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NEWS AND COMMENTARY

Loss of MHC haplotpe diversity through domestication

Let's talk turkey: immune competence in domestic and wild fowl

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A major goal in conservation and evolutionary biology is to determine whether endangered populations harbour sufficient genetic variation to maintain effective protection against harmful pathogens and to understand what factors contribute to maintaining genetic variance for disease resistance. In vertebrates, the major histocompatibility complex (MHC) is an important genetic region involved in immune responses and it is the most polymorphic and gene-dense region in the whole genome (Kelley *et al*., 2005). In birds, the MHC-B locus contains most of the genes responsible for antigen processing and presentation and is considered to be the homologue to the mammalian MHC (Kaufman *et al*., 1999). The high polymorphism levels in this region are thought to be maintained through mechanisms such as evolutionary arms races between the pathogens and the hosts maintaining rare alleles (negative frequency-dependant selection on MHC alleles), heterozygote advantage and by sub-populations of the same host species needing to adapt to different local pathogens, thereby increasing diversity across geographical regions (Ekblom *et al*., 2007).

Historically, genetic variation in the MHC region has been estimated using the Southern blot technique or PCR-based methods. However, with the increasing availability of sequence data, it is possible to design primers that amplify target regions and in this issue, Chaves *et al*. (2011) show that single-nucleotide polymorphism haplotyping can be used to capture variation within the MHC-B locus. The authors applied this method to compare MHC diversity of individuals from three different subspecies of wild turkey (*Meleagris gallopavo*, Figure 1) from the United States with the commercial turkeys. One major aspect of this study is that markers in many different genes in the MHC region were sequenced. This is a substantial improvement compared with other studies in birds, which have only focused on the peptide binding exons of MHC class I and IIB genes. The novel approach was made possible by utilising sequence information from the whole MHC-B region of domestic turkeys, currently one of the most well-characterised avian MHC regions (Chaves *et al*., 2010). Using markers outside of the highly polymorphic and duplicated MHC class I and IIB genes also circumvents problems that are usually encountered during genotyping studies.

To assess haplotype diversity among the wild and commercially bred birds, the authors first sequenced nine regions across the MHC-B locus in 40 individuals and identified 238 single nucleotide variants. Compared with what has been found in other regions of the turkey genome, this is a fivefold increase in polymorphism and almost a twofold increase compared with what has been found on the MHC-B in domesticated lines. Furthermore, many variants (112/238) had not been identified previously in commercial breeds. Using 37 polymorphic loci with a high minor allele frequency (>0.2), the authors characterised the haplotype structure for both the wild and domesticated birds and found that the majority of the identified haplotypes (66 out of 99) were detected in wild turkey, and only one haplotype was shared between wild and domesticated individuals. These analyses gave a very clear pattern: MHC diversity (measured in terms of both number of single nucleotide variants and haplotypes) was higher in wild populations of turkey than in domesticated ones.

A loss of genetic variation is expected during selective breeding, for a number of reasons, including small effective population sizes. In the case of the MHC, it is also possible that certain types of artificial selection regimes, such as selection for higher growth rates, may lead to reduced variation, for example as a result of a negative genetic trade-off between fast growth rate and certain aspects of immune competence. In addition, other, more subtle, mechanisms maintaining MHC variation may also be reduced in an artificial breeding setting. For example, MHC-dependant mate choice, as found in house sparrows (*Passer domesticus*, Bonneaud *et al*., 2006) would increase offspring heterozygosity. Restricting mate choice in an artificial setting could therefore generate an unwanted side effect of reduced diversity. Thus, the reduced level of variation in MHC observed in commercial turkey may have several different underlying causes. Regardless of the reasons for reduced variation, the consequences can be detrimental if MHC diversity has been reduced to the point where the population no longer carries the resistant genotypes needed to combat a disease outbreak. Although the larger MHC haplotype diversity observed in wild populations of turkey may function as an important 'MHC pool' for introducing disease resistance to domesticated breeds, it would be a significant challenge to associate haplotype variation with resistance to specific diseases, and a better approach may be to focus on maintaining diversity in commercial lines.

The use of high throughput sequencing techniques (and in particular the next-generation sequencing) has been predicted to substantially increase the feasibility of MHC genotyping, especially in birds in which this region is relatively small, making it possible to cover the entire MHC exons in a single read (Babik, 2010). An added advantage is that individually sequence-coded primers ('tag primers') can be used, which allows simultaneous genotyping of multiple individuals in a single run, and as sequencing can be carried out at a high coverage, even rare variants can be accurately assessed to give a detailed measure of MHC diversity (Babik, 2010). The parallel development of bioinformatics methods means that these new approaches are becoming applicable in a wider range of studies. However, when a reference haplotype is available, the ability to genotype the interspersed MHC regions and identify a set of high frequency single-nucleotide polymorphisms has the advantage of facilitating a fast and comparatively inexpensive screening of a large number of individuals. Once individuals with variant MHC haplotypes are identified, expanded sequencing can be applied for a closer examination. Another important application of fast screening is that associations between MHC haplotypes and resistance to particular pathogens can be investigated. A striking example is that chickens with an MHC B-21

Figure 1 Turkeys from wild populations (shown here displaying to impress females) harbour significantly more MHC-B diversity than their domesticated counterparts and may act as an important gene-pool source in case of future disease outbreaks in breeding stocks. Photo credit Alex Badyaev.

haplotype are 95% resistant to a virus causing Marek's disease, whereas individuals with a B-19 haplotype suffer 100% mortality (Briles *et al*., 1977). With this type of information, outbreaks of disease in breeding stocks with severe economic consequences can be avoided. As more sequence data become available for other species of birds, the approach used by Chaves *et al*.[5] should alleviate some of the problems associated with genotyping the MHC complex and give an increased insight into the causes and consequences of MHC diversity.

Conflict of interest

The authors declare no conflict of interest.

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