Influence of HLA on human partnership and sexual satisfaction

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The major histocompatibility complex (MHC, called HLA in humans) is an important genetic component of the immune system. Fish, birds and mammals prefer mates with different genetic MHC code compared to their own, which they determine using olfactory cues. This preference increases the chances of high MHC variety in the offspring, leading to enhanced resilience against a variety of pathogens. Humans are also able to discriminate HLA related olfactory stimuli, however, it is debated whether this mechanism is of behavioural relevance. We show on a large sample (N = 508), with high-resolution typing of HLA class I/II, that HLA dissimilarity correlates with partnership, sexuality and enhances the desire to procreate. We conclude that HLA mediates mate behaviour in humans.

Body odours can create immediate sexual attraction. Both, men and women of various cultures seek out perfumes which highlight their body odour in the most desirable way. The famous novel “Perfume” by Patrick Suskind describes a perfume made of body odours that drives people into ecstasy and makes them forget civilized behaviour. However, recent research indicates that the ‘olfactory match’ between people, rather than a universally irresistible smell might be the key to olfactory attraction1. We investigated the relation of HLA dissimilarity, which is perceived through the olfactory chemosignaling, with human mate choice.

In animals, immunologic compatibility determines individual variation of mate choice and is partly conveyed by olfactory cues2–4. The individual genetic major histocompatibility complex (MHC) represents a part of the adaptive immune system. MHC molecules are located on the surface of cells and play a key role in discriminating between endogenous and exogenous, potentially pathogenic material. Genes of the MHC gene cluster are expressed in a co-dominant way. When given a choice, mice and sticklebacks prefer mates with dissimilar MHC molecules compared to their own2,3. This is advantageous from an evolutionary point of view: The co-dominant expression increases the chances of high MHC variety in the offspring of MHC dissimilar compared to MHC similar couples, which in turn leads to enhanced resilience amongst a variety of pathogens5.

MHC related mate choice is guided by the sense of smell in vertebrates. Parts of the heavy chains of the MHC glycoproteins are detected in various body fluids like saliva, urine and sweat6. In addition, it has been suggested that MHC molecules influence microorganisms of the skin which are involved in the formation of body odours7. The precise mechanisms by which those MHC molecules shape the body odor are still under discussion8. However, MHC determined odors activate vomeronasal and olfactory neurons4.

In humans, MHC is called human leucocyte antigen (HLA). HLA alleles are grouped into class I (encompassing amongst others HLA-A, HLA-B and HLA-C), class II (encompassing amongst others HLA-DR, HLA-DQ and HLA-DP) and class III alleles (e.g. HSP 70, TNF α and Factor B). HLA class I molecules are expressed by almost every nucleated cell in the body. Their function lies in the presentation of proteins to T cells. HLA class II molecules are located in cells of the immune system and show fragments from phagolysosomes to T cells9.

For a long time it has not been clear whether the mechanism of MHC related mate choice is evolutionarily conserved in humans. However, in 1995 it was shown that HLA similarity affects human body odour preference. In this study, 49 women preferred the body odour of HLA dissimilar men in comparison to similar men10. Preference of body odours of HLA dissimilar persons has been replicated in various studies11–13, however another study showed no impact of HLA on body odour preferences14 and it has been suggested that an intermediate level of HLA dissimilarity might be optimal in terms of body odour preference15.

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Most of those studies examined only a few of the HLA loci (mainly -A, -B and -DR) at comparably low resolution (e.g. HLA subgroups) and for most studies, HLA similarity was not determined for each HLA loci, but a total score was analysed (for excellent overview compare20,21). Taken together, those studies suggest that HLA compatibility may influence body odour preference such that dissimilar body odours are preferred over similar ones. Oral contraception may disrupt this effect21.

It is an interesting question, how humans are able to perceive HLA related peptides. Humans have no functional vomeronasal organ17,18, hence perception must be established through a different pathway. In fact, receptors expressed in the olfactory epithelium may be involved in this chemosensory communication19 and it has been shown recently that women are able to differentiate pure HLA related peptide ligands1. However, the mechanisms are not delineated yet (compare20,21 for ongoing debate).

In animals, immunologic compatibility is a major factor in mate choice2-3. In humans, studies show mixed effects4-6. A study from 1983 reports that married couples shared more HLAA and -B alleles that expected by chance22. However, the mixed ethnicities in this study may have caused this effect and after control of ethnicity, no effect of HLA was observed. Other studies report - in line with the animal results - that couples share fewer alleles than expected by chance23,24 and results are influenced by cultural background22,25. To our knowledge, only one study examined whether HLA related mate choice is behaviourally relevant in humans. The authors showed in 48 couples that partners who shared few HLA alleles were more satisfied with their sex life compared to partners who shared many HLA alleles26.

We investigated whether HLA similarity affects different aspects of partnership, such as general satisfaction, sexual satisfaction and the desire to procreate with the respective partner. Further, body odour attractiveness was examined. As it has been reported, that women prefer body odours of HLA heterozygote men before homozygote ones22, we additionally tested the impact of homo- and heterozygosity.

Methods

The study was approved by the ethical board of the University of Dresden (EK 195062013) and was carried out in accordance with the approved guidelines. Written informed consent was obtained from all participants.

Participants. Over a period of nine months, heterosexual couples were recruited at the University campus. Couples were only included if both partners were aged 18 years and older and had normal olfactory function as ascertained by use of the “Sniffin’Sticks” screening test27. In total, 254 couples were included. The group of women was aged between 18 and 60 years (mean: 24.3 years; s.d.: 5.6), male participants were aged between 18 and 55 years (mean: 26.14 years; s.d.: 6.0). The duration of partnership was 1 month to 32 years (mean: 4 years; s.d.: 57.9 months). Most of the couples (91%, n = 231) had no children. Four women were pregnant at the time of examination. Those four were excluded from the analysis. 52.3% (n = 132) of the couples shared a household together.

Procedure. Participants were asked to provide a DNA sample using buccal swabs for HLA-typing. Afterwards, they filled out a questionnaire (compare Supplementary Information) including descriptive questions (age, duration of partnership, numbers of children, health status) and rating about the satisfaction with the partnership (“How satisfied are you with your partnership?”) and with partnership sexuality (“How satisfied are you with your partnership sexuality?”) on a scale from 0 to 10 (“not satisfied at all” to “extremely satisfied”). Further, body odour attractiveness was measured using a scale from 0 (not at all) to 10 (extremely attractive). Statistical analysis.

The statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, version 19.0, SPSS Inc., Chicago, Illinois, USA).
Data were analysed with a general mixed model approach. The fixed effects of HLA class (2), HLA match (2) and the interaction on partnership satisfaction and partnership sexuality were examined. In the first step, each couple served as subject, sex (2) and HLA locus (6) as repeated measurement. For the 2.2\% of the samples, where only an intermediate resolution could be achieved, the most probable typing was used and the individual probability of correct HLA typing was added as weighting coefficient in the analyses. Partnership duration was included as covariate in a second model. As the dependent variables were correlated \( (r = 0.58, p < 0.001) \), the respective other dependent variable was added as random effect in addition to partnership duration in a third model. In the second step, the effect of sex was analysed. Therefore, only HLA class I alleles (3) (which showed significant effects in the first step) were included in the model and the main effect of HLA match (2) was examined, separately for men and women. Accordingly, each individual served as subject in this analysis. In the third step, analysis focused on individual HLA class I alleles. Therefore three mixed models were calculated per sex with HLA match (2) as fixed main effect and this data was Bonferroni-corrected (factor 3).

The non-parametric variable of longing for children was analysed using a Chi-square test. For this analysis, women aged older than 40 were excluded \( (N = 10) \). In the first step, the impact of HLA match (2) on longing for children (3) was tested separately for HLA class I and II. As class II revealed no significant results, further analysis focused on class I. Sex differences were examined in the second step. The impact of HLA match (2) on longing for children (3) was tested separately for men and women. As there were no significant effects in men, the last step focused on women. Here, the impact of HLA match (2) on longing for children (3) was tested separately for each HLA class I allele (3). This data was Bonferroni-corrected (factor 3). In a second model, participants, who already had children \( (N = 16) \) were excluded from the analysis.

The effects of HLA class (2) and HLA match (2) on body odour attraction were examined similar to the mixed model analysis performed for partnership satisfaction and partnership sexuality. As body odour attraction was correlated to partnership satisfaction \( (r = 0.46, p < 0.001) \) and partnership sexuality \( (r = 0.49, p < 0.001) \), a model including these variables as covariates was analysed.

The effect of homo- and heterozygosity on ratings was examined using a generalized mixed model approach, similar to the one above. In the first step, the fixed effects of HLA class (2), HLA homo-/heterozygosity (2) and the interaction were examined. As there were no significant effects, further statistical testing was abandoned. The level of significance \( (\alpha \text{-level}) \) was set at \( p < 0.05 \) for all analyses.

**Results**

**HLA class I dissimilarity relates to partnership and sexual satisfaction.** Partnership and sexual satisfaction were significantly related to HLA class I match. For both, partnership and sexual satisfaction, there was a significant interaction effect of HLA class I and HLA similarity (partnership satisfaction: \( F(249, 1) = 14.1, p < 0.001 \); sexual satisfaction \( F(249, 1) = 5.1, p = 0.023 \)). HLA class I dissimilarity was significantly associated with higher partnership satisfaction \( (F(249, 1) = 18.7, p < 0.001) \) and higher sexual satisfaction \( (F(496, 2) = 6.9, p = 0.008) \), while no such effect was found for HLA class II. Sex specific analysis revealed that overall HLA class I dissimilarity was related to higher partnership satisfaction in women \( (F(1, 249) = 9.9, p = 0.002) \) as well as in men \( (\text{men: } F(1, 240) = 8.8, p = 0.003) \), while overall HLA class I dissimilarity was related to higher sexual satisfaction in women only \( (F(1, 240) = 7.9, p = 0.005) \).

Sex and HLA type specific analysis revealed that sexual satisfaction in women was related to HLA-B dissimilarity \( (F(1, 240) = 14.5; p = 0.001) \). Partnership satisfaction in women was related to HLA-B \( (F(1, 240) = 8.3; p = 0.001) \) as well as HLA-C \( (F(1, 240) = 6.6; p = 0.03) \). In men, higher partnership satisfaction was related to HLA-C dissimilarity \( (p = 0.033, d = 0.25) \). Further, HLA-B dissimilarity was related to enhanced sexual satisfaction in men \( (p = 0.027, d = 0.32) \), despite the lack of an overall HLA class I effect. No effect was observed for HLA-A (Fig. 1, Supplementary Table 1).

Control for relationship duration did not impact the results. The impact of HLA class I on partnership satisfaction was stable after control of partnership sexuality \( (F(249, 1) = 14.7, p < 0.001) \). However, HLA class I dissimilarity did not significantly increase sexual satisfaction, after control of partnership satisfaction.

**Women are more likely to want children with HLA class I dissimilar partners.** HLA class I dissimilarity was significantly related to a positive answer to the question of whether participants wanted to have (more) children with their partner \( (\text{Chi}^2 = 11.3, p = 0.003) \). No such effect was observed for HLA class II. However, while sex specific analysis revealed a preference of HLA dissimilarity in women \( (\text{Chi}^2 = 16.6, p < 0.001) \), no such effect was observed for men. Within the group of women, dissimilarity in HLA class I allele B and C was related to the wish to have children with their partner, though after Bonferroni correction, only the impact of HLA-C remained significant \( (\text{Chi}^2 = 8.9, p = 0.03, \text{compare } \text{Fig. 1 and Supplementary Table 1}) \). Exclusion of participants who already had children, did not impact the results.

**HLA class I dissimilar partners are preferred in terms of body odor attractiveness.** There was a significant interaction between the HLA similarity and HLA class \( (F(249, 1) = 6.3, p = 0.012) \), indicating that only HLA class I dissimilarity was significantly associated with higher body odor attractiveness \( (F(249, 1) = 8.2, p = 0.004) \). No such effect was observed for HLA class II \( (F(1, 1.5) = 0.4, p = 0.55) \). Sex specific analysis revealed, that HLA class I dissimilarity was related to women’s rating of partner body odor pleasantness \( (F(249, 1) = 4.2, p = 0.04, \text{compare Fig. 1 and Supplementary Table 1}) \), while no such effect was observed for men. Within the group of women, dissimilarity in HLA-B and -C class I alleles were related to higher body odor attractiveness rating of the respective partner, however those effects did not hold after Bonferroni correction.

There was no significant interaction between HLA similarity and HLA class \( (F(249, 1) = 0.1, p = 0.8) \) on body odor attraction after control for relationship duration and partnership satisfaction.
HLA-heterozygote people are not preferred over HLA-homozygote. Heterozygosity was more frequent than homozygosity for each of the HLA alleles (compare Supplementary Table 2). However, sexual and partnership satisfaction, were independent of whether people were in a relationship with HLA heterozygote or homozygote partners. Similarly, no significant effects were obtained for the partner’s body odor attractiveness. Further, the desire for children was not affected by homozygote or heterozygote partners.

Discussion
The current investigation revealed that immunologic compatibility matters in terms of (1) partnership satisfaction, (2) sexual satisfaction, and (3) the wish to have children. Hence, subjects were generally most satisfied with their relationship if their partner exhibited a dissimilar HLA type. This effect was only evident for HLA alleles of class I, while no effect was found for class II alleles.
This supports and extends work from previous studies showing that humans are able to discriminate intran- 
sally administered HLA-related peptides1 and prefer the body odour of HLA dissimilar individuals2–12,28. These 
results are also in line with studies showing that immunologic compatibility relates to mate choice in mammals9–13 
and humans10–13. However, some authors report no preference of HLA dissimilarity in humans14,15. Differences 
in methodology may explain some of the variation: We examined established couples and used questionnaires 
while others examined body odour ratings of strangers. We further analysed the whole range of HLA class I and 
II alleles at comparably high resolution, while previous studies focused on few alleles. One has to keep in mind, 
that partnership satisfaction and partnership sexuality were correlated to each other thus whilst the impact of 
HLA class I on partnership satisfaction remained stable after correction of partnership sexuality, the converse 
did not. Further, our participants were rather satisfied with their partnership and partnership sexuality. This is in 
accordance to results from a representative German survey, where the vast majority of men stated to be somewhat 
very satisfied with their partnership and sexuality34. Women were not included in this survey.

In our study, both sexes were significantly more attracted by their partner’s body odour if the couple had dis-
similar HLA class I alleles. However, self-report body odour attractiveness ratings were influenced by partnership 
satisfaction and further studies are warranted where participants actually smell unmarked samples of their part-
ner’s body odor. In line with our results, studies performed on strangers show that women prefer the body odour 
of HLA dissimilar compared to similar men10–13.

All beneficial effects of HLA dissimilarity were present in men and women. But as we examined couples, sex 
specific analyses have to be treated with caution. When a man is unsatisfied with his relationship, it may be due 
to HLA similarity or due to being engaged with a woman who is unsatisfied. In general, HLA similarity affected 
women more than men, especially in terms of sexual satisfaction and the wish to have children. In line with this 
female sexual dissatisfaction is related to HLA similarity. We speculate that the majority of women’s investment 
on offspring leads to a stronger, but most likely subconscious, emphasis on factors contributing to a healthy offspring.

HLA alleles contributed differently; class I alleles were found to be of much stronger importance than class II 
alleles. Especially HLA-B and - to somewhat lesser extent – HLA-C dissimilarity was related to enhanced part-
nership and sexual satisfaction and to the wish for children. Interestingly, it was found in birds, that MHC class I 
(corresponding to HLA, in humans), mainly -B, is pivotal for parasitic resistance35. However, in fish36 and mice37, 
diversity of MHC class II relates as well to parasite load and a conclusive explanation for why HLA class I was 
related to mate behaviour in humans while HLA class II was not, is lacking. The correlational approach of our 
study does not provide sufficient explanation here. Furthermore this correlational approach limits the interpreta-
tion: We assume, that HLA match between couples impacts partnership and sexual satisfaction as well as the wish 
for children and odour attractiveness rating. However, it is also possible, that the coherence is determined by an 
underlying third variable such as linkage effects due to non-HLA loci.

In contrast to HLA similarity, HLA heterozygosity was unrelated to any of the examined aspects of partner-
ship satisfaction. Heterozygosity might be related to enhanced resistance against pathogens compared to homozy-
gosity in humans38–39 and a similar mechanisms has been reported in mice4. However in a population of ox, goat 
and sheep no strong indications for an advantage of heterozygosity were found40 and it has been argued that 
this heterozygosity does not preclude health, but makes an individual and a population more vulnerable to infectious 
disease at a time of exposure41.

Heterozygote individuals hence may be preferred as mate partners, because they can better take care of the 
offspring4. In line, women prefer faces of heterozygote men42,43 and there is one study showing that body odour 
attraction is higher for T-Shirts worn by HLA-B heterozygous compared to HLA-B homozygous 
donors44. However no preference of heterozygote individuals in term of partnership satisfaction, sexual satis-
faction, the wish to procreate, or body odour rating was found in our study. In contrast to previous studies, high 
resolution HLA analysis performed here included the level of the 2-field HLA subgroup and hence was more 
sensitive to dissimilarity. Compared to 1-field analyses, this approach enhanced the chance for heterozygosity on 
the individual level and for non-match between partners on the partner level.

In conclusion, attraction is a miracle to most of us and only some of the many factors mediating mate choice 
involve odours. However, within the world of human olfaction, there seems to be no perfect mate but a perfect 
partner and this depends on HLA match.

References
1. Milinski, M., Croy, I., Hummel, T. & Boehm, T. Major histocompatibility complex peptide ligands as olfactory cues in human body 
odor assessment. Proc Biol Sci 280, 20122389, doi: 10.1098/rspb.2012.2389 (2013).
2. Boehm, T. & Zufall, F. MHC peptides and the sensory evaluation of genotype. Trends in neurosciences 29, 100–107, doi: 10.1016/j.
tins.2005.11.006 (2006).
3. Yamazaki, K. et al. Control of mating preferences in mice by genes in the major histocompatibility complex. J Exp Med 144, 
1324–1335 (1976).
4. Stowers, L. & Marton, T. F. What is a pheromone? Mammalian pheromones reconsidered. Neuron 46, 699–702, doi: 10.1016/j.
neuron.2005.04.032 (2005).
5. McClelland, E. E., Penn, D. J. & Potts, W. K. Major histocompatibility complex heterozygote superiority during coinfection. Infect 
Immun 71, 2079–2086 (2003).
6. Wobst, B. et al. Molecular forms of soluble HLA in body fluids: potential determinants of body odor cues. Genetica 104, 275–283 
(1998).
7. Singh, P. B. et al. Rearing rats in a germ-free environment eliminates their odors of individuality. J Chem Ecol 16, 1667–1682, doi: 
10.1007/bf01014099 (1990).
8. Penn, D. & Potts, W. How do major histocompatibility complex genes influence odor and mating preferences? Advances in 
immunology 69, 411–436 (1998).
9. Ting, J. P. & Trowsdale, J. Genetic control of MHC class II expression. Cell 109, Suppl, S21–S33 (2002).
10. Wedekind, C., Seebeck, T., Bettens, F. & Paepke, A. J. MHC-dependent mate preferences in humans. Proc Biol Sci 260, 245–249, doi: 
10.1098/rspb.1995.0087 (1995).
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Additional Information
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