Commentary

Response to "MHC-dependent mate choice in humans: Why genomic patterns from the HapMap European American data set support the hypothesis" (DOI:10.1002/bies.201100150)

HapMap genotypes do not confidently support a role for the MHC locus in human mate selection

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In 2008, Chaix et al. [1] reported that HapMap Phase 2 genotypes provided evidence that the major histocompatibility (MHC) locus is implicated in mate choice in European-Americans. In 2010, we reported that this result went from marginally significant to insignificant with any one of several minor changes to the methods, and was not reproduced in an independent cohort (namely HapMap Phase 3 genotypes) [2]. More recently, Laurent and Chaix [3] challenged our conclusions. Here we reaffirm our assessment that HapMap genotypes do not confidently support a role for the MHC locus in human mate selection.

The MHC locus contains genes involved in immunity, among others. Whether the MHC locus plays a role in mate choice in a number of species remains controversial (see [1–3] for more background). Chaix et al. examined HapMap Phase 2 genotypes and reported that they provided evidence for MHC-dependent mate choice in European-Americans. Specifically, they found that MHC relatedness was significantly lower among mates than permuted couples (Original Result 1), and mates were more different from each other at the MHC locus than at almost all other genomic windows (Original Result 2). Neither of these results was found in Yorubans [1]. We subsequently reported that Original Result 1 was not robust and not corroborated in an independent European-American (HapMap Phase 3) cohort (our Reponse 1), and that Original Result 2 was ambiguous (our Response 2) [2]. Laurent and Chaix recently challenged our conclusions [3].

We urge the reader to directly consider the evidence presented in [2], but we do wish to address several points raised by Laurent and Chaix.

Laurent and Chaix address our concern that the observed signals may have been driven by a small proportion of outliers by noting that (a) most *p*-values showed high significance; and (b) the distributions of MHC relatedness coefficients among spouses presented in [1] showed no such outliers. We do not find (a) to be a persuasive counter-argument, as a single outlying data point may cause multiple tests involving that data point to yield spuriously significant results. With respect to (b), we agree in the sense that we also did not observe unusually dissimilar mate pairs. However, outlier non-spouse pairs showing high MHC relatedness may also yield spuriously significant differences. Indeed, by simultaneously plotting relatedness in mates and opposite-sex

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Table 1. Fraction of genomic segments with relatedness lower than the MHC locus. Adapted from Derti et al. [2]. Similar results were obtained when considering recombination rate (not shown)

samples	mates (%)	non-mates (%)
phase 2	0.6	3.9
phase 3	1.6	91.0

non-mates, we showed that the most salient difference between the distributions consisted of sporadic instances of extreme similarity among non-mates [2].

Laurent and Chaix did not address other arguments for non-robustness of Original Result 1. For instance, we reported that the original result was rendered statistically insignificant simply by increasing the number of random trials and either excluding the single most MHC-dissimilar couple ($P = 0.052$, $Z = -0.36$, $N = 27$) or using median rather than mean relatedness ($P = 0.288$, $Z = -0.31$, $N = 28$). Corrections for multiple hypothesis testing would drive these results further from significance.

Summarizing our analysis of European-Americans in HapMap Phase 3 for differences in MHC dissimilarity, Laurent and Chaix write, "(t)he *p*-value is above the significance threshold, but the same tendency as in HapMap 2 is observed". Although this statement is technically accurate for the entire Phase 3 cohort ($P = 0.143$, $Z = -0.24$, $N = 45$), if one considers a result with a *p*-value of 0.143 to be indicative of a tendency, it is an incomplete summary of our findings. Whatever tendency there might be seems to be driven by couples present in both HapMap phases ($P = 0.067$, $Z = -0.34$, $N = 24$). The more relevant results, representing a truly independent validation attempt, were those from the Phase-3-only cohort. These results showed no evidence of any trend relating MHC dissimilarity to mate selection ($P = 0.351$, $Z = -0.08$, N = 24). Thus our examination of an independent cohort did not corroborate the original finding of Chaix et al.

With respect to Original Result 2, Chaix et al. compared relatedness at the MHC locus and other genomic segments of the same length in Phase 2 samples, but only among mates. Their original study did not compare their results with a similar analysis carried out for non-mates, so that it was unclear how Original Result 2 related to mate selection phenomena. We conducted this analysis for both mates and non-mates in Phase 2 and Phase 3 (Table 1). Laurent and Chaix write that "only spouses display an extreme relatedness pattern at the MHC level when compared to the rest of the genome, contrary to what Derti et al. claimed." In fact, they are mistakenly attributing to Phase 3 samples our summary of Phase 2 findings. They also highlight the contrast between Phase 3 mates (where the MHC locus is extremely dissimilar compared with the whole genome) and non-mates (the MHC locus is quite similar compared to the whole genome), and cite this contrast as evidence corroborating the original finding of Chaix et al. However, they fail to mention our corresponding Phase 2 analysis, showing that the MHC locus is almost as extremely dissimilar in non-mates as it is in mates. We attributed these conflicting results to the large standard deviations of MHC relatedness.

It seems that we all agree that a correction for four hypothesis tests in [1] would render Original Finding 1 insignificant, notwithstanding any of the issues discussed above. We do not feel strongly that all related hypothesis tests within a given publication should be considered within a common multiple testing framework, but some readers may.

We also agree that failure to demonstrate significance may simply result from a lack of power, and that absence of evidence is not evidence of absence. Further genotyping may yet reveal a connection between MHC and mate selection. For now, however, we must reaffirm our conclusion that a role for the MHC locus in mate selection cannot yet be confidently claimed on the basis of genetic evidence from HapMap genotypes.

References

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