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NEWS AND VIEWS

PERSPECTIVE

New(t)s and views from hybridizing MHC genes: introgression rather than trans-species polymorphism may shape allelic repertoires

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One of the key features of major histocompatibility complex (MHC) genes is the frequent occurrence of trans-species polymorphism, that is 'the passage of allelic lineages from ancestral to descendant species' (Klein *et al.* 2007). Selectively maintained ancestral polymorphism may, however, be hard to distinguish from introgression of MHC alleles between hybridizing species (Fig. 1). In this issue of Molecular Ecology, Nadachowska-Brzyska *et al.* (2012) present data that suggest that the latter can be observed in two closely related species of newts, *Lissotriton vulgaris* (*Lv*) and *L. montandoni* (*Lm*) from south-east Europe. Strikingly, allelic MHC variation displayed more structure between geographically separated populations of *L. vulgaris* than across species in the hybrid zone. This suggests that high MHC variation in *L. montadoni* may result from mainly unidirectional gene flow between species, while differentiation between northern and southern populations of *L. vulgaris* might reflect local adaptation.

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This study unites two important aspects. First, on the more technical side, it nicely demonstrates the utility of next-generation sequencing (NGS) to obtain detailed major histocompatibility complex (MHC) genotypes on the DNA sequence level from hundreds of individuals, whether model or non-model species. Owing to the large number of sequences per individual, it is possible to generate sufficient coverage (Babik *et al.* 2009) and take necessary PCR artefact precautions (Lenz & Becker 2008) assuring high genotyping quality, and contrary to former indirect genotyping methods, provides genotype and actual sequence information in one step. Being a high-throughput method, parallel 454 tag-sequencing shows its real strength in large data sets (Wegner 2009) such as time series or large-scale geographical studies. In the paper presented here, Nadachowska-Brzyska *et al.* (2012) followed the second approach and collected 526 specimens from 35 populations covering both species (*Lm* and *Lv*) including all known subspecies of *Lissotriton vulgaris*. Such a detailed sampling scheme may be necessary to identify subtle population genetic processes such as gene introgression.

Second, and more important, this study shows the utility and necessity of comparing genomic regions experiencing selection (i.e. MHC genes) to selectively neutral markers (i.e. microsatellites). By doing so, the truly novel aspects of this study appear. Both marker types support previous findings of mitochondrial introgression (Babik *et al.* 2005) and reveal larger pairwise genetic differentiation within species (i.e. between northern and southern populations of *Lv*) than between species in areas of sympatry. The detailed genotype analyses of MHC loci revealed novel gene-specific differences. For example, a multidimensional scaling approach gave low weights and no discriminatory power to MHC genotypes stemming from northern *Lv* and *Lm* populations in contrast to southern *Lv* populations. Additionally, Bayesian genotype assignment tests showed higher admixture probabilities especially for MHC genotypes in populations of *Lm*. Both analyses show strong grouping according to microsatellites suggesting that selectively favoured MHC genes can introgress at higher rates than the rest of the genetic background.

The occurrence of genetic similarity in the area of sympatry as well as the asymmetry in allele sharing suggests that hybridization and introgression caused the observed pattern. Such selectively favoured MHC gene introgression is a fascinating idea, but further analyses are needed to disentangle the underlying signatures of trans-species polymorphism from introgression (Fig. 1). One possible way to tease apart the differences would be to investigate recombination rates on the chromosome(s) carrying the MHC genes. Under trans-species polymorphism, one would expect that haplotype blocks should be smaller than under gene introgression, which should cause linkage disequilibrium in a larger genomic region around the MHC. Comparing haplotype block sizes between potentially introgressing (i.e. northern *Lv* and *Lm*) and non-introgressing populations (i.e. northern and southern *Lv*) could shed light on the mechanisms of how and when MHC genes

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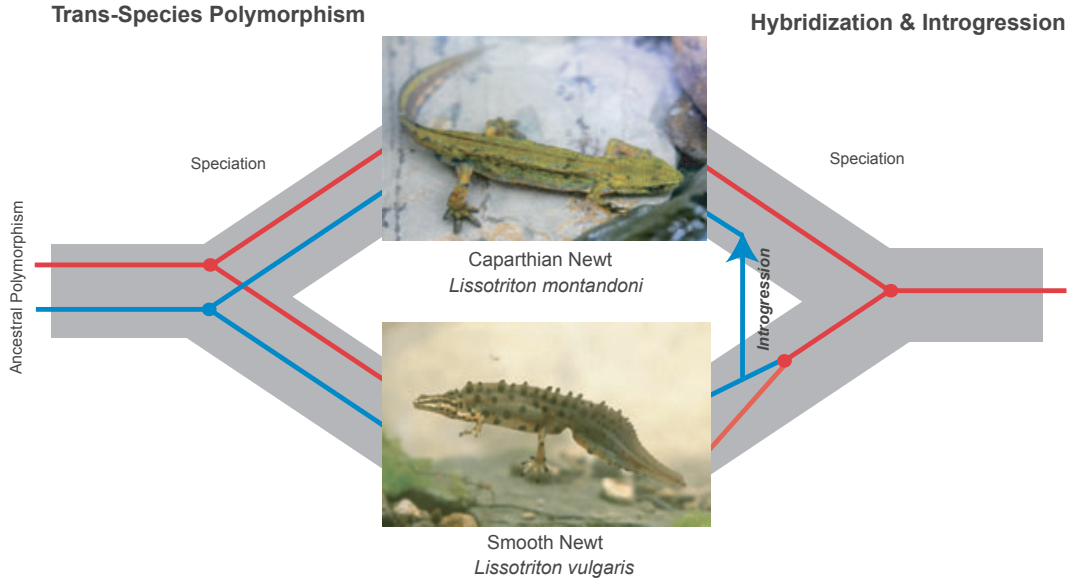

Fig. 1 Potential mechanisms generating shared repertoires of major histocompatibility complex alleles between southeast European newt species: Trans-species polymorphism (left side) maintaining ancestral polymorphism across speciation events and introgression (right side) where alleles arising in one species after speciation introgress into the other by hybridization. The study Nadachowska-Brzyska *et al.* 2012 suggests that the latter can be observed in two closely related newt species. Photos by Benny Trapp and Magdalena Herdegen.

crossed species boundaries. In addition to the mechanisms responsible for the special genetic structure observed within and between the newt species, the actual selective cause of natural and sexual selection that could explain MHC introgression deserves further attention.

An obvious selective cause is parasite-mediated natural selection, which should favour those newts with MHC genotypes conferring resistance against predominating parasites. When living in sympatry, the two newt species can be expected to face similar, yet partly non-overlapping parasite assemblages, and thus introgression of resistance alleles could be advantageous. Both classical mechanisms of parasite-mediated balancing selection can drive the evolution of MHC introgression: negative frequency-dependent selection and heterozygote advantage. Assuming the first mechanism, if a resistance allele exists in one species, introgressing it into the second species may confer a longer-term advantage. This is because it will have already been tested by selection in the first species, but will be rare by definition in the second. This MHC allele may then confer a selective advantage until the frequency increase of this allele causes prevalent parasites of the second species to counter adapt. Under heterozygote advantage, it becomes clear that maintaining the possibility of introgression allows the newt species to maintain larger inter- and intraindividual MHC diversity and therefore increases the possibility for individuals to fight a broader range of parasites and pathogens. Both mechanisms would result in higher survival and reproductive output of locally adapted individuals allowing introgressed MHC alleles to be maintained in the species' populations. In this context, it is remarkable to note that *Lm* showed higher allelic richness probably resulting from directional introgression from *Lv* to *Lm*. It is also interesting to speculate about the potential adaptive reasons for this pattern of directional introgression. Obvious candidates are higher parasite richness or different genomic architecture (i.e. lower number of loci) of *Lm* that could potentially change the trade-off between immunogenetic diversity and auto-immunity (Woelfing *et al.* 2009) into a trade-off between immunogenetic diversity and cost of hybridization.

On the other hand, sexual selection may also contribute to the introgression of MHC alleles into the genome of related species. Female mate choice for males displaying their ability to successfully resist parasitism (Hamilton & Zuk 1982) may enhance the probability of shared MHC alleles between species. For instance, MHC-based sexual selection is known to involve olfactory mechanisms in fish, mice and humans (Milinski 2006). During mate choice, females use an odour-based selection strategy to achieve the best MHC diversity in their offspring and can potentially increase mating frequency with mates that carry MHC alleles conferring resistance against currently prevalent parasites (Eizaguirre *et al.* 2009b). If parasite selection is strong enough that the benefits overcome the cost of hybridization, MHC-based mate choice may allow genes to cross species' boundaries. Irrespective of whether the mechanism of resistance to parasites is negative frequency-dependent selection or heterozygote advantage, MHC-based female mate choice may confer pleiotropic effects (Eizaguirre *et al.* 2009a) and act as an accelerator of gene introgression.

Because hybridization essentially represents the unique opportunity to capitalize on breeding experiments carried out by nature itself, research on hybridization attracts more and more attention. The present study opens not only a new perspective for host–parasite studies but also for investigating the pace of introgression of specific genomic regions. It remains to be determined how general these patterns are, or whether the *L. vulgaris* species complex merely represents a case of a species that seems to hybridize easily and facilitate introgression.

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