brown 1989; Eklund *et al*. 1991; Potts *et al*. 1991; Manning *et al*. 1992; Eklund 1997, 1999; Arcaro & Eklund 1999), rats (Brown *et al*. 1987; Singh *et al*. 1987), and humans (Wedekind *et al*. 1995; Wedekind & Füri 1997; Ober 1999; Ober *et al*. 1997). Strong MHC homozygote deficiency has been reported in numerous small, isolated populations where the opposite would be expected in the absence of selection. This deficiency generally cannot be explained by differential mortality of homozygotes, indicating that disassortative mating is occurring.

Most work on MHC-based mate preferences has used inbred strains of laboratory mice identical at all loci except the MHC (reviewed in Jordan & Bruford 1998; Arcaro & Eklund 1999; Penn & Potts 1999). These studies have repeatedly demonstrated MHC-disassortative mating, in both males and females (e.g. Yamazaki *et al*. 1976, 1978; Egid & Brown 1989; Eklund *et al*. 1991; Arcaro & Eklund 1999), with homozygotes displaying the strongest preference (Yamazaki *et al*. 1976). Similar patterns have been found in outbred populations, although in outbred mice females appear to have stronger preferences than males (Eklund 1997) and a number of studies have not found any male preference (Yamaguchi *et al*. 1978; Yamazaki *et al*. 1978; Arcaro & Eklund 1999).

In human populations the frequency of MHC heterozygotes are typically higher than expected by chance (Degos *et al*. 1974; Black & Salzano 1981; Hedrick & Thomson 1983; Kostyu *et al*. 1993; Markow & Martin 1993). The best studied population are the Hutterites, a Caucasian religious isolate in North America originating from approximately 400 founders in the 1870 s (for review see Ober 1999). MHC-haplotypes of alleles at 16 loci have been defined in over 1000 Hutterites (Ober *et al*. 1998; Weitkamp & Ober 1999) revealing that couples sharing either certain MHC alleles or the whole MHC haplotype have significantly elevated rates of foetal loss (Ober *et al*. 1998). In addition to the possibility of a reduction in MHC homozygotes due to foetal loss, within 411 couples, mate choice was nonrandom, with fewer couples matched for MHC haplotype than expected (Ober *et al*. 1997), but no evidence for avoidance of particular MHC loci (Weitkamp & Ober 1998). This suggests that nonrandom mating with respect to MHC haplotypes may account for the observed homozygous deficiency (Ober 1999). Similar associations between spontaneous abortion rates and MHC-matching have been shown in outbred human populations (Komlos *et al*. 1977; Schacter *et al*. 1984; Jin *et al*. 1995). Furthermore, the MHC sequences common in Hutterites represent about half of the MHC sequences common in other outbred Caucasian populations, suggesting the association between MHC haplotypes and foetal loss may be general (Weitkamp & Ober 1999). Not all studies on MHC and mate preferences have found nonrandom mating (e.g. Nordlander *et al*. 1983; Sans *et al*. 1994; Hedrick & Black 1997) possibly because other factors influence mate choice (e.g. social status, education, ethnicity, etc.). Also, it may not be common to encounter identical, or even similar, MHC haplotypes in a large, outbred population (Grob *et al*. 1998).

There are few studies of nonrandom mating in relation to MHC in mammals other than mice and men. Studies of Soay sheep (Paterson & Pemberton 1997) and African buffalo (Wenink *et al*. 1998) found no evidence for MHC-disassortative mating, but other factors such as male–male competition may determine mating success in these species, with little opportunity for female choice. In fish, amphibians, reptiles and birds, MHC also varies considerably (e.g. Flajnik *et al*. 1993; Sato *et al*. 1996; Edwards *et al*. 1999; Wittzell *et al*. 1999), but so far no conclusive examination of MHC-based mate choice in these groups has been undertaken.

There is some suggestion that MHC-based mate choice occurs in the ring-necked pheasant. MHC genotype is correlated with viability and spur length, a character females use in mate choice (von Schantz *et al*. 1989, 1996). There is also a deficit of MHC homozygotes in the population, although there is no evidence that females differ in mate choice according to their own genotype.

How can individuals choose mates on the basis of MHC?

How individuals choose a mate with a particular MHC haplotype is unclear, although it is likely that genes controlling olfactory function located within the region are responsible. In humans, polymorphic olfactory receptor genes are located in the MHC (Fan *et al*. 1995), and both males and females prefer the odour of MHC-dissimilar individuals (Wedekind *et al*. 1995; Wedekind & Füri 1997), although there is no evidence that females prefer males with certain MHC haplotypes (Wedekind & Füri 1997). MHC preference in mice has a learnt component (Beuchamp & Yamazaki 1997). By rearing individuals in foster families with a MHC haplotype different to their own, MHC preferences can be eliminated (e.g. Eklund 1997; Arcaro & Eklund 1999), or even reversed (Beuchamp *et al*. 1988). Mice from wild populations kept under seminatural conditions, which also show MHC-dissimilar mate preferences (Potts *et al*. 1991, 1994) can similarly have their disassortative mate preferences reversed by cross-fostering (Penn & Potts 1998). As well as premating mate choice, in mice the MHC also influences fertilization (Wedekind *et al*. 1996; Rülicke *et al*. 1998). Either eggs select specific sperm on the basis of their own and the sperm haplotype, or the second meiotic division in the eggs is influenced by sperm haplotype. Proteins coded for by the MHC appear to be expressed on sperm (Fellous & Dausset 1970; Arnaiz-Villena & Festenstein 1976; Halim *et al*. 1982; Martin-Villa *et al*. 1999), making a choice of MHC genotype at the gametic level plausible. Infertile males in humans have recently been found to differ in their HLA-II alleles compared to males with normal sperm (van der Ven *et al*. 2000). Female genotype also affects sperm transport in mice with more sperm reaching the oviduct when females mate with males from a strain different to their own (Nicol & McLaren 1974).

Although the MHC is confined to vertebrates, there are indications that similar systems, where mate choice and genetic compatibility are under the control of a tightly linked set of loci may exist in other taxa. In the internally fertilizing colonial tunicate *Botryllus* fertilization of gametes is controlled by a highly polymorphic histocompatibility locus that also controls allorecognition (Scofield *et al*. 1982). In the ascidian *Botryllus primigenus*, fertilization does not occur if the sperm shares an allele with the diploid maternal genome (Oka 1970; cited in Bishop 1996) and a similar sperm/maternal genome incompatibility system appears to exist in some populations of *B. schlosseri* (Scofield *et al*. 1982). In another clonal ascidian with internal fertilization *Diplosoma literanum*, sperm are screened by a section of the oviduct, inhibiting the passage of self sperm, but also creating the potential for other forms of selection (Bishop 1996). Similar maternal cells are involved in regulation of fertilization in the externally fertilizing aclonal ascidian *Ciona intestinalis* (De Santis & Pinto 1991).

(*Lacerta agilis*), the proportion of a polyandrous female's brood sired by a particular male was an inverse function of his relatedness to the female (Olsson *et al*. 1996). Similarly, in the compound ascidian *Diplosoma listerianum*, there was an inverse relationship between relatedness measured through random amplified polymorphic DNA (RAPD) band sharing and number of larvae produced, ranked as either none, few or many (Bishop *et al*. 1996). In *Drosophila mojavensis* (Markow 1982) and *D. nigrospiracula* (Markow 1997), despite having enough stored sperm, females mated to brothers laid fewer of their eggs. This suggests that females mated to their brothers attempt to avoid producing low fitness offspring by delaying oviposition in the hope of finding an alternative mate. These studies indicate that mate choice to increase genetic compatibility through the positive effects of heterozygosity, including avoiding deleterious recessives, is widespread and may occur before or after mating.

Mating between unrelated individuals

There is evidence from a number of species that heterozygote advantage is widespread in relatively outbred populations (Mitton 1993; Bensch *et al*. 1994). Brown (1997, 1998) has argued that this should drive female choice for heterozygous males. If the relative proportions of the two homozygotes are unequal, a mutant female who chooses to mate with a heterozygous male will have more heterozygous offspring (Borgia 1979). However, for the average female this benefit will be offset by greater production of the lower fitness genotype of the unequally fit homozygotes. Therefore, simply mating with a heterozygous male will not generally increase the fitness of a female's young (Partridge 1983). There is evidence from *Colias* butterflies (Watt *et al*. 1986), and a number of other insect species (reviewed by Brown 1997) that heterozygous males are more likely to mate, but no evidence that females mating with such males have offspring with higher genetic fitness. The only exceptions are a limited number of situations where the loci responsible for homozygote disadvantage are either also responsible for some trait which can be used in mate choice, or are closely linked with such a trait. The best example is the MHC (Box II). Another possible case is the white throated sparrow *Zonotrichia albicollis* (Thorneycroft 1976; Houtman & Falls 1994) which has two colour morphs controlled by a chromosomal inversion. One type of homozygote is very rare suggesting that one allele is a strongly deleterious recessive. Nearly all matings are heterokaryotypic, which appears to be due to a combination of universal preference for the nonlethal homozygote, combined with superior competitive ability of heterozygotes. A second potential example is the seaweed fly, *Coelopa frigida* (Day & Gilburn 1997; Gilburn & Day 1999a) where around 10% of the genome is within a single inversion system, which has two karyotypes, α and β that do not recombine. Heterokaryotypic offspring have higher viability than homokaryotypes and are intermediate in size between the two homokaryotypes (αα are large and ββ are small). Mate choice for genetic compatibility would predict that small females should choose to mate with large males, and large females should mate with small males. There is some evidence that this does occur in some populations (Gilburn & Day 1994). However, further research suggests that the inversion system does not generally promote female choice for genetic compatibility, and suggests that past results may be due to pleiotropic effects of selection on female mating propensity (Gilburn & Day 1999b).

Evidence for pre- or postcopulatory mate choice due to deleterious recessives or overdominance. Numerous examples of inbreeding avoidance occurring both before and after mating. Avoidance mechanisms accentuate effects of homozygote disadvantage. Some evidence in unrelated individuals in white throated sparrows and perhaps seaweed flies. Good evidence in the MHC (see Box II).

Coadapted gene complexes

Between species

The clearest examples of mate choice for compatible genotypes are in the almost universal preference for conspecific partners. Indeed under some definitions, the ability of members of the opposite sex to recognize one another and mate defines the species itself (e.g. Patterson 1985). There are many examples of divergence in mating behaviour being driven by the cost of mating with members of the wrong species — a process known as reproductive character displacement (see Butlin 1989). In these cases gross genetic incompatibilities drive mate choice between species, which may incidentally affect mate choice within species.

There are two general explanations for why matings between species tend to produce offspring of lower fitness (a tautology under the biological species concept). First, there may be major differences in the genetic systems of the two groups (such as chromosome number, structure, etc.) which disrupt functions such as meiosis in hybrids. Second, within species, different genomic elements are coadapted (Dobzhansky 1948), making the phenotype liable to suffer if two divergent genomes are mixed. Coadapted gene complexes are groups of traits which have high fitness when they occur together, but reduced fitness when they do not. Coadaptation may be both external, providing a phenotype which is adapted to a specific environment; or internal, where genes are adapted to the presence of other alleles at other loci (Templeton 1986). External coadaptation occurs in situations where different species or races

are adapted to different environments so hybrids fall between the two and are disadvantaged in either situation. For instance, hybrids between races of the butterfly *Heliconius erato* are fully viable and fertile, but have coloration which exposes them to extreme predation, allowing the two forms to remain distinct (Mallet 1993). Internal coadaptation manifests itself as hybrid disadvantage even under standard conditions. For example, crosses between normally parthenogenetic strains of *D. mercatorum* derived from the same ancestral population show substantial hybrid viability disadvantages (Templeton *et al*. 1976). This inviability is due to interactions between loci, both within and between chromosomes and chromosome arms, indicating that coadaptation occurs between genes at unlinked loci. A potentially widespread and rapidly evolving source of coadaptation within species or races may result from coevolutionary arms races between the sexes. Because males are selected to increase their fertilization success even if this reduces female fitness there is a continuous conflict between the two. This is illustrated by work on *D. melanogaster* where females experimentally prevented from coevolving with males suffered reduced survivorship within 41 generations (Rice 1996). This continual coadaptation between the sexes could create genetic incompatibilities between species or populations.

Coadaptation can be used to define biological species as units between which genetic incompatibilities due to internal or external coadaptation of the genome reduce gene flow to a level below which recombination does not break down the coadapted gene complexes of the two groups. Under this definition, coadaptation of the genome, initially due to selection, creates genetic incompatibilities which are maintained through the deleterious effects of their disruption in hybrids. There may be a few species which are separated by changes in a single locus which fall outside this definition, but they are likely to be rare.

Between populations within species

Within species where, by definition, gene exchange is not severely limited, recombination will tend to prevent retention of more than one coadapted gene complex at any given set of loci. This effect will be reduced if the gene complex is small, or there is some form of recombination suppression. One factor which will prevent recombination between groups of individuals is spatial (or temporal) subdivision into geographical populations.

If populations are divided and subsequently come into contact, they may have evolved different coadapted gene complexes, such that hybrids have reduced fitness. This creates a selection pressure to choose members of your own population as mates, which will reduce gene flow further (reinforcement). However, cross-population matings create the potential for recombination to break down the association between genes responsible for reduced hybrid fitness and genes for assortative mating between populations. Recombination creates individuals with a mating preference for one population and genes associated with hybrid disadvantage from the other population, increasing gene flow and hence resisting divergence between the groups. There are numerous examples of assortative mating and assortative fertilization (see Howard 1999) success between divergent populations, but in most cases these are a by-product of divergence in mating signals in allopatry, and hence mate choice is not actually being driven by genetic compatibility. There are only a few convincing cases of assortative mating being driven by selection against genetic incompatibility due to outbreeding (Butlin & Tregenza 1997). Nevertheless, in pied flycatchers (*Ficedula* spp.) (Sætre *et al*. 1997), and sticklebacks (*Gasterosteus* spp.) (Rundle & Schluter 1998) there is strong evidence that reinforcement has occurred.

Analogous to reinforcement is the possibility of sympatric speciation driven by assortative mating. Recent models incorporating realistic assumptions about genetic architecture suggest that sympatric speciation can result from mate choice for individuals which are genetically more compatible due to coadaptation between multiple independent loci controlling ecological traits and marker traits used in mate choice (Dieckmann & Doebeli 1999; Kondrashov & Kondrashov 1999; Tregenza & Butlin 1999). Although there are no unequivocal examples of sympatric speciation driven by mate choice for genetic compatibility it does provide the most convincing explanation for the monophyletic cichlid species flocks found in African crater lakes (Schliewen *et al*. 1994).

Evidence from laboratory crosses between isogenic lines suggests that genetic incompatibilities encountered as a result of outbreeding may lead to postcopulatory variation in mating success, which could be a form of mate choice. Clark *et al*. (1999) examined fertilization success of males from six lines of *Drosophila melanogaster* and found interactions between male and female strain in the outcome of sperm competition. However, 'own line' sperm were not more successful and there was no evidence that differential fertilization success brought benefits to the female's offspring, so females do not appear to be choosing sperm from more compatible males. In sea urchins (Palumbi 1998, 1999) there is even more convincing evidence for choice at the gamete recognition level. Several species exhibit female selection for particular male genotypes at the locus for the sperm protein bindin. Within the genus *Echinometra* there is substantial intraspecific variation in bindin genotypes which is associated with positive assortative fertilization. However, although the bindin alleles are clearly under selection it is not clear whether females benefit from choosing sperm with a similar genotype to their own.

Within populations

The idea of an optimal level of outbreeding in which individuals 'strike an optimal balance between inbreeding and outbreeding' (Bateson 1983) is intuitively appealing. However, it is unlikely coadapted gene complexes will generally drive the evolution of such behaviour. Except in the case of small, very tightly linked groups of loci, multiple coadapted gene complexes can only be maintained in a panmictic population if they occur in a region of the genome in which recombination is suppressed, allowing coadaptation to develop. The most frequent sources of such recombination suppression are inversions and if the complex is on the Y chromosome. If coadapted regions are protected from recombination, females are not expected to exercise mate choice to maintain coadapted gene complexes, so they may not be a common source of variation in genetic compatibility. However, there may be benefits due to overdominance between inversion karyotypes (see heterozygosity section above).

Shields (1982) has argued that coadaptation should develop in the absence of barriers to gene flow, particularly with regard to highly dispersive species where gene flow could be limited by philopatry. In a study of pied flycatchers (*Ficedula hypoleuca*) Ratti *et al*. (1995) found that breeding pairs with low genetic similarity have more young who are not sired by the male of the pair. They also found a suggestion that more distantly related birds produce fewer fledglings, suggesting that pied flycatcher females may be engaging in extra-pair matings to reduce unspecified costs of outbreeding. However, in general there is little evidence of reduced fitness due to break up of coadapted gene complexes as a result of matings between animals which do actually meet in natural situations.

Evidence for pre- or postcopulatory mate choice due to coadapted gene complexes. Abundant between species and populations but in one or two cases this is likely to be a by-product of divergence, rather than as a selected trait. Very little evidence within populations — theoretically unlikely, no good empirical examples.

Selfish genetic elements and compatibility

Selfish genetic elements, defined broadly to include both selfish DNA and cytoplasmic symbionts or parasites, have effects which promote their own transmission at the expense of other genes. Several examples of female choice for male genotype are situations in which females choose according to whether males carry selfish elements, or are resistant to them. For instance, there is evidence that female stalk-eyed flies prefer males carrying suppressors of X-linked selfish elements (Wilkinson *et al*. 1998), although recent models (Lande & Wilkinson 1999; Reinhold *et al*. 1999) suggest that females may instead be choosing males which lack meiotic drivers altogether (Pomiankowski & Hurst 1999). Similarly, in the parasitoid wasp *Nasonia vitripennis*, females mated to two males, one of which carries a meiotic drive B chromosome, preferentially fertilize their eggs with sperm from the nondrive male (Beukeboom 1994). If all females are susceptible to the negative effects of the selfish elements they will all tend to avoid carrier males – a mating decision which cannot therefore be regarded as choice for genetic compatibility. However, selfish elements clearly do have the potential to create genetic incompatibilities because their effects frequently depend on interactions with the host genotype and according to whether selfish elements are present in both parents. For instance, multiple meiotic driver and suppresser genotypes could be segregating in a population, so that some females will be sensitive to some drivers but not others. Zeh & Zeh (1996) reviewed a number of potential scenarios in which selfish elements could drive postcopulatory choice. However, with the exception of the *t*-complex in mice (Box III), as yet the only available evidence for selfish elements driving variation between females in their choice of father for their offspring comes from crosses between populations where other forms of genetic incompatibility (see main text) are common.

Other situations where selfish elements might drive mate choice

There are a number of situations in which we might expect nonrandom offspring paternity resulting from intragenomic conflict (see Zeh & Zeh 1996). Cellular endosymbionts, for example the bacteria *Wolbachia*, cause incompatibilities by induction of parthenogenesis, feminization, male killing and reduced hatching success in crosses between uninfected females and infected males (Stouthamer *et al*. 1999). There is no strong evidence that animals can tell when they are infected with *Wolbachia* or other intracellular parasites and modify their mating behaviour accordingly. However, it has recently been suggested that male *Acrea encedon* butterflies prefer to mate with uninfected females (Jiggins *et al*. 2000), although the possibility that this is due to differences in female behaviour cannot be ruled out. A second plausible source of genetic compatibility are maternal effect lethals — genes which kill offspring of heterozygous females when they mate with either wild-type or heterozygous males. An example being the MEDEA gene in *Tribolium castaneum* (Beeman *et al*. 1992) which has the potential to create differences in mate choice because females homozygous for MEDEA can mate with any male whereas heterozygous females must reject wild type and heterozygous mates if they are to avoid losing a proportion of their offspring. Thirdly, imprinted genes may create compatibility differences between individuals. If

Box III

The t-complex in mice

Most populations of house mice, *Mus domesticus* and populations of three other species of *Mus* (Delarbre *et al*. 1988) include individuals heterozygous for a variable recessive haplotype at a region of tightly linked loci known as the *t*-complex. The *t*-complex is a large chromosome segment — about 1% of the total genome, linked by four inversions (Artz *et al*. 1982). The *t*-complex contains the MHC, and there is some evidence for interactions affecting mating behaviour between the MHC and other regions of the complex (Lenington *et al*. 1988; Lenington & Egid 1989). More than 25 different *t*-haplotypes have been found, most of which are homozygous lethals (Silver 1985). Despite strong selection against them, *t*-alleles persist because they are associated with segregation distortion in males (Bruck 1957; review in Lyttle 1991), with heterozygous males passing *t*-alleles to more than 90% of their offspring. Although heterozygous males produce equal numbers of *t* and wild type sperm, the wild type sperm are damaged in some way, reducing their fertilization ability (Fraser & Dudley 1999).

Despite segregation distortion, only around 25% of wild mice are heterozygous. This lower than expected frequency of *t*-alleles in natural populations appears be due to avoidance of heterozygous mates (Lenington 1983, 1991). Genes within the *t*-complex are associated with specific odours (Drickamer & Lenington 1987), and both males and females discriminate against the genotypes of the opposite sex based on odour (Lenington 1991). Comparing mice with the same MHC, wild female house mice avoid heterozygous males and prefer homozygous wild type males (Lenington 1983; Lenington & Egid 1985, 1989), as do inbred females (Levine *et al*. 1980). However, the magnitude of a female's avoidance of heterozygous males is related to her own genotype, indicating that genetic compatibility influences mate choice. Heterozygous females show greater avoidance than homozygous wild type females (Lenington 1983, 1991; Williams & Lenington 1993), although this is independent of the particular *t*-haplotype of the female (Williams & Lenington 1993). Female preference is also affected by other factors such as parental genotype (Lenington & Egid 1989), and becomes stronger during oestrus (Williams & Lenington 1993). In addition to female effects, males are more aggressive towards heterozygous females, and less likely to copulate with them than homozygous wild type females (Lenington 1983).

It is likely that a gene which influences female preference lies within the distal portion of the *t*-complex itself (Lenington 1991). Having a preference gene located within the *t*-complex enables both homozygous and heterozygous females to avoid the deleterious effects of mating with heterozygous males. Heterozygous females mating with heterozygous males will produce recessive lethal offspring, whereas the daughters of homozygous wild type females will not suffer directly, but will have heterozygous daughters which will suffer if mated with heterozygous males. However, because their heterozygous daughters inherit the preference gene (in the *t*-complex), they will also prefer homozygous wild type males (Lenington 1991). The fact that heterozygous females, who suffer more directly from mating with a heterozygous male show greater discrimination suggests that there may be costs associated with discriminating against heterozygous males, although as yet, these are unclear.

genes imprinted by males cause embryos to sequester high levels of resources from a female, then from the female's point of view, these need to be balanced by maternally imprinted genes which optimally suppress such effects to maximize the female's lifetime reproductive success (Moore & Haig 1991). Therefore, females might be expected to choose males whose embryo resource transfer imprinting matches their own suppression imprinting. No examples of such behaviour have been found, and how females might identify male imprinting type has not been speculated upon.

As well as the influence of particular classes of selfish element, females may exploit interactions between selfish elements. For example, females carrying feminizing cytoplasmic bacteria might benefit from mating with males carrying Y-drivers. Several *Drosophila* and *Nasonia* species harbour both meiotic driver genes and cytoplasmic bacteria including *Wolbachia* (e.g. Breeuwer & Werren 1993; Merçot *et al*. 1995) and multiple meiotic drive systems may also be widespread (e.g. Smith *et al*. 1998). Preferential fertilization by females according to whether males carry meiotic drivers, suppressors or cytoplasmic bacteria, in relation to their own genetic and cytoplasmic make-up, could provide another factor which might drive mate choice according to genetic compatibility.

Although several of the selfish elements described above have been shown to cause incompatibilities between populations, none have been demonstrated to drive mate choice dependent on individual genotype between individuals which are actually likely to meet in the wild. The only exception is segregation distortion, where there is evidence for differences in mate preference according to genotype in the mouse *t*-complex. However, the possibility that intragenomic conflict and intracellular symbionts may drive mate choice has been the subject of very little research, and postcopulatory choice (which has received less attention than precopulatory choice) may frequently be important for differential fertilization success of sperm from more

Table 1 Summary of potential sources of genetic compatibility differences between mates. Evidence that such sources exist, whether they theoretically have the capacity to drive mate choice for more compatible partners and whether there is evidence that they do so. Between population examples exclude sources which also act within populations

Potential source of genetic compatibility (GC)		Evidence that this source GC creates differences in mate compatibility in nature	Theoretical plausibility of evolution of mate choice driven by this source of GC	Empirical evidence for mate choice due to this source of GC
Heterozygote advantage	Between species	n/a		
	Between populations	Abundant—deleterious recessives important in hybrid vigour	Limited—except in the case of inbreeding avoidance. Requires compatibility alleles and choice alleles to be protected from recombination	No
	Within populations	Abundant—inbreeding avoidance	As above	Some—the MHC*
Coadapted gene complexes	Between species	Abundant—can define species	Yes—reproductive character displacement†	Abundant—interspecific matings are rare
	Between populations	Abundant	Yes—recent models for sympatric speciation‡	Some—pied flycatchers§ and sticklebacks¶
	Within populations	No	No—coadaptated gene complexes must not recombine so there is no benefit from choice as a result of coadaptation itself	No
Selfish genetic elements** (Segregation distorters, Maternal effect lethals, Cytoplasmic symbionts)	Between species	Yes***	Yes—reproductive character displacement†	No—but little research
	Between populations	Abundant††	?—Depends on the selfish element—requires coinheritance of selfish element and genes for choice as in reinforcement*	No—but little research
	Within populations	Abundant	As above	Some—*t*-complex in mice**

*Box II; †Butlin (1989); ‡Tregenza & Butlin (1999); §Sætre *et al*. (1997); ¶Rundle & Schluter (1998); **Box III; ***Breeuwer & Werren (1995); †† Hurst *et al*. (1996).

compatible males. However, it is also possible that within populations selfish elements, including endosymbionts and the suppressers of such elements may tend to sweep to fixation. Equally, genes involved in conflicts between the sexes, such as imprinted genes, may tend to evolve continuously, preventing the evolution of preferences for specific genes in the opposite sex. It may be that only in potentially rare cases where selfish elements and mate preference alleles are tightly linked (as appears to be the case in the *t*-complex) can selfish elements lead to the evolution of pre- or postcopulatory mate choice for genetic compatibility.

Future directions

Evidence for differences between males in their success in siring offspring as a result of their genetic compatibility with particular females is confined to a subset of potential sources of genetic compatibility (Table 1). Between individuals from the same population, this list is reduced still further. Within populations, examples are confined to avoidance of mating with close relatives, and a handful of cases such as the MHC and the *t*-complex, where chromosome regions protected from recombination harbour both the alleles which create incompatibilities and alleles which influence mate choice. However, there are a number of similar genetic systems, particularly chromosomal inversions, in a variety of taxa which could also drive differential fertilization success. The potential for genetic compatibility to drive mate choice between populations (reinforcement) has recently gained empirical and theoretical support but needs more work to assess its prevalence. Because of their ability to spread rapidly, selfish genetic elements may be common sources of incompatibility between populations, suggesting their potential to drive reinforcement. Within populations, the possibility that selfish elements could drive mate choice and differential fertilization success according to which elements the female carries is particularly exciting, not least because so much remains to be learnt. For example, can females carrying parasitic endosymbionts detect that they are infected and modify their mate choices accordingly? Do females carrying maternal effect lethals differ in mate choice compared to wild-type females? Studies must consider the potential for both pre- and postcopulatory choice, and the possibility that females use conditional strategies that do not require alleles for mate choice dependent on their own genotype. For example, if a female mates to a male with imprinted genes which do not match her own, with resultant effects during pregnancy, she may reject him as a future mate. Finally, the possibility that females make different mate choices depending upon the environment they anticipate for their offspring, and the role such a process may have in the maintenance of polyandry and genetic variability deserves further investigation.

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This review reflects the authors' research interests in sexual selection and why females frequently mate with multiple males. TT is a NERC research fellow and is conducting work using insect model systems to examine genetic benefits of polyandry and speciation. NW is a Royal Society university fellow working on sperm competition and sexual conflicts in insects. Both are currently in the School of Biology at the University of Leeds.
