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MHC-heterozygosity and human facial attractiveness

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Abstract

Females gain direct or indirect fitness benefits by choosing between males with traits indicating "good genes," but we usually know very little about the nature of these genes. However, it has been suggested that genetic quality may often be defined as heterozygosity at certain loci. Here, we show that heterozygosity at three key loci in the major histocompatibility complex (MHC) is associated with facial attractiveness: Faces of men who are heterozygous at all three loci are judged more attractive by women than faces of men who are homozygous at one or more of these loci. MHC genes code for proteins involved in immune response. Consistent with this function, faces of MHC heterozygotes are also perceived to be healthier. In a separate test, in the absence of any other cues, patches of skin from the cheeks of heterozygotes are judged healthier than skin of homozygotes, and these ratings correlate with attractiveness judgements for the whole face. Because levels of MHC similarity can influence mate preferences in animals and humans, we conducted a second experiment with genotyped women raters, finding that preferences for heterozygosity are independent of the degree of MHC similarity between the men and the female raters. Our results are the first to directly link facial attractiveness and a measure of genetic quality and suggest a mechanism to help explain common consensus concerning individual attractiveness.

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In a relatively monogamous species like humans, evolutionary benefits from choosing heterozygous mates could include prolonged parental care and reduced risk of contracting disease for females and their offspring.

Keywords: MHC; HLA; Mate choice; Disassortative; Good genes; Beauty

1. Introduction

Sexual selection theory asserts that males maximise reproductive success through seeking multiple matings, while females achieve this goal through discrimination of mate quality, or choosiness (Bateman, 1948; Trivers, 1972). Through mate choice, females gain direct and indirect benefits, where direct benefits include resources provided by males to females or offspring, and indirect benefits refer to genetic properties that enhance fitness of resulting progeny (Andersson, 1994; Kirkpatrick & Ryan, 1991). Females may base their discrimination on phenotypic or behavioural variation among candidate males in traits that signal genetic quality (Hasselquist, Bensch, & Schantz, 1996; Petrie, 1994) or genetic complementarity (usually dissimilar genotype: Potts, Manning, & Wakeland, 1991; Yamaguchi et al., 1981), or both (Colegrave, Kotiaho, & Tomkins, 2002; Roberts & Gosling, 2003).

In most cases, we know little about the exact nature of the good genes involved, although Brown (1997, 1999) has recently suggested that genetic quality, in this sense, may often be defined as heterozygosity at certain loci. He proposed that heterozygosity should be correlated with the expression of condition-dependent male traits and that females should value heterozygosity in their offspring and, in some cases, their mates. Many studies investigating influences of heterozygosity on mating patterns have focussed on genes in the major histocompatibility complex (MHC, known in humans as human leukocyte antigen loci, HLA). MHC genes encode proteins involved in immunological self/nonself recognition and are among the most polymorphic in the genome (Mungall et al., 2003).

It is now well-established that MHC disassortative mating preferences exist in several species, with beneficial effects in terms of offspring heterozygosity (Bernatchez & Landry, 2003; Jordan & Bruford, 1998; Penn & Potts, 1998), but the extent to which heterozygosity in mates plays a role in female mate preferences is less clear. Preferences for heterozygosity in mates could result in direct benefits to females, for example, through reduced risk of disease transmission or provision of high-quality paternal care (Kirkpatrick & Ryan, 1991) because heterozygous males are often less susceptible to infectious diseases (Carrington et al., 1999; McClelland, Granger, & Potts, 2003; McClelland, Penn, & Potts, 2003; Penn, Damjanovich, & Potts, 2002; Thursz, Thomas, Greenwood, & Hill, 1997). Although heterozygote mating advantages have been demonstrated less often than predicted by theory (Brown, 1997, 1999), higher reproductive success has been found in male rhesus macaques, *Macaca mulatta*, which were heterozygous at a Class II locus (Sauermann et al., 2001), and in male spotless starlings, *Sturnus unicolor*, of intermediate heterozygosity

(Aparicio, Cordero, & Veiga, 2001). Mate choice for males with high MHC-allelic diversity occurs in sticklebacks (Reusch, Haberli, Aeschlimann, & Milinski, 2001), while in humans, Thornhill et al. (2003) found that women prefer odors of men who are relatively heterozygous at MHC loci. Such odor effects may not be independent of other cues (Cornwell et al., 2004), and this raises the intriguing possibility that MHC genes might also be involved in facial preferences because facial attractiveness plays a key role in human mate choice.

Facial characteristics are thought to advertise underlying "good genes" to potential mates (Penton-Voak et al., 2001; Perrett, May, & Yoshikawa, 1994; Thornhill & Gangestad, 1999). These characteristics include indicators of healthiness and developmental stability (Fink, Grammar, & Thornhill, 2001; Fink & Penton-Voak, 2002; Jones et al., 2001; Thornhill & Gangestad, 1999) and, potentially, immunocompetence (Penton-Voak et al., 2001; Perrett et al., 1998; Rhodes, Chan, Zebrowitz, & Simmons, 2003). Only recently, however, has the potential link between MHC genotype and facial preferences been investigated. In addition to odor preferences, Thornhill et al. (2003) tested facial preferences for MHC heterozygosity but found no significant effects. While the reason for the discrepancy between facial and odor preferences is unclear, it emphasises the need for further investigation of the potential links between MHC and facial attractiveness.

Here, we test the hypothesis that MHC heterozygosity influences women's preferences for male faces. We presented women with photographs of men genotyped at three MHC loci and asked them to score each image for attractiveness. We compare scores of men who were heterozygous at all three loci with those who were homozygous at one or more of these loci. In addition, we compare two potential condition-dependent facial characteristics of men in each group, each of which have been previously linked to facial attractiveness: fluctuating asymmetry (Penton-Voak et al., 2001; Perrett et al., 1999) and visible skin condition (Fink et al., 2001; Jones, Little, Burt, & Perrett, 2004; Jones, Little, Feinberg, et al., 2004). Finally, because MHC similarity is known to influence the attractiveness of human odor (Jacob, McClintock, Zelano, & Ober, 2002; Thornhill et al., 2003; Wedekind & Furi, 1997; Wedekind, Seebeck, Bettens, & Paepke, 1995), we tested whether these attractiveness judgements were independent of levels of MHC similarity.

2. Methods

2.1. Genotyping of male participants

Participants were students or staff at the University of Newcastle. To minimise possible confounding variables, we included only participants who were white. Ninety-two men aged between 18 and 31 (mean = 21) contributed to the study.

Approximately 5 ml of blood was collected using vacuettes (Greiner Bio-One, Stonehouse, Gloucestershire, UK) lined with EDTA to prevent clotting. Genomic DNA was typed at three key MHC loci (HLA-*A*, -*B*, and -*DRB1*), by polymerase-chain reaction using sequence-specific primers (PCR-SSP). We used these three loci because, with over 300

known alleles each, they are the most polymorphic HLA loci, according to the HLA database (http://www.ebi.ac.uk/imgt/hla/stats.html), and because they have been used in previous studies of HLA-associated mate preferences (Jacob et al., 2002; Thornhill et al., 2003; Wedekind & Furi, 1997; Wedekind et al., 1995). Among the men, 13 different alleles were recorded at HLA-*A*, 27 at HLA-*B*, and 13 at HLA-*DRB1*. Sixty-nine men were heterozygous at all three loci, while 23 were homozygous at one or more loci. Of these, 8 were homozygous at HLA-*A*, 5 at HLA-*B*, 6 at HLA-*DRB1*, 3 at both HLA-*A* and -*DRB1*, and 1 at both HLA-*A* and -*B*.

2.2. Image scoring

Digital color photographs of the men's faces were taken under standard lighting conditions using a Nikon Coolpix 775 digital camera and a resolution of 1600×1200 pixels. Men were instructed to look directly at the camera and adopt a neutral expression. Each image was normalised on the interpupillary distance (Penton-Voak et al., 2001) and digitally masked so that only the face was visible, minimising potentially confounding information about hairstyle and clothing (e.g., Roberts et al., 2004). These images were presented to 50 female participants (age 18–49 years, mean = 23) in random order, on a liquid crystal display computer screen (on-screen face size approximately 12×18 cm). Women rated the attractiveness of these faces using a seven-point rating scale (high scores = attractive).

2.3. Skin ratings/symmetry estimates

Estimates of horizontal and vertical facial symmetry were obtained using the *x*–*y* coordinates of seven bilateral landmark points on the 2D facial images, as defined previously by Penton-Voak et al. (2001) and Scheib, Gangestad, and Thornhill (1999). Both studies found that symmetry, as measured using these landmarks, correlates positively with perceived attractiveness.

All women were also asked to rate the apparent healthiness of patches of skin from each man's image using a seven-point scale (high score=healthy). Skin patch images were squares of skin from the right cheek of each man, the equivalent of a 2.5-cm square, the lower edge being aligned with the bottom of the nose and the right-hand edge immediately next to the right nostril. Images were magnified by 300% to facilitate ratings (Jones, Little, Burt, et al., 2004). This process slightly blurs the images, but the degree of blurring is constant across images. Although magnification made rating skin patches easier for participants than without it, skin patches remain poor substitutes, in our view, for the assessment in vivo of either the same skin area or, indeed, skin covering the entire face. Hence, magnification should be seen as an aid towards ecologically valid levels of mate quality discrimination rather than providing unrealistically high resolution. Skin patches were presented in randomised order, in a different order than the whole faces. Cues to facial identity, shape, or facial hair were not visible in the skin patches. These methods have been successfully used by Jones, Little, Feinberg, et al. (2004) and Jones, Little, Burt, et al. (2004); example skin patch stimuli (though from different individuals than those used here) can be seen in Jones, Little, Burt et al.

All women were asked to complete both the facial attractiveness and the skin patch healthiness rating tasks. The order in which these tasks were completed was alternated between female raters.

2.4. MHC similarity

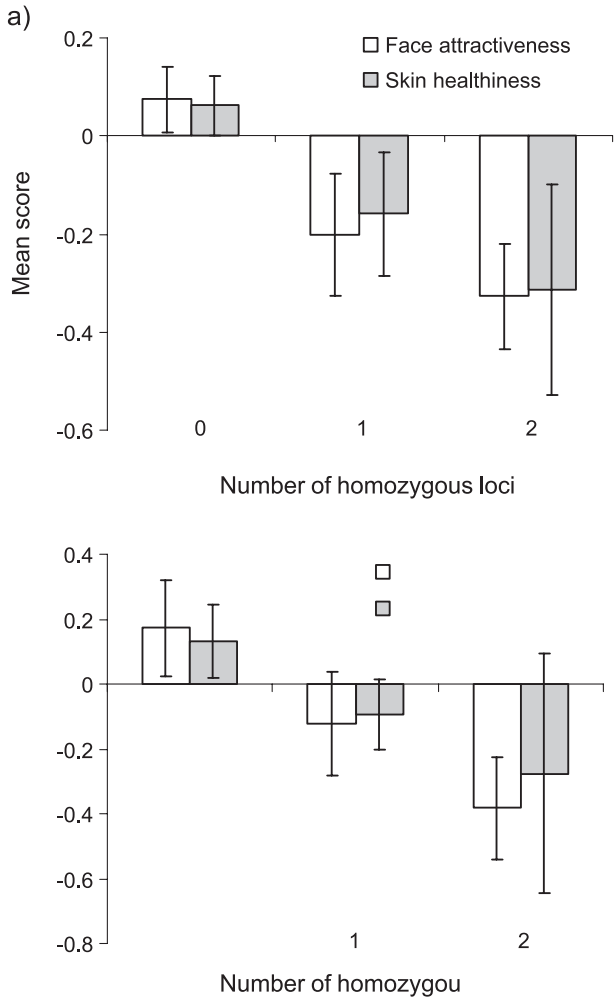
We carried out a second experiment (Study 2) to check that the effects of heterozygosity were independent of relative levels of genetic similarity between raters and men in the images. Thirty-six women participated, having been genotyped at the same loci as the men. Only 5 also took part in the first experiment. MHC similarity between females and each male was computed as the total number of alleles in common across the three loci (see also Thornhill et al., 2003; Wedekind et al., 1995).

In addition to genetic similarity, we also controlled more closely a number of additional factors. First, we controlled the country of origin (to standardise the degree of allelic diversity) by excluding 13 non-British men from mainland Europe (all 36 women were also white and of British origin). Second, we excluded three men with beards because facial hair might influence facial judgements. Of the remaining 76 men, 20 were homozygous at one or more loci (6 at HLA-*A*, 4 at HLA-*B*, 6 at HLA-*DRB1*, 3 at both HLA-*A* and -*DRB1*, and 1 at both HLA-*A* and -*B*). Finally, as it is known that the stage of menstrual cycle influences women's facial preferences (Penton-Voak & Perrett, 2001; Penton-Voak, Perrett, Castles, et al., 1999), all women raters were tested in the late follicular phase, between 10 and 14 days after the beginning of their cycle, and none of the participants were using hormone-based methods of contraception. In this smaller experiment, women rated the facial attractiveness and skin healthiness of the 20 men with one or more homozygous loci and 20 heterozygotes selected at random from the remaining 56 men (heterozygotes were selected using the "Select random sample of cases" function in SPSS version 11). All women saw the same 40 faces. Within this sample, age matching of both men and women was improved in comparison with the first experiment (range: men 18–25; women 18–34). The order in which women rated faces for attractiveness and skin patches for perceived healthiness was alternated. Within each task, images were also presented in a randomised order.

2.5. Analyses

We used standardised image scores (number of standard deviations from the mean for each rater; Sokal & Rohlf, 1995, p. 110) to control for individual differences in the use of the rating scale (e.g., Pollard, Shepherd, & Shepherd, 1999). As expected, significance levels are improved slightly after standardisation; however, the difference in facial attractiveness scores of the homozygotes and heterozygotes that we report is also significant using raw scores ($p = .023$; for the raw skin healthiness ratings $p = .052$). We calculated the mean standardised scores for each image across all raters and compared the scores for men with one or more homozygous loci against those who were heterozygous at all three loci. For illustrative purposes only, we present the mean scores of all three levels of heterozygosity in

Fig. 1. We pooled men with one and two homozygous loci primarily because of the small number of men (four) with two homozygous loci. Calculating heterozygosity across several loci is a common technique and correlates with the fitness and expression of secondary sexual traits in birds (Aparicio et al., 2001; Foerster, Delhey, Johnsen, Lifjeld, & Kempenaers, 2003) and with disease progression in humans (Carrington et al., 1999; Tang et al., 1999). All data were normally distributed and analysed using SPSS Version 11 with two-tailed tests.



3. Results

3.1. Study 1: effects of heterozygosity

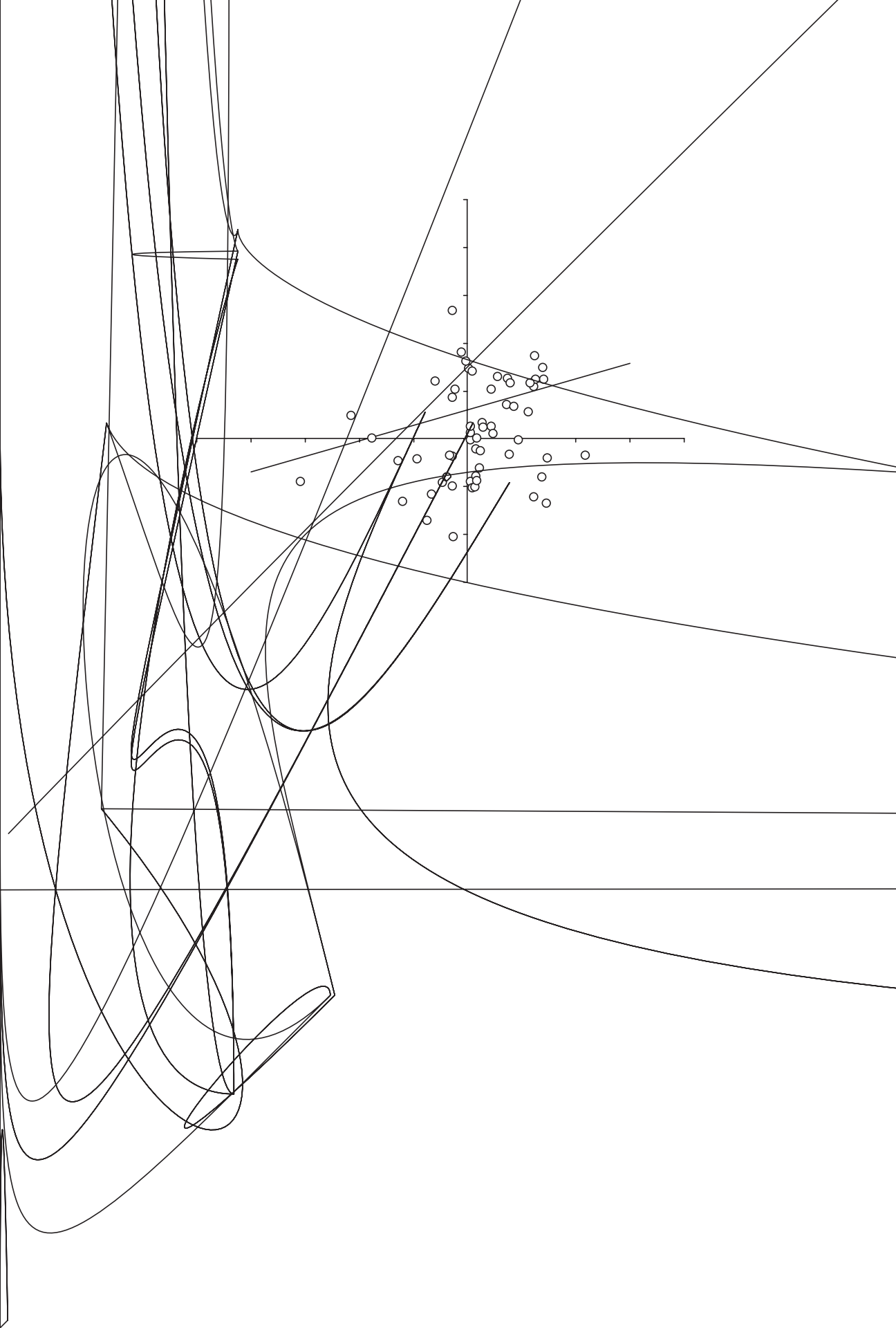
We found a significant effect of heterozygosity on ratings of facial attractiveness (Fig. 1a). Faces of men who were heterozygous at all three loci were judged more attractive than were the faces of men who were homozygous at one or more loci [independent samples t test, $t(90) = 2.29$, $p = .024$]. Interrater reliability was high (Cronbach's $\alpha = .95$), and mean attractiveness ratings for heterozygotes were higher than for homozygotes in 49 of the 50 women (sign test, $p < .001$), indicating a high level of agreement among women.

We also tested associations between heterozygosity and two potential health indicators that have been linked to facial attractiveness: fluctuating asymmetry (Penton-Voak et al., 2001; Perrett et al., 1999) and visible skin condition (Fink et al., 2001; Jones, Little, Burt, et al., 2004; Jones, Little, Feinberg, et al., 2004). We found no significant effect of heterozygosity on horizontal measures of facial symmetry [mean±S.E.: heterozygous = 39.9±2.6, homozygous = 42.5±4.8; $t(90) = 0.50$, $p = .62$], on vertical symmetry [heterozygous = 14.6±.73, homozygous = 12.6±1.3; $t(90) = 1.38$, $p = .17$], or on the mean of these measures ($p > .9$). Attractiveness scores in this sample were also not correlated with either measure of symmetry (horizontal, $r = .03$; vertical, $r = -.067$). However, the skin of heterozygous men was perceived by women as more healthy than was the skin of homozygous men [Fig. 1; $t(90) = 2.02$, $p = .046$], and mean ratings of whole-face attractiveness for each man were positively correlated with mean skin healthiness ratings (Fig. 2a; $r = .301$, $n = 92$, $p = .004$). There was again strong agreement among women: The mean healthiness ratings of skin of heterozygotes were higher than those of homozygotes in 45/50 women, and interrater reliability was high (Cronbach's $\alpha = .94$).

3.2. Study 2: controlling for genetic similarity

We investigated the potentially confounding influence of levels of MHC similarity between female raters and males by recording facial attractiveness and skin healthiness ratings from a second group of women who were also genotyped. In this group, there was again a marked preference for faces of heterozygous men, with mean scores given by each rater to heterozygotes being higher than the mean homozygote scores [paired t test, $t(35) = 8.28$, $p < .001$; Fig. 1b]. Women again judged skin from the heterozygous men to be healthier than was the skin of the homozygous men [paired t test, $t(35) = 6.38$, $p < .001$], and the mean ratings of whole-face attractiveness for each man were also positively correlated with the mean skin healthiness ratings ($r = .325$, $n = 40$, $p = .041$; Fig. 2b).

To test the effect of heterozygosity independently of similarity, we used a three-way ANOVA with the standardised attractiveness score for each image as the dependent variable, male heterozygosity and the number of shared alleles as fixed factors, and female rater as a random factor. This analysis revealed a significant and independent effect of heterozygosity [$F(1,1194) = 4.66$, $p = .031$]. The main effect of MHC similarity also approached significance [$F(5,262) = 2.08$, $p = .069$], but there was no effect of rater ($p > .9$) and no significant



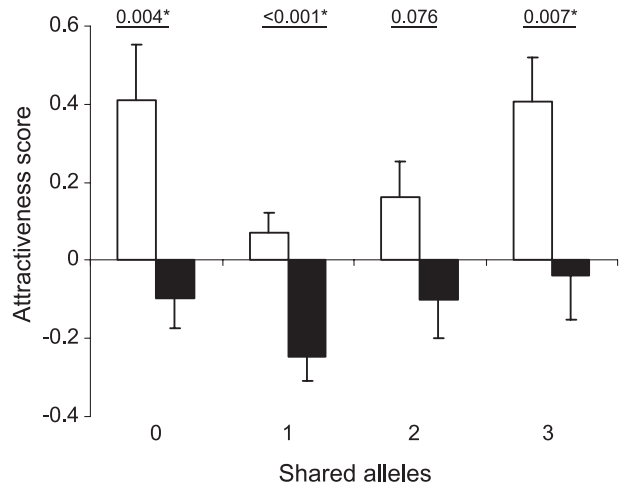


Fig. 3. Mean standardised attractiveness scores (±S.E.) of MHC-heterozygous (□) and homozygous (■) men, subdivided according to the number of shared alleles with female raters; n=35, 36, 36, and 23 women for zero, one, two, and three common alleles, respectively (sample size varies because not all women share particular numbers of shared alleles with at least one homozygote and at least one heterozygote). p values are shown from paired t tests; asterisk (*) indicates that the comparison survives a Bonferroni correction for multiple tests.

interaction terms, although the Similarity×Rater interaction approached significance ($p = .051$). After model simplification (removing interactions in which $p > .1$), the final model revealed significant positive effects on attractiveness of heterozygosity [$F(1,1279) = 41.36$, $p < .01$] and the number of shared alleles [$F(5,253) = 2.26$, $p = .049$], while the Rater×Similarity interaction was also significant [$F(119,1279) = 1.27$, $p = .033$; no main effect of rater, $p > .9$].

We further investigated the independent effect of heterozygosity by calculating the mean scores given by each rater to heterozygotes and to homozygotes who shared zero, one, two, or three MHC alleles with her. For each degree of similarity, we compared these mean scores using planned paired t tests. The mean facial attractiveness scores were significantly higher for heterozygotes than for homozygotes when rater and male image shared zero, one, or three alleles [zero: $t(34) = 3.10$, $p = .004$; one: $t(35) = 4.28$, $p < .001$; three: $t(22) = 2.95$, $p = .007$] and tended toward significance when two alleles were shared [$t(35) = 1.83$, $p = .076$; Fig. 3].

4. Discussion

Our results suggest that females find the faces of MHC-heterozygous men more attractive than faces of homozygotes. They lend support to the idea that average heterozygosity at the MHC may be important in mating decisions (Brown, 1999). Arguably, this preference for heterozygosity might not be MHC specific but could rather arise through a general eschewal of relatively inbred males (or those with high average homozygosity at many loci), provided that MHC homozygosity is correlated with inbreeding and any associated deleterious effects.

However, current evidence suggests that this is not always the case because Carrington et al. (1999) found no correlation in several human cohorts between homozygosity at MHC loci and homozygosity at several microsatellite loci, either within the MHC region or on different chromosomes. This indicates that the preference for heterozygous faces revealed here may indeed be specific to MHC heterozygosity and is therefore likely to be mediated by MHC-correlated phenotypic traits.

Our second study shows that high average heterozygosity carried a significant effect independently of the degree of MHC similarity between women raters and the photographed men. The absence of an interaction between heterozygosity and rater is indicative of a general preference across women. Consistent with other studies (e.g., Langlois et al., 2000), we found a high degree of agreement between women in attractiveness ratings of the men, and our results suggest that heterozygosity contributes to this agreement, along with other previously documented characteristics including masculinity, symmetry, and averageness (e.g., Penton-Voak et al., 2001; Rhodes et al., 2001). However, the number of shared alleles between the pictured males and the female raters also appears to be positively correlated with facial preferences. This is a surprising result in the light of odor preferences for MHC-dissimilar individuals (Wedekind & Furi, 1997; Wedekind et al., 1995), although it is consistent with other face studies that indicate assortative preferences and phenotypic facial similarities within human couples (Griffiths & Kunz, 1973; Hinsz, 1989; Penton-Voak, Perrett, & Pierce, 1999). However, the interaction between rater and similarity indicates variability between women in the strength of their preference. While Fig. 3 appears to suggest that women give lowest scores to men of intermediate similarity (sharing one or two alleles), in fact, this nonmonotonic pattern is due to some women giving higher scores to faces of MHC-similar men while others preferred faces of MHC-dissimilar men. More work is needed to understand both this variability in preference and why the dominant preference appears to be assortative rather than for MHC-dissimilar faces, and we are actively pursuing this. Nonetheless, this result adds further evidence that MHC genotype is correlated, in some way, with facial appearance.

Although we found only four men with two homozygous loci in our sample, preventing statistical comparison with those having single-locus homozygosity, their lower mean attractiveness and skin healthiness scores (Fig. 1) suggest that homozygosity at multiple loci may compound associated negative effects. Sample sizes are small, thus, this trend should be interpreted with caution, but it is consistent with studies that find separate, additive effects of homozygosity at different loci on progression to AIDS in HIV+ patients, suggesting that multilocus homozygosity enhances negative health effects (Carrington et al., 1999; Tang et al., 1999).

While we find that male heterozygosity is associated with attractiveness, Thornhill et al. (2003) detected no such effect. Although both studies investigated heterozygosity at the same three loci, there are some methodological differences that could explain the differences in results. First, ethnic diversity of participants was greater in the study of Thornhill et al. (only 62% of men and 48% of women were reported as Caucasian), introducing a potentially large confounding effect on attractiveness ratings. An ethnically diverse sample will also promote heterogeneity in MHC alleles, potentially altering homozygote frequencies in the population (e.g., Budowle, Koons, & Moretti, 1998). Second, there was wider variation in the age of participants in Thornhill et al.'s sample than in ours, particularly in the men (range 18–54).

Third, unlike Thornhill et al., we masked images to minimise the potentially confounding influences of hair style/condition and clothing. Each of these differences is likely to reduce variance (unrelated to MHC heterozygosity) in judgements by raters in our study. While Thornhill et al. did find correlations between heterozygosity and odor, perception of odor may be less sensitive to ethnicity and age than are facial judgements, and the confounding cues of hair and clothing would have been absent. Nonetheless, further work in different populations is clearly required to clarify the strength of the observed effects.

In view of the central role of MHC genes in immune response, differences in apparent healthiness are a likely explanation for the observed preference for heterozygote faces. MHC-heterozygote advantage in resistance to infectious diseases has been found in several recent studies, notably with regard to infections in mice by *Salmonella* and *Listeria* (Penn et al., 2002), and in humans by Hepatitis B (Thursz et al., 1997) and HIV (Carrington et al., 1999). In addition, of particular relevance to this study, HLA-Cw*0602 heterozygotes have a markedly lower risk of developing psoriasis, a chronic inflammatory skin disease (Gudjonsson et al., 2003). We have identified apparent skin healthiness as a potential mechanism for the effect that we describe, although it may not be the only one. Like Jones, Little, Feinberg, et al. (2004) and Jones, Little, Burt et al. (2004), we find that skin condition might, in itself, be a direct visual cue to mate quality, as it correlates with attractiveness judgements even when information about facial shape is removed. Further work is required to determine the precise nature of the cues used to assess skin healthiness, although candidates would include coloration, texture, and blemishes.

Our results are consistent with previous studies that find a correlation between perceived health and facial attractiveness (Cunningham, 1986; Jones et al., 2001; Thornhill & Gangestad, 1999). However, of three studies using measures of actual, rather than perceived health (Kalick, Zebrowitz, Langlois, & Johnson, 1998; Rhodes et al., 2003; Shackelford & Larsen, 1999), only one (Shackelford & Larsen, 1999) has found a similar relationship. One reason for this may be that modern medicine will tend to disguise or weaken effects that have evolved in ancestral times (Jones et al., 2001; Thornhill & Gangestad, 1999), although the studies by Kalick et al. (1998) and Rhodes et al. (2003) used images collected before the widespread use of vaccinations and, especially, antibiotics. A second explanation is that the two studies, to find no relationship between health and attractiveness, used monochrome photographs, while the other (Shackelford & Larsen, 1999), like our own, used color images. This pattern of results suggests that color may be necessary to discriminate subtle variation in healthiness associated with heterozygosity.

In contrast to mate preferences based on MHC dissimilarity, a preference for heterozygotes is more likely to have been selected for direct benefits to females than through indirect fitness advantages for offspring. Avoidance of homozygous males could still increase offspring heterozygosity (e.g., if a male is homozygous for an allele that a female also carries), but such cases will be relatively rare, especially in view of the polymorphic nature of the MHC. In a relatively monogamous species like humans, evolutionary benefits from choosing healthy mates are likely to include a prolonged period of high-quality parental care and reduced risk of contracting disease for females and their offspring (Kirkpatrick & Ryan, 1991). Further research is needed to clarify the relative influences on the mate choice of these direct benefits

compared with those indirect benefits that might result from choosing genetically compatible mates. The balance between these two selective forces may explain much of the variation in individual preferences. Although judgements of facial attractiveness typically show considerable agreement among raters, even across cultures (Langlois et al., 2000), individual differences with respect to MHC type are also likely to be evident. Thus, while studies that focus on relative genetic similarity suggest that "there is someone for everyone" (Jacob et al., 2002), a preference for heterozygotes implies wider agreement among women on attractiveness judgements of individual men.

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