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REVIEW

MHC-correlated mate choice in humans: A review

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Summary Extremely high variability in genes of the major histocompatibility complex (MHC) in vertebrates is assumed to be a consequence of frequency-dependent parasite-driven selection and mate preferences based on promotion of offspring heterozygosity at MHC, or potentially, genome-wide inbreeding avoidance. Where effects have been found, mate choice studies on rodents and other species usually find preference for MHC-dissimilarity in potential partners. Here we critically review studies on MHC-associated mate choice in humans. These are based on three broadly different aspects: (1) odor preferences, (2) facial preferences and (3) actual mate choice surveys. As in animal studies, most odor-based studies demonstrate disassortative preferences, although there is variation in the strength and nature of the effects. In contrast, facial attractiveness research indicates a preference for MHC-similar individuals. Results concerning MHC in actual couples show a bias towards similarity in one study, dissimilarity in two studies and random distribution in several other studies. These vary greatly in sample size and heterogeneity of the sample population, both of which may significantly bias the results. This pattern of mixed results across studies may reflect context-dependent and/or life history sensitive preference expression, in addition to higher level effects arising out of population differences in genetic heterogeneity or cultural and ethnic restrictions on random mating patterns. Factors of special relevance in terms of individual preferences are reproductive status and long- vs. short-term mating context. We discuss the idea that olfactory and visual channels may work in a complementary way (i.e. odor preference for MHC-dissimilarity and visual preference for MHC-similarity) to achieve an optimal level of genetic variability, methodological issues and interesting avenues for further research.

Contents

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1. Introduction

Protein products of the major histocompatibility complex (MHC, termed human leukocyte antigen, HLA, in humans) play a fundamental role in immune processes of vertebrates. In particular, antigens coded by MHC class I genes are responsible for recognition of cells containing proteins of foreign origin. Individual alleles of MHC genes code proteins that differ in the spectrum of short peptides they bind and transport across the cellular membrane. On the cell surface, MHC glycoproteins present these peptides to T-cells. Under normal conditions, negative selection in the thymus eliminates most self-peptide reactive T-cells. Therefore, mature T-cells can recognize and be activated only by foreign-peptide presenting cells. Activation of T-cells is the principal component of both cellular and antibody immune response (Austyn and Wood, 1994).

Most of the genes in the MHC region express extremely high intrapopulational polymorphism. Such polymorphism in virtually all vertebrates can hardly be interpreted as an incidental phenomenon, and dozens of evolutionary theorists, population geneticists, immunologists and behavioral ecologists have attempted to elucidate the evolutionary pressures that have shaped it. Most would argue that MHC polymorphism has arisen a through one of four kinds of balancing selection (Brown and Eklund, 1994; Brown, 1995; Hedrick and Loeschcke, 1996; Apanius et al., 1997; Penn and Potts, 1998b, 1999; Penn, 2002).

The first is the idea that polymorphism is maintained by heterozygote advantage. As MHC gene expression is co-dominant, MHC heterozygotes express absolutely more types of functional MHC proteins than homozygotes and are thus able to present a broader spectrum of peptides. The second hypothesis postulates that MHC polymorphism is a result of frequency-dependent selection in an evolutionary arms race between pathogens and the vertebrate immune system. According to this scenario, pathogens rapidly evolve the ability to escape recognition of most common host genotypes, for example by mutation that eliminates all peptides with affinities to common variants of the host MHC genes. Mutant variants then spread rapidly until this spread is halted by a gradual increase in the proportion of the host population with an initially rare allele that enables them to counter the variant form. Alternatively, Hedrick (2002) proposed a model focusing on the maintenance of MHC polymorphism under variable selection over time due to a varying degree of pathogen presence. It shows that temporal variation in resistance itself can maintain polymorphism even without co-dominant-based heterozygote advantage as described above. Finally, the fourth hypothesis postulates that MHC polymorphism is maintained by sexual selection. A vast majority of studies, initially carried out mostly on rodents, show negative assortative (or disassortative) mating in relation to MHC (for reviews see Jordan and Bruford, 1998; Penn, 2002; Piertney and Oliver, 2006). In other words, individuals of one or both sexes prefer partners possessing a relatively dissimilar MHC genotype to their own. It is worth noting that this sexual selection hypothesis also operates through frequency-dependent selection (i.e. due to preference for dissimilarity, individuals with rare alleles have a higher chance of being selected).

Selection of MHC-dissimilar partners increases offspring heterozygosity at the MHC. Because some studies indicate that MHC-heterozygosity is associated with advantage under immune challenge (e.g. Carrington et al., 1999; Penn et al., 2002), such disassortative preference can potentially

increase pathogen resistance in resulting progeny. However, a more general result of disassortative mating could be inbreeding avoidance, the consequence of which is an increase in average genomic heterozygosity, rather than heterozygosity specifically at the MHC. The effect of inbreeding avoidance across many loci is a decreasing risk of progeny being homozygous for a recessive deleterious allele with negative effects on fitness (Apanius et al., 1997; Penn and Potts, 1999; Penn, 2002). However, the question remains open as to what level of outbreeding is most advantageous. Studies on sticklebacks (*Gasterosteus aculeatus*) have found that highly MHC polymorphic individuals have a higher parasitic load and are less preferred as mates (for a review, see Milinski, 2003). The lower resistance of individuals with very high numbers of MHC alleles is probably caused by elimination of high numbers of T-cell clones in the thymus. This suggests that an optimal level may be more desirable than a maximal level of heterozygosity (Nowak et al., 1992).

To make matters even more complicated, both the pathogen-driven selection hypothesis and the inbreeding avoidance hypothesis do not specifically predict which criteria are used for the selection of ''desirable'' partners. It may be achieved through the preference for individuals bearing rare alleles relative to those in the population, or for individuals bearing alleles which are absent in the genotype of the choosing individual. The mechanism may vary between species. In conclusion, it is necessary to say that none of the hypotheses are mutually exclusive. For instance, MHC polymorphism may originate in natural selection for both rare alleles and heterozygosity. Subsequently, it could be maintained by sexual selection through either advantages of offspring heterozygosity and inbreeding avoidance.

Closely following a plethora of animal studies exploring the potential for sexual selection to influence MHC diversity (reviews in Jordan and Bruford, 1998; Penn, 2002; Bernatchez and Landry, 2003; Piertney and Oliver, 2006), empirical work on MHC-correlated mate choice in humans has also increased considerably during the last decade. These studies have mostly been based on odor preferences measured in the laboratory, although a few examine facial attractiveness and others focus on actual mate selection (see Table 1). The aim of this paper is to critically review all published human studies in each of these main areas, to summarise current findings and to propose directions for future research.

2. Evidence for MHC-correlated odor preferences

2.1. Disassortative preferences: a discovery

As already discussed, MHC-correlated mate choice has been observed across many genealogically and ecologically distant species; therefore it may also be expected in humans. This idea was first tested experimentally by Wedekind et al. (1995). Since the mouse studies of Yamazaki and colleagues indicated that MHC-associated mate choice was mediated by odor cues (Yamazaki et al., 1976, 1979), Wedekind et al. asked a group of women to rate the body odors of similarly aged men, the odor being captured (and assessed in the absence of visual information about the men) by presenting to women the T-shirts previously worn in bed by the men for two consecutive nights. In total, 44 men and 49 women (18 of whom were using hormonal contraceptives) took part in the experiment. Women not using oral contraception were selected, wherever possible, in the second week following menstruation (mean 12.4 d) because odor sensitivity is higher at this stage. Incidentally, testing women at this stage is potentially critical for another important reason: subsequent studies have reported preference shifts across different cycle stages for various aspects of mate quality (for a review, see Gangestad and Cousins, 2001).

On average, women not using the contraceptive pill rated as more pleasant the odors of men with MHC antigens that were dissimilar to their own. The smell of MHC-dissimilar men also reminded them of their current or previous mate's smell more frequently than did the smell of MHC-similar men. In contrast, women using the contraceptive pill preferred the smell of MHC-similar men. The authors suggested that the effect of hormonal contraception physiologically mimics pregnancy and interpreted their findings in terms of a shift in preference during pregnancy towards kin, who would be most likely to assist in offspring care. These results received wide attention and provoked speculation on mate choice consequences in women who found their mate while using the pill (Vollrath and Milinski, 1995; Boero, 1996). Although the explanation regarding pill use mimicking pregnancy is an attractive one, the actual effect of female steroid hormone substitutes in hormonal contraceptives on mate choice decisions remains basically unknown and does not precisely mimic all hormonal or other physiological differences that characterise pregnancy. In fact progesterone/estrogens are only two of a complex cocktail of pregnancy hormones and levels of all these hormones vary with pregnancy term (Bazer, 1998). Moreover, the frequency of pill use may correlate with other behavioral variables, for example the likelihood of being paired rather than single, or of being less sexually restricted. Such factors might potentially have as significant an effect on odor preference as contraception itself (Roberts et al., 2008).

Wedekind et al.'s study was also criticized for sensitizing odor raters (they were given nasal sprays and encouraged to read Süskind's novel *Das Parfum*) and for revealing the aims of the experiment to the raters (Hedrick and Loeschcke, 1996). Hedrick and Loeschke also suggest that, due to the relatively small sample size and only slight difference in rated attractiveness between MHC-similar and MHC-dissimilar subjects, the results are of low biological relevance. We find these arguments unconvincing as it is unclear how processes such as general olfactory sensitization and providing information regarding aims could have produced the systematic and specific effect of MHC on odor attractiveness that Wedekind et al. found in a blind test. Indeed, as Wedekind and Seebeck (1996) retorted, their experiment was designed to determine whether it was at all *possible* for MHC to influence human odor preferences and thus that the control of potential confounding variables and fostering of olfactory awareness was a legitimate experimental strategy. Furthermore, the effect of sample size is accounted for in the results of the statistical tests — it could as easily be argued that the effect was sufficiently robust to be detected even with the relatively small sample size that was used.

Table 1 Summary of studies on MHC-correlated mate choice in humans. It shows authors of the studies, HLA loci typed, source of data used for the analysis (i.e. body odor, facial images or MHC frequencies in couples), the type of statistical analysis (i.e. direct comparison between attractiveness judgments of MHC-similar/dissimilar or relatively heterozygous/homozygous individuals; correlation between attractiveness judgments and MHC-similarity or heterozygosity; computation of observed vs. expected levels of allele-sharing), target's gender and their sample size (F indicates women, M indicates men), rater's gender (and sample size), and the main finding of the analysis (disassortative, assortative or intermediate preference for MHC allele-sharing preference for heterozygosity, or no significant effect (ns).

Authors	HLA loci	Experimental procedure	Target sex (*N*)	Rater sex (*N*)	Preference
Body odor preference					
Wedekind et al. (1995)	A, B, DR	Similar/dissimilar	M (44)	F (49)	Disassortative
Wedekind and Füri (1997)	A, B, DR	Correlation	F (2), M (4)	F (58)	Disassortative
			F (2), M (4)	M (63)	Disassortative
Jacob et al. (2002)	A, B, C, DR, DQ	Correlation	M (6)	F (49)	Intermediate [a]
Thornhill et al. (2003)	A, B, DR	Correlation	F(48)	M (77)	Disassortative
			M (56)	F (65)	ns
Santos et al. (2005)	A, B	Correlation	F (29)	M (29)	ns
			M (29)	F (29)	Disassortative
Roberts et al. (2008)	A, B, DR	Similar/dissimilar	M (97)	F (110)	ns
Facial preference					
Thornhill et al. (2003)	A, B, DR	Correlation, het/hom	F(48)	M (77)	ns
			M (56)	F (65)	ns, Heterozygosity
Roberts et al. (2005b)	A, B, DR	Similar/dissimilar	M (75)	F (92)	Assortative
Roberts et al. (2005c)	A, B, DR	het/hom	M (92)	F (50)	Heterozygosity
Coetzee et al. (2007)	A, B	het/hom	F (59)	M (59)	ns
Lie et al. (2008)	Microsatellites	het/hom	F (77)	M (11)	ns
			M (77)	F (13)	Heterozygosity
Marital choice					
Pollack et al. (1982)	A, B, C, DR	Allele-sharing	61		ns
Rosenberg et al. (1983)	A, B	Allele-sharing	1017		Assortative [a]
Nordlander et al. (1983)	A, B	Allele-sharing	826		ns
Giphart and D'Amaro (1983)	A, B, C	Correlation	>3000		Disassortative [a]
Sans et al. (1994)	A, B, C	Allele-sharing	183		ns
Jin et al. (1995)	A, B, DR	Allele-sharing	542		ns
Ober et al. (1997)	A, B, C, DR, DQ	Allele-sharing	411		Disassortative
Hedrick and Black (1997)	A, B	Allele-sharing	194		ns
Ihara et al. (2000)	A, B, C, DR, DQ	Allele-sharing	150/300		ns
Garver-Apgar et al. (2006)	A, B, DR	Allele-sharing	48		ns

[a] Note particular comments in the text on the interpretation of these results.

2.2. Further tests: correlations between dissimilarity and odor hedonics

In a subsequent experiment carried out in Wedekind's laboratory, women rated the odors of six T-shirts worn by four males and two females (Wedekind and Füri, 1997). In this study, gender of the target subject was not taken into account. As in the previous study, it was found that both men and normally cycling women showed a tendency to rate the odors of MHC-dissimilar subjects as more attractive through a negative correlation between the number of shared alleles and pleasantness ratings. Results did not reach a formal level of significance ($p = 0.07$) when ratings by each sex were considered separately, but the effect was significant ($p = 0.02$) when ratings by male and female smellers were combined. This correlation was not evident in women using hormonal contraceptives, suggesting pill use had disrupted odor preference: in contrast to men and normally cycling women, and consistent with the previous results of Wedekind et al. (1995), pill users rated MHC-similar odors as more pleasant, although the correlation was not significant.

A methodologically somewhat different experiment was performed by Jacob et al. (2002). They collected odor samples (again, T-shirts) from 6 men (age 23–46); 49 women (age 13–56) took part in odor ratings. In this study, female raters were asked to choose a sample which they would most and least like to smell on an everyday basis. The most preferred odor donors shared significantly more alleles (2.3 on average) with the raters than the least preferred donors (1.5 shared alleles). The median match between smeller and donor was 2 (range 0–7). Based on these figures the authors suggested that an intermediate genetic distance is preferred. Moreover, they found a higher preference for the smell of donors carrying the same alleles as the smellers inherited from their fathers, but not their mothers.

This study, however, raises several issues. First, the raters come from a religious Hutterite community where a relatively high level of inbreeding was found. Whether this would

have an effect on odor ratings is debatable, but a more serious point is whether the results based on a highly specific sample of raters and a relatively small sample of donors can be generalized. The method of data analysis has also been criticized (Wedekind, 2002). It is based on raters as the unit of analysis, but each sample was rated repeatedly. Due to the very small number of donors it is possible that one of donors with a relatively rare haplotype was judged as less pleasant for other reasons, which could have led to the significant results reported. Such potential confounds might include the variation in ethnicity among odor donors (who derived from Ashkenazi Jewish, Dutch, English, German, Polish, Scottish, Sikh and Spanish ancestry) and their age (which varied from 23 to 47). Wedekind (2002) also noticed that the number of alleles shared by the donors and raters differs between those which were inherited from the father and those inherited from the mother. This fact could have biased the preference for alleles inherited from the father. McClintock and colleagues reanalyzed their data in defence to this critique and came to the same conclusion as in their original paper (McClintock et al., 2002).

A further comprehensive study on body odor preferences and its relations to MHC, fluctuating asymmetry, facial attractiveness and menstrual cycle phase was reported by Thornhill et al. (2003). The authors asked 56 men and 48 women (not using hormonal contraception) to sleep for two consecutive nights in a T-shirt. Odors captured on these T-shirts were rated by 77 men and 65 women. The data were analyzed using two different methods: following Wedekind et al. (1995), they analyzed results considering both the donor and the rater as the unit of analysis. Using the donor as unit of analysis (i.e. comparing ratings for each donor in relation to the MHC-similarity of the rater), analysis revealed that preference for female odors was correlated with MHC-dissimilarity among male raters, but there was no similar significant correlation for male odors smelled by MHC-similar or dissimilar female raters. Furthermore, there were no significant MHC-correlated preferences recorded when the rater was used as the unit of analysis. Male odor attractiveness was also negatively correlated with fluctuating asymmetry; however, no correlation between MHC and fluctuating asymmetry was found. The authors therefore proposed there are two distinct pheromone systems in action: one of these involves MHC, the other reflects other phenotypic traits related to male quality.

Recently, new evidence on MHC-correlated disassortative odor preferences was published by a Brazilian team (Santos et al., 2005). They asked 29 male and 29 female students to wear an absorbent cotton necklace on their chests for 5 days; these students also served subsequently as odor raters. All were serologically typed for *HLA-A* and *-B*. In addition, urine samples were obtained. During the 4 days after odor sample collection, rating sessions took place. Raters assessed all 29 samples of the opposite sex for pleasantness using a three-choice test. The analysis was performed by χ^2-tests (number of shared alleles $\times$ score categories). The only significant result was found for women rating male odors, such that as individuals shared more alleles, the higher the proportion of samples judged as 'indifferent'. This study has several methodologically debatable points. First, nine of the female subjects used hormonal contraception which might have potentially influenced odor preferences (cf. Wedekind et al., 1995; Wedekind and Füri, 1997). This fact was not, however, taken into account. Additionally, the statistics used are to some extent problematic as it operates with a high number of observations as if they were independent, but in fact they are not because each rater and donor contributes more than once to the sample.

Finally, Roberts et al. (2008) have repeated and extended Wedekind et al.'s (1995) experiment based on comparing ratings of three MHC-similar and three dissimilar odor donors. In this study, a total of 110 women and 97 men took part, all of whom were typed at the same loci (A, B, DR). Participants were tested twice: once when women were not using the pill and were tested in the late follicular stage of the cycle, and then again 3 months later. Just less than half of female participants initiated contraceptive pill use approximately 2 weeks after the first test (at the beginning of the following menstrual cycle); this design thus allowed for the testing of preferences before and after initiation of pill use, and for comparison with a control group who did not begin pill use. Roberts et al. found no significant effect of MHC-dissimilarity on preferences either in the first test (when all women were in the follicular phase of their cycle), nor of similarity in the second test among the pill-using group. Although these patterns thus did not replicate Wedekind et al.'s results, analysis revealed a significant shift in preferences among pill users, such that they preferred MHC-similar men to a greater extent after initiating pill use than before, which was not reflected among the control group. These results provide the first direct test of the effect of pill use in an actual alteration in preference and they exclude the possibility that there were correlational behavioral differences between groups. Furthermore, Roberts et al. (2008) reported that, although there was no correlation between pill use and relationship status (in or not in a current partnership), there was a significant effect of relationship status on MHC-correlated odor preference, such that currently paired women preferred MHC-dissimilar odors while single women tended to prefer MHC-similar odors. Had this pattern been reversed, this result would have provided a correlational explanation for Wedekind et al.'s results; as it is, perhaps it is suggestive that current intimate contact with partners confers a higher sensitivity and ability to discriminate the odors of MHC-dissimilar men.

2.3. Processing of MHC-correlated odors

A recently published paper by a German team showed that MHC-correlated axillary odor may have an impact on brain activity (Pause et al., 2006). Their data are based on a sample of 20 female and 20 male subjects who were tested using odor samples obtained from 61 donors of both sexes. Both raters and odor donors were typed for *HLA-A* and *-B* loci. Each subject was presented with two HLA-similar and one HLA-dissimilar stimuli using an olfactometer, and their brain activity was recorded by electroencephalography. It was found that MHC-similar samples were processed faster and evoked potentials were larger than MHC-dissimilar samples. Unexpectedly, the results were not different whether the subjects smelled the same-sex or opposite-sex samples. However, when men smelled same-sex samples, it activated their frontal brain regions. In contrast, the same condition in women (i.e. smelling women's samples) activated the

parietal area. Faster and larger brain responses to the odor of MHC-similar individuals suggest a processing advantage to such odors, and the authors conclude that avoiding MHC-similar partners (i.e. inbreeding) is of higher biological significance than attraction to MHC-dissimilar partners, whose odors elicited relatively weaker responses.

More evidence about MHC and perceptual responses to body odor comes from the laboratory of Frank Eggert. In their first study, they chose 19 women out of 400 who reported an acquainted person with strong odor; consequently both the women and the acquainted person were MHC-typed (Ferstl et al., 1991, 1992). Higher MHC-similarity was found between women and their strong-smelling acquaintances. It was reported that 10 out of these 19 women shared the same alleles at locus A and B. In addition, subjects labelled as strong-smelling shared the same alleles with target subjects in 60% of cases. Frequency of this allele in a control group with no strong odor was found only in 23% of cases, which was comparable to that in the general population. In an independently published study (Eggert et al., 1994), apparently based on the same subjects, it was found that whether the strong smell was judged positively or not did not appear to make a difference. Men labelled strongly smelling in the negative sense were also found to be more MHC-similar to the target female subjects compared to positively strong-smelling men.

In another study (Eggert et al., 1999), 82 women were asked whether their acquaintances would also take part in the study. Women rated the odors of MHC-similar women as more pleasant. In contrast, the odors of MHC-similar men were found to be unpleasant. The authors also took into account how close the friendship was between themselves and the acquaintance. Within-sex close friends (i.e. man—man, woman—woman) were more MHC-similar. On the other hand, in inter-sex close friends (i.e. woman—man), a lower degree of MHC-similarity was found. These results were confirmed in a follow-up study: 50 female and 54 male medical students took part. They rated the degree of friendship with a particular person twice during 1 year. There was a lower degree of MHC-similarity between close male friends, but no difference was found between women friends in the first rating. Close friends of the opposite sex (in both men and women) were more MHC-similar. A contradictory effect was found during the second round of testing, i.e. closer friends of the opposite sex were MHC-dissimilar. Close friends of the same-sex were found to be more MHC-dissimilar in men and more MHC-similar in women.

Although all these reviewed results have been repeatedly published in collections (Ferstl et al., 1991, 1992; Eggert et al., 1994, 1999), the full details of the methods used are not available and the published experimental design is rather unclear. For instance, it was stated that the degree of friendship was assessed on a five-point scale; however the results are shown in two bar figures. Moreover, none of the studies report results of statistical tests and one can only speculate about the significance of the presented differences. For these reasons, these studies should be interpreted cautiously, although they hint at intriguing effects.

2.4. Odor and MHC-heterozygosity

While most studies have examined the effects of MHC on odors within the context of disassortative mate preferences, there has been recent interest in the possibility that heterozygosity in odor donors might also be discriminable and preferred. This follows Brown's (1997) influential paper summarising a view of mate choice focussed on heterozygosity, mainly in offspring (hence the disassortative preferences already discussed), but also potentially in mates. In a later paper, Brown (1999) extended this specifically to consider heterozygosity at the MHC. In other species, male heterozygosity appears to confer advantage in terms of higher reproductive success (Sauermann et al., 2001; Foerster et al., 2003; Seddon et al., 2004) and with the expression of some sexually selected male traits which appear to be used in mate choice (Ditchkoff et al., 2001; Foerster et al., 2003).

To investigate whether heterozygosity might itself be found attractive in humans, Thornhill et al. (2003) tested this, in addition to disassortative preferences. In common with studies in other species, they found a correlation between male odor attractiveness and heterozygosity in the MHC at locus B; further analysis suggested that this preference was stronger outside of the fertile phase of their cycle. No correlation was found between female heterozygosity and attractiveness of their body odor.

Wedekind et al. (2006) recently investigated how a preference for heterozygosity might be mediated. Ratings of body odor attractiveness or pleasantness are commonly highly correlated with odor intensity, with more intense odors rated as less pleasant. The data used in this paper came from their original MHC study (Wedekind et al., 1995). They found that body odor of men homozygous at least at one of the three typed loci was judged more intense by MHC-dissimilar female raters, but not by MHC-similar raters. Similar data on the effect of heterozygosity on pleasantness were not presented.

2.5. MHC-correlated perfume preferences

Are odor preferences that are correlated with a smeller's own MHC-type restricted to the perception of conspecific body odor, or might they also correlate with other odors, such as those used in perfumery? To explore this issue Milinski and Wedekind (2001) focused on correlations between perfume preference and MHC. They sent a set of essences to a group of students (drawn from the same participants as in other studies: Wedekind et al., 1995; Wedekind and Füri, 1997). They first asked participants to judge perfume ingredients on the basis of whether they would like to wear a particular scent themselves. In a follow-up experiment, participants were asked to complete the same task as well as to judge the perceived suitability of particular scents for their partner. Thirty-six essences were used in the first test and 18 of them were chosen for the second. As MHC genes are highly polymorphic, the analyses were restricted to the two most common genes for each of the three loci (i.e. 6 in total). The data were analyzed by comparing each sub-sample carrying a particular MHC gene to all the others. This was done for all essences, separately for men and women. The obtained number of significant *t*-tests was then compared to the expected number of significant *t*-tests by chance alone.

In both experiments, an association between MHC and perfume preference for oneself was found. No such effect was observed for judgments in relation to a partner. Some partial results showed a somewhat different preference of

women using oral contraceptives, consistent with previous work. We assume, although it is not clear from the paper, that pill use was confirmed concurrent to sending out the essences rather than using the data given during MHC typing (as there was several years' delay between these two experiments, patterns of pill use could have changed considerably). In the light of these results, the authors conclude that perfumes are not used for suppressing one's body odor, but for promoting and augmenting it, and perhaps amplifying the perfume wearer's body odor cues in such a way that clarifies their MHC type to any potential mate.

3. Methodology of odor studies

As the previous section has demonstrated, several laboratory studies suggest a preference for odors of relatively MHC-dissimilar individuals of the opposite sex, although results across the six main studies are mixed (Table 1). To summarise, a preference for MHC-dissimilarity in women smelling male odors has been found in two studies (Wedekind et al., 1995; Santos et al., 2005), a preference for an intermediate level of dissimilarity in one (Jacob et al., 2002), while no significant preference has been found in two more studies (Thornhill et al., 2003; Roberts et al., 2008). In addition, Wedekind and Füri (1997) report a disassortative preference to a set of four male and two female odors. In terms of men smelling women (or both men and women: Wedekind and Füri, 1997) disassortative preferences have been found in two out of three studies.

How can we explain these variable findings? It may be that loss of human olfactory sensitivity may have occurred in our recent evolutionary past and that this has led to the weakening of otherwise clearer effects found in other species (arguably this may be more important in men, since women appear to emphasise the importance of odor more than men, especially in mate choice: Havlicek et al., 2008). However, this objection is countered by evidence from non-MHC odor studies that indicate remarkable human sensitivity to biologically relevant odors (Schaal and Porter, 1991). These include studies showing responsiveness to odors correlated with body symmetry (Thornhill and Gangestad, 1999b; Rikowski and Grammer, 1999), menstrual cycle phase (Singh and Bronstad, 2001; Havlicek et al., 2006), social dominance (Havlicek et al., 2005) and general genetic similarity (Roberts et al., 2005a).

Alternatively, human odor preferences for levels of MHC-similarity may simply be weak and their detection may accordingly be strongly dependent on methodology. This argument is more difficult to discuss at the current state of play, since there remain relatively few studies and these use variable methodologies. We critique some of the key issues below, although there are many other minor differences across studies.

3.1. Source of the odor stimulus

A first difference across studies is the source and nature of the odor stimulus. Most employ the same media (T-shirts) for a standard sampling length (two consecutive nights). Although the shirts could in theory be accumulating odor from anywhere on the upper torso, it is presumed that axillary odor contributes the most to overall body odor (e.g. Havlicek and Lenochova, 2008). However, Santos et al.'s (2005) study is an exception even at this fundamental level, since they chose to use cotton sachets rather than T-shirts, worn on the chest, and for 5 days rather than 2. Although we cannot say with any certainty that this is an inferior method to axillary sampling, it seems sensible to us that axillary focussed sampling should be the preferred method (either on T-shirts or using more direct methods, e.g. Havlicek et al., 2005), not least because the axillary region is known to be the richest site of apocrine glands and the strongest source of body odor in the upper torso (Stoddart, 1990).

3.2. Treatment of the odor stimulus

In addition to the source of the presented odors, the way in which they were treated before and during presentation to raters is variable across studies. Most used odor samples that were presented for rating soon after wearing. For example, in the two studies by Wedekind et al. (1995) and Wedekind and Füri (1997), odor donors wore shirts on Sunday and Monday nights, delivered them on Tuesday morning and these were rated on the same day. This highly organised schedule should probably be considered the ideal, although it presents difficulties in terms of ensuring female smellers are all in the late follicular phase at the time of odor rating. At least in the second study (Wedekind and Füri, 1997), this was achieved by repeating testing sessions for five consecutive weeks.

In contrast, for logistical reasons, two studies (Jacob et al., 2002; Roberts et al., 2008) chose to freeze samples between collection and presentation. Could this have affected the results? Three lines of evidence suggest this is likely to have only minimal effect. First, one study reporting significant MHC-correlated effects on odor preferences used frozen samples (Jacob et al., 2002), while one study that failed to find an effect used unfrozen shirts (Thornhill et al., 2003). Second, other studies reporting non-MHC related effects find significant and predicted results using frozen samples. These include correlations between odor ratings and detection of genetic relatedness in twin pairs (Roberts et al., 2005a), between odor ratings and facial attractiveness and bodily symmetry (Rikowski and Grammer, 1999) and between ovulatory status and attractiveness of female body odor (Singh and Bronstad, 2001). Finally, two studies have directly compared the reliability of axillary odor perception using samples that were either fresh or frozen for different length of time. Roberts et al. (2008) asked smellers to rate four samples from the same man, one of which was presented freshly collected and the other three had been frozen for either 1, 2 or 3 months. There were no significant differences in intensity or pleasantness ratings across shirts frozen for variable periods. Lenochova et al. (2009) carried out two similarly designed studies. They found no qualitative changes between fresh samples and samples collected from the same individual but frozen for a period of 2, 4 or 16 weeks. In the second experiment of their study, again no changes in hedonic ratings between fresh samples and samples frozen for 6 months were found.

Even among samples that were not frozen before presentation, there were differences in the interval between collection and assessment. While samples of Wedekind and

colleagues were assessed on the first day after shirt-wearing (i.e. up to perhaps 10 h post-wearing assuming a 07:00 rise time and 17:00 end time), those of Thornhill et al. (2003) were assessed on the same, and the next, day after wearing (i.e. up to 34 h post-wearing). The torso samples of Santos et al. (2005) were again different, being rated on the same day (i.e. up to 10 h) for women samples and on the following day for male samples (i.e. 24–34 h post-sampling). It is not clear how important these differences are, but, due to microbiologic activity (Gower et al., 1994), samples may have undergone systematic changes in odor quality under these different timelines. This objection is supported by the fact that only the data rated on the first day produced a significant effect on ratings.

3.3. Experimental design

The reviewed studies fall into one of two distinct approaches to experimental design, specifically in the rating protocol. The first approach is based on a balanced rating design in which subjects rate the odors of a fixed number of MHC-similar and -dissimilar individuals. The number of odors that can be presented at one time is limited by problems of olfactory habituation and adaptation (e.g. Jacob et al., 2003), and was six (three similar, three dissimilar) in the studies of Wedekind et al. (1995) and Roberts et al. (2008). This design is relatively demanding in a logistical sense as it requires the odor donors to be predetermined in advance of a testing session, for each individual rater. Furthermore, because of the polymorphic nature of MHC, it requires a relatively large pool of potential odor donors even for just one rater, in order to ensure a minimum complement of MHC-similar individuals. However, it is a highly sensitive method that arguably maximises detection of a possible effect.

The second approach is what we have called the correlational approach (Table 1). This is based on presentation of a number of samples to all raters (i.e. without attempt to select extremely similar or dissimilar odor donors in advance of testing), either 6 (Wedekind and Füri, 1997; Jacob et al., 2002) or 10 (Thornhill et al., 2003) at a time. Judgments are made on a rating scale anchored at either end by opposite adjectives (e.g. pleasant/unpleasant) or a smaller number of fixed alternatives (Santos et al., 2005) and are then correlated against the number of shared alleles between odor rater and donor. Although potentially less powerful than the balanced design method, its main advantage is that it allows analysis of the degree of preferred dissimilarity along a continuum of similarity, by means of higher order correlations. Another potential advantage is that it requires less preparation in terms of predetermining odor donors for particular raters. However, when this method is used it is important to use several stimuli sets, as Thornhill et al. (2003) did for example, rather than relying on only one set and running the risk of results being biased by a small number of unusual samples (see Wedekind's (2002) critique of Jacob et al.'s (2002) study).

3.4. Identity of loci under study

Some of the differences in reviewed studies might arise from the number and identity of the HLA loci typed (see Table 1). Four studies typed their participants at *A*, *B* and *DR* loci, one at only two loci (*A*, *B*) and one at five loci (*A*, *B*, *C*, *DR* and *DQ*). This might be important for a number of reasons. First, class I loci (*A*, *B* and *C*) may be more influential than class II loci in shaping individual odors because products of these genes are expressed in cells throughout the body. Second, and obviously, there may be locus-specific effects. As we have reviewed several studies suggest that locus B is particularly influential (Hedrick and Black, 1997; Thornhill et al., 2003). Indeed, this is exactly what might be predicted based on levels of polymorphism across different loci. Third, the total number of loci used to assess genetic dissimilarity influences the absolute number of shared alleles between individuals, because using more loci will tend to increase the mean level of allele-sharing across all paired combinations. Finally, individual loci vary greatly in the extent of their polymorphism (for example, the current number of known alleles at HLA-B is approximately three times that for HLA-C: http://www.ebi.ac.uk/imgt/hla/stats.html). Although loci are usually treated equally in the data analysis, this may not necessarily reflect their biological significance.

3.5. Rating questions

The way we phrase questions to the experimental participants really matters, as is widely recognized by psychologists. This fact applies equally to studies on odor preferences; thus some differences in the results could be attributed to the preference phrasing. Most studies use rating scales for odor pleasantness and intensity (Wedekind et al., 1995; Wedekind and Füri, 1997; Thornhill et al., 2003; Roberts et al., 2008). In contrast, Jacob et al. (2002) asked participants "which odor they would choose to smell all the time and which odor they would avoid". It is not clear whether such phrasing can be considered as falling within a mate choice context or rather a social partner context. The latter possibility is partly supported by results of Ferstl et al. (1992) who found that close friends tend to share more MHC alleles. Furthermore, Santos et al. (2005) asked raters to indicate which they found pleasant or unpleasant, and to which they were "indifferent", which may produce a different pattern of assessments than simple rating scales.

While there is probably little confusion in the raters' minds about how to rate an odor's intensity, it is possible that different raters interpret "pleasantness" in different ways. Although this is a descriptor commonly used in olfactory perception studies investigating odors other than axillary odor, MHC studies are specifically interested in judgments related to potential mate choice. It is possible that researchers need to pay more attention to rating context than previously, or at least to include additional context-specific questions in addition to intensity and pleasantness scales.

It should be noted in this regard that both Wedekind et al. (1995) and Thornhill et al. (2003) also asked participants to rate the "sexiness" of odors, and that these were sufficiently positively correlated with pleasantness judgments that they chose either not to present these ratings (Wedekind et al., 1995) or to conflate them (Thornhill et al., 2003). However, use of the adjective "sexiness" may not be explicit enough for raters unused to judging a T-shirt in a jar. After all, this is an unusual question, especially in relation to a judgment that may usually occur at a subconscious level. It may also tap the

same psychological dimension as ''pleasantness'', as evidenced by the high positive correlations recorded between them. In contrast, Roberts et al. (2008) followed pleasantness and intensity rating questions with the following scale: ''Is this how you would like your long-term partner to smell?'', where the scale was anchored at either end by the terms ''Not at all'' and ''Very much so''. Their logic was that this question specifically framed the task in a long-term context, building on a distinction commonly shown to elicit different qualitative judgments from short-term contexts in the facial attractiveness literature (e.g. Little et al., 2002a). Interestingly, it was this question more than either of the others which detected significant effects in terms of MHC preference differences correlated with relationship status and changes in preference related to oral contraceptive use (Roberts et al., 2008).

Thus precise phrasing is necessary to specify the social context that researchers are interested in. Results could, for instance, differ whether we ask about preferences in terms of long-term or short-term relationships. As noted above, several studies show that preferences vary depending on relationship context (for a review, see Little et al., 2002b). For example, in a short-term context women find masculine men more attractive compared to long-term context (e.g. Little et al., 2002a). With the exception of Roberts et al. (2008), and to some extent also Jacob et al. (for details see above), no other studies on MHC-correlated preferences specified this context of their preferences. Another relevant aspect is whether judges are in a committed relationship or not, since this may influence either their motivation or their preference, or both. With regard to the latter, those who are coupled might tend to base their judgments more in the sense of a short-term context while single individuals may tend to be more tuned to a long-term context. Such variation in preferences among paired and single women was found when assessing the odor of dominant men (Havlicek et al., 2005). We suggest that future studies should address these issues.

3.6. Repeatability of ratings

Evidence for MHC-correlated preferences would be strengthened if it could be shown that ratings are repeatable over time. In Wedekind and Füri's (1997) study, some of the raters (40 out of 121) and 2 of 6 odor donors had participated also in the authors' previous study (Wedekind et al., 1995), resulting in 18 combinations of raters and donors that had previously been tested. These 18 ratings across studies for odor intensity and pleasantness were not significantly correlated, although as Wedekind and Füri argue, this is a small sample and cannot be taken as strong evidence against repeatability. However, Roberts et al. (2008) did demonstrate repeatability of odor ratings both in ratings 1 h apart, and 3 months apart. Future studies should aim to test repeatability where possible, in support of the claim that preferences are robust.

4. How does the MHC influence body odor?

The primary function of MHC molecules is self/non-self recognition; it still remains open how the same type of molecules can influence body odor. To solve this issue, several hypotheses have been proposed, which we will describe briefly below; for a fuller account, the reader is referred to Penn and Potts (1998a). Most ideas have originated or focused on rodents, where the most significant source of scent is urine. In humans, however, urine is presumably of minor communicative relevance compared to axillary odor. First, MHC molecules may influence body odor directly. It has been found that MHC molecules occur in body liquids as saliva, sweat, urine and plasma (Wobst et al., 1998). On the other hand, the relatively large size of MHC molecules and their non-volatility makes this hypothesis improbable. Secondly, it has been speculated that body odor is influenced by peptides which are specifically transferred by particular MHC molecules. However, recent findings on mice show that non-volatile MHC peptide ligands can trigger dose-dependent neural responses in both the vomeronasal (Leinders-Zufall et al., 2004) and main olfactory organs (Spehr et al., 2006). Male mice also showed preference for the disparate MHC peptide mixture dissolved in same-strain female urine (Spehr et al., 2006). This is further supported by research on stickleback fish: specific peptide ligands were added to the water stream coming from male sticklebacks, and reaction of female sticklebacks to this stimulus was influenced by the MHC genotype of the male (Milinski et al., 2005). A third hypothesis proposes that MHC molecules specifically bind some volatile compounds and carry them to apocrine glands. Fourthly, MHC molecules might influence or even determine a spectrum of symbiotic micro-organisms living on the skin surface. Presence or absence of some micro-organisms and their metabolites may strongly influence individual body odor (Rennie et al., 1990, 1991).

5. MHC and facial attractiveness

Facial attractiveness plays a crucial role in sexual partner choice in humans (for reviews, see Thornhill and Gangestad, 1999a; Little and Perrett, 2002; Roberts and Little, 2008). Ober et al. (1997) speculated that other sensory modalities might potentially be involved in MHC-correlated mate preferences, but until only recently this had not been pursued, probably because, in contrast to the mechanisms described in the previous section, it is not obvious how MHC-genotype might be perceived in a visual trait like the face. However, some evidence now suggests that facial preferences may indeed correlate with both MHC-similarity and heterozygosity.

5.1. MHC-similarity

To date, only two studies have addressed the potential for a link between MHC-similarity and mate preference in faces. Roberts et al. (2005b) asked whether faces bear the same kind of disassortative cues as in odor by carrying out a visual analogue of Wedekind et al.'s (1995) experiment. The authors used facial images of 75 men previously typed for *HLA-A*, *-B* and *DRB1*. Images of three MHC-similar and three MHC-dissimilar men were rated by each of 92 women. Unexpectedly, faces of MHC-similar men, not MHC-dissimilar, were rated as more attractive, particularly when ratings were made in the context of judging attractiveness for a long-term relationship.

In the other study, Thornhill et al. (2003) did not overtly investigate MHC-similarity and facial attractiveness judgments at the level of individual opposite-sex pairs. Instead,

they asked 14 women and 15 men, who were independent of the MHC-typed target group (for sample size, see Table 1) to rate facial attractiveness on a 10-point scale. They then compared the mean attractiveness rating for each image, calculated from this independent panel, against the mean number of alleles that the stimulus shared with the rest of the sample (i.e. a mean dissimilarity score). Using this design, they found no effect of either mean MHC-similarity or allele rarity on facial attractiveness.

5.2. MHC-heterozygosity

Four studies have investigated effects of MHC-heterozygosity on face perception. Roberts et al. (2005c) examined the possibility that heterozygosity might be reflected in facial attractiveness. They presented facial images of 92 men to 50 female volunteers to rate. Men who were heterozygous at all three loci were rated more attractive than men with one or two homozygous loci. Attempting to find a potential mechanism for this effect, heterozygosity was not correlated with measures of facial asymmetry, but was positively correlated with perceived healthiness of skin, as measured using ratings of patches taken from the cheek part of the image and independently presented without any other visual cue. In a second experiment, they repeated the test with genotyped raters and showed that the effect of MHC heterozygosity is independent of MHC-similarity (Roberts et al., 2005c).

Coetzee et al. (2007), in a study with South African Tswana participants, showed images of 59 females to 59 males, each genotyped only at *HLA-A* and *-B*. They found no relationship between attractiveness judgments and MHC-heterozygosity in women's faces (they did not test preferences for male faces). Similarly Thornhill et al. (2003) found no effect of heterozygosity on facial attractiveness in both female and male faces as rated by individuals of the opposite sex.

Most recently, Lie et al. (2008) used facial images of 77 males and 77 females and estimated heterozygosity at 12 microsatellite markers (all in linkage disequilibrium with at least one HLA locus, including *HLA-A*, *-B* and *-DRB1*) and another 11 microsatellite markers on different chromosomes. Male and female images were rated for attractiveness by opposite-sex raters. The level of heterozygosity in the MHC, but not in other genetic markers, was positively correlated with facial attractiveness in males. In common with Coetzee et al. (2007) and Thornhill et al. (2003), this relationship was not found in females.

5.3. Methodology of face studies

Several studies on facial attractiveness show that MHC-correlated choice is not restricted to odor preferences. However, again, the evidence is mixed. One study (Thornhill et al., 2003) found no effect of mean MHC-similarity on facial attractiveness in both female and male faces. On the other hand, Roberts et al. (2005b) found that facial images of MHC-similar men were judged as more attractive to women. The main difference between these two studies is that Thornhill et al. (2003) did not genotype their raters and instead used a measure of mean MHC-similarity of stimuli compared with the rest of the sample. This, in effect, is a measure of rarity of MHC-haplotype, rather than similarity between rater and stimulus as measured by Roberts et al. As this approach is less sensitive to individual-level preferences, it may lack the power to detect the effect; to accurately assess effects of MHC-similarity on facial preferences, it is essential to use genotyped raters. In contrast, assessment of MHC-heterozygosity need not rely on genotyped raters.

In addition, studies of MHC effects on facial preferences need to take account of numerous potential confounds that are well known in mainstream facial perception research. While it is beyond the scope of this review to deal with these in detail, key issues that should be controlled as far as possible include directionality of gaze, facial expression, standardising background and lighting conditions, and so on. Furthermore, in humans, cultural variables such as hairstyle and clothing should be obscured as these can change discrimination of biologically relevant traits (see Roberts et al., 2004, for an example). Finally, facial judgments are susceptible to influence of ethnic differences between raters and stimuli. In the MHC-similarity studies described here, Roberts et al. (2005b) presented masked images (obscuring hair and clothes), used an ethnically homogeneous sample, and excluded men with beards, while Thornhill et al. (2003) do not report details on image presentation (e.g. masking) and there was relatively large heterogeneity in ethnicity within this sample. The extent to which these differences contributed to the null findings in the latter study are unknown, but could have been critical.

5.4. Reconciling face and odor studies

The fact that facial preferences appear to be assortative, compared with generally disassortative odor preferences, is certainly surprising to many researchers (Roberts et al., 2005b also express this themselves) but in fact the result is consistent with most facial attractiveness research. Human couples can be matched at rates above chance, and preferences are known to be influenced by self-resemblance (Griffiths and Kunz, 1973; Hinsz, 1989; Bereczkei et al., 2002). Roberts et al. (2005b) proposed a hypothesis by which preference for odors of MHC-dissimilar but faces of MHC-similar individuals, on average, might be a way of achieving an intermediate rather than maximal level of genetic variability in a preferred mate, since they could work in tandem to screen out either extreme. Most studies tend to focus on detrimental effects of inbreeding, but there are also advantages to a moderate degree of assortative mating (Partridge, 1983; Puurtinen et al., 2005) through maintaining locally advantageous genetic combinations and adaptations. This could also help to explain absence of strong effects of MHC in actual mate choice studies.

6. MHC-correlated mate choice

At least for studies based on odor perception, the laboratory-based behavioral studies reviewed above suggest that, where a preference exists, individuals prefer potential partners with dissimilar MHC type to their own. Such an effect might therefore also be expected in determination of marriage partners, outside of the laboratory environment. In other words, married couples are expected to share fewer alleles than would be found if they coupled at random. The degree of

disassortative mating based on MHC alleles in married couples has been the aim of several studies; however, as we will describe, these studies return mixed effects.

6.1. MHC-similarity in established couples

Results on a possible MHC association between couples came for the first time as a by-product of a study focusing on a correlation between MHC (all participants typed for *HLA-A*, *-B*, *-C* and *-DR* loci) and odor sensitivity for the compound androstenone (Pollack et al., 1982). No such association was found. Moreover, no assortative mating preference for MHC was found in a sample of 61 couples. It must be noted, however, that this is a rather small sample size and, due to hypervariability of the MHC, finding a positive association was rather unlikely.

A second study (Rosenberg et al., 1983) used a much larger sample of 1017 couples typed at *HLA-A* and *-B* loci for other medical purposes (e.g. transplantations). Rosenberg et al. compared the expected (taken from the whole sample) and observed frequencies in couples and found that couples shared more MHC alleles than would be expected by chance, suggesting assortative mating. However, the samples used were highly ethnically heterogeneous, including individuals of Afro-American, Japanese, Hispanic and others. As differences in HLA frequencies between populations vary considerably, the authors themselves note that this fact may have overestimated the expected frequencies and thus their results can be explained more simply through assortative mating within ethnic grouping.

Other studies that failed to demonstrate a deviation from random mating include that of Jin et al. (1995), who developed a new test for evaluating random mating for highly polymorphic loci. They used their test on a Caucasian population dataset (approximately 500 couples) collected for other purposes. The test was run separately for each locus (*A*, *B* and *DR*), but no conclusive evidence of non-random mating was found. Nordlander et al. (1983) also found no evidence for greater than expected *HLA-A* and *-B* allele-sharing in 826 Swedish couples. Mating was also no different from random in a ''caucasoid'' Uruguayan sample of 183 couples typed at *HLA-A*, *-B* and *-C* (Sans et al., 1994). A Japanese team (Ihara et al., 2000) typed five MHC loci (*HLA-A*, *-B*, *-C*, *-DR* and *-DQ*) in 150 couples from Tohoku region, northeast Japan and four MHC loci (the same as Tohoku excluding *—DQ*) in 300 couples from various regions of Japan. The referential data on general population frequencies were not available and therefore Monte-Carlo methods were used instead. In both samples, frequency of shared alleles in couples was not different from randomly generated values.

However, each of these studies have been carried out in parts of the world where modern lifestyles could obscure odor cues and population mobility has maintained and probably increased heterogeneity in MHC allele frequencies. In contrast, a study based on Amazonian Indians (Hedrick and Black, 1997) avoids these problems and could provide an insightful measure of the true extent of disassortative mating. They used *HLA-A* and *HLA-B* data obtained from members of 11 different tribes (194 couples in total) and found no significant departure from levels of allele-sharing expected under random mating (Hedrick and Black, 1997). In fact they point out that, if anything, there was a (non-significant) deficiency in the number of couples who shared very few alleles, particularly at the *HLA-B* locus.

Only one study has demonstrated a disassortative preference in line with that expected based on the odor preference studies. Ober et al. (1997) performed serologic analyses of five MHC loci in 411 Hutterite couples. As already mentioned above, the Hutterites are a highly endogamous, religious community, where using any kind of contraception is not allowed. In contrast to the two previous studies, they found a lower frequency of identical MHC haplotypes in couples compared to expected frequencies, suggesting disassortative mating with respect to the MHC.

One further study deserves mention, a rather underappreciated study by Giphart and D'Amaro (1983) which adopted a slightly different analytical approach in order to investigate whether specific allele combinations were more likely to occur by chance within couples. They reasoned that, under random mating, for any one maternal HLA antigen, the frequency of the paternal antigen should not be different from among the entire paternal population. Using 30 of the most common antigens in the population (8 at *HLA-A*, 16 at *-B* and 6 at *-Cw*), and data from over 3000 Dutch families, they showed that there were at least 4 significant associations (even after controlling for multiple comparisons). In each of these four cases occurring at above-expected frequencies, the antigen combination was different, indicating a degree of disassortative mating based on specific allele combinations. However, two of these allele combinations (A2/B40 and B7/B40) were not found at levels different from chance in a subsequent Swedish study (Nordlander et al., 1983).

6.2. Behavioral evidence

Up to now only one study has focused more specifically on self-reports of sexual and relationship satisfaction in 48 couples typed for *HLA-A*, *-B* and *-DR* loci (Garver-Apgar et al., 2006). These authors found that women's responsiveness to their partner and their sexual satisfaction was negatively correlated with the number of MHC alleles they shared with their partner. Both the self-report and partner-report data showed the same effect. Moreover, the extent to which women reported having had extra-pair affairs correlated with the number of MHC shared alleles. Importantly, these observed effects appeared to be driven specifically by MHC-similarity with their current partner rather than being a result of absolute variability in promiscuity or behavior within relationships, because the effects held when general sexual attitudes (measured by the Sociosexual Orientation Inventory, SOI) were taken into account, and because the number of MHC alleles the women shared with their current partner did not correlate with the number of their extra-pair affairs during their previous relationships, with SOI score, or with satisfaction in relationships in general. Reported tendency for unfaithfulness towards their current partner, and rejection of his sexual advances was found to be stronger during the late follicular phase when probability of conception was highest. There was no effect of MHC on sexual responsiveness or tendency to engage in extra-pair sex in male subjects. These results suggest that the degree of MHC allele-sharing with current partners significantly affects women's behavior in a manner that is not representative

of either their general behavior or their previous behavior in other relationships (where, presumably, they would have shared different numbers of alleles with their partner).

6.3. Methodology of mate choice studies

The third line of evidence we have reviewed comes from studies on MHC-correlated choice in couples. As in the odor preference studies, these have tended to produce somewhat mixed conclusions. One study based on the data from a relatively genetically homogeneous Hutterite population found negative assortment in MHC loci (Ober et al., 1997). Other studies, based on Caucasian, South American Indians, Japanese and ethnically heterogeneous populations found no evidence for non-random assortment related to MHC. The mixed evidence across studies is arguably not entirely surprising even if MHC does play a role in shaping mate preferences and ultimate choice of partner. First, due to high MHC polymorphism any putative effect may be found only in large samples. It is highly possible that most of the studies actually lack sufficient statistical power to find effects. Second, actual mate choice is influenced by many psychosocial factors (e.g. Buston and Emlen, 2003) and other physical traits, many of which will have distinct and independent effects on mate preference (Roberts and Little, 2008). Despite this complexity, studies on MHC-correlated mate choice only compare the expected and observed frequencies without taking these other variables into account. Thus computing frequencies from crude population samples may have a low chance of detecting an existing effect. In addition, the comments made above in relation to the loci examined are also relevant here. Because of these reasons, we believe studies such as those by Garver-Apgar et al. (2006), who found a higher tendency to seek extra-pair affairs in women who share a higher proportion of MHC alleles with their partner, to be potentially a much more powerful, and sensitive, approach to investigating the influence of MHC on relationship formation and outcome (see also Roberts and Little, 2008). More studies of this kind are needed.

7. Making sense of MHC effects in humans

All MHC studies may be subject to the same kinds of confounding factors that need to be taken into account in any study of human mate preference. The most obvious of these is that female reproductive state should be taken into account in MHC studies (Jordan and Bruford, 1998). Different patterns of results are found, for example, in women who use hormonal contraceptives compared to those who have normal menstrual cycles. In Wedekind's studies (Wedekind et al., 1995; Wedekind and Füri, 1997), contraceptive pill users on average preferred the odors of MHC-similar, rather than MHC-dissimilar men. Other studies investigating preferences and behavior unrelated to MHC have also found different patterns in pill users and non-users, and similarities between pill users and pregnant women support Wedekind et al.'s (1995) suggestion that pill use could change behavior towards that normally characteristic of pregnancy (e.g. Jones et al., 2005). In the first direct test of whether pill use actually alters preferences, using a longitudinal "before versus after pill use" design as distinct from a correlational difference between pill users and non-users, Roberts et al. (2008) showed that pill use may alter preferences for MHC-correlated odors such that relative preference for MHC-similarity increases in women after initiating pill use compared to a control group who do not use the pill.

In light of this study, further work needs to consider whether such effects may also occur in faces and whether patterns of pill use, particularly at the time of meeting long-term or marriage partners, might contribute to the mixed results found in real couples. Since the Hutterite community studied by Ober et al. (1992, 1997, 1998; Ober, 1999) do not use hormonal contraception, perhaps this could have contributed to the detection of underlying disassortative preferences (although the same could have been said for the Amerindians studied by Hedrick and Black, 1997).

There are also potentially profound consequences of such disruption of adaptive mate preferences by the use of hormonal contraceptives. First, several studies have linked fertility problems with rates of allele-sharing among couples. In a prospective study, for example, rates of fetal loss were higher in Hutterite couples who shared more alleles either across a 16-locus haplotype or B-linked loci (Ober et al., 1998). Patterns of recurrent spontaneous abortion (three or more consecutive miscarriages without specific diagnosed cause) are also linked to HLA allele-sharing (see review in Beydoun and Saftlas, 2004). Second, potentially increased levels of allele-sharing will increase levels of HLA homozygosity in offspring successfully conceived, with possible consequent health implications (see e.g. Carrington et al., 1999; Penn et al., 2002). Finally, as Vollrath and Milinski (1995) and Boero (1996) pointed out pill-induced changes in male preferences might have knock-on effects on marital relationships. For example, a woman who meets her partner while using oral contraceptives might find him less attractive when she discontinues pill use. If this change in preference is sufficiently powerful, it could eventually lead to marital breakdown.

Another potentially significant factor is the menstrual cycle phase of female raters. During the last decade, many studies have found changes in preferences across the cycle. In the fertile phase of the cycle, women prefer more masculine (Jones et al., 2008) and symmetrical faces (Little et al., 2007) (although see Koehler et al., 2002 for opposite results). These changes are commonly interpreted as an adaptation for cues of high-quality genes when conception is most likely (Gangestad and Cousins, 2001). Concerning MHC-correlated studies only, Wedekind et al. (1995) and Roberts et al. (2008) tested their subjects in a specific phase of their cycle (follicular phase). The other studies did not control for menstrual cycle phase, which may potentially contribute to differences between obtained results. However, as it is expected that cycle phase is randomly distributed among raters, we believe that this factor introduced rather higher noise in the data set than strong systematic bias. To date, no study has compared ratings obtained in various phases of the cycle from the same raters. It would be interesting to test whether changes in preferences across the cycle, similar to those previously found for other attributes, might also be applicable for MHC-correlated choice.

While much attention has been focussed on the possible confounding influence of oral contraceptives, it must be considered that other modern cultural practices could also

potentially disrupt MHC-correlated preferences. Since odor is the prime candidate for mediating any MHC-correlated choice, the use of chemicals and bactericidal agents aimed at neutralising and masking malodors (see Stoddart, 1990), must also have some influence on the natural expression of odor-based preferences and hence may obscure findings in relation to non-random mating patterns with respect to MHC (although Milinski and Wedekind, 2001 argue that perfumes may enhance body odor individuality rather than mask it). In the same way, in view of the association between heterozygosity and judgments of facial attractiveness and skin healthiness, there is a real possibility that cosmetics which mask poor skin condition (Law-Smith et al., 2006) could obscure detection of heterozygosity in faces — this may be one reason why the same result is not found in females (see Lie et al., 2008).

Finally, future studies should examine the extent to which any putative association with mate preference or choice is directly due to MHC, or whether this is a reflection of a genome-wide association. In other words a study demonstrating, say, a correlation between a preference and low frequency of MHC allele-sharing may in fact be a by-product of a preference for generally low allele-sharing at many different loci, of which MHC is only one. Such studies ideally therefore need to compare allele-sharing at other markers, as well as MHC, in order to interpret the effect more specifically. An example of this is a recent study reported by Lie et al. (2008) which compared facial preferences in relation to MHC-heterozygosity. While Roberts et al. (2005c) have shown that faces of MHC-heterozygotes are judged as more attractive and healthy, Lie et al. replicated this result but also showed that heterozygosity at 11 other microsatellite markers did not influence preferences in the same way. Wherever possible, this approach should be taken in future work.

8. Conclusions

We have attempted to summarise current knowledge in three main approaches to the study of MHC-correlated mate choice in humans. These include (1) odor preferences, (2) facial preferences and (3) actual mate choice. It is clear that there is mixed evidence for a role of MHC in human mate choice, both within and across each of these areas of investigation. Although this makes it difficult to draw definitive conclusions, the large number of studies showing some MHC involvement suggests there is a real phenomenon that needs further work to fully elucidate. Methodologies and results vary widely, and it remains difficult to gain a confident grasp on the true extent to which MHC might influence partner choice. More work is clearly needed, and we have raised what we think are important considerations that need to be considered in future research. These include various methodological aspects as sources and treatment of odor stimuli, research design, identity of HLA loci and phrasing of rating questions. Other potentially relevant factors are raters' reproductive status and context of the preference (e.g. long term vs. short term).

There are good reasons for understanding the nature of the influence of MHC on human mate choice, apart from academic interest and comparison with other species. These include the probability of successful conception and pregnancy, consequences for child health through enhancement of heterozygosity in offspring and potentially even quality of family relationships. Furthermore, the potential for modern cultural practices such as use of perfume, cosmetics or hormonal contraceptives to disrupt adaptive preferences and perhaps even eventual partner choice, is a potent argument for such research attention in the coming years.

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Conflict of interest

Both authors declare that they have no conflict of interest.

Contributors

Both authors have contributed to the writing of the manuscript.

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