

## NEWS AND VIEWS

## PERSPECTIVE

**Inversions and the origin of behavioral differences in cod**

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How does adaptation manage to occur in the face of overwhelming gene flow? One popular idea is that the suppression of recombination, for example the fixation of a chromosomal inversion, can maintain linkage disequilibrium between groups of locally adapted alleles that would otherwise be degraded by gene flow. This idea has captured the imagination of many geneticists and evolutionary biologists, but we still have only a basic understanding of its general importance. In this issue of *Molecular Ecology*, Kirubakaran *et al.* (2016) examine the role of recombination suppression in a particularly fascinating example of adaptation in the face of gene flow: the evolution of migratory differences between interbreeding populations of cod. Along the north coast of Norway, two types of cod breed in the near-shore waters: a ‘stationary’ form that lives near the coast year round, and a ‘migratory’ form that lives far offshore and only returns to the coast to breed. Using a combination of approaches, Kirubakaran *et al.* (2016) deftly demonstrate that the migratory form has completely fixed two adjacent inversions containing a suite of genes closely connected to migratory behaviour and feeding differences. This work provides an excellent example of how recombination suppression can facilitate adaptive divergence, and helps us understand the geographic and temporal scales over which genomic structural variation evolves.

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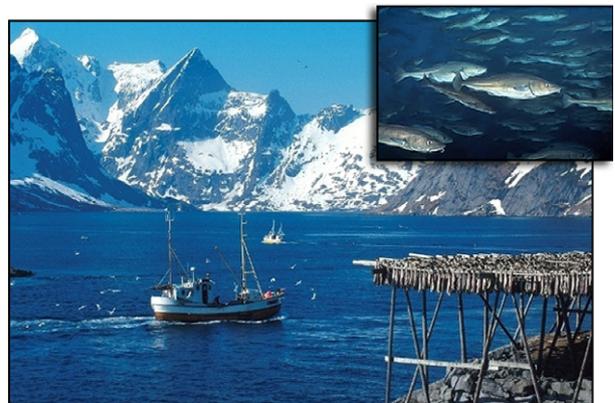
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Kirubakaran *et al.* (2016) leveraged a rich body of data to explore different lines of evidence that the behavioural differences between the stationary Norwegian coastal cod (NCC) and the migratory northeast Arctic cod (NEAC) (Fig. 1) were related to the presence of an inversion. The first pieces of the puzzle were genetic maps derived from crosses of both types of fish. Using a huge mapping population obtained from cultivated stocks of both

types, the authors performed classic genetic mapping with over 10 000 SNP markers derived from a SNP array. When they compared the relative order of these SNPs between NCC and NEAC populations, they found two adjoining inversions, together comprising a region of around 17 megabases – well over half of the chromosome on which it was found (Fig. 2). Interestingly, the rest of the genome appeared to be largely the syntenic, suggesting that these inversions likely harboured the genes involved in migratory differences between NCC and NEAC populations.

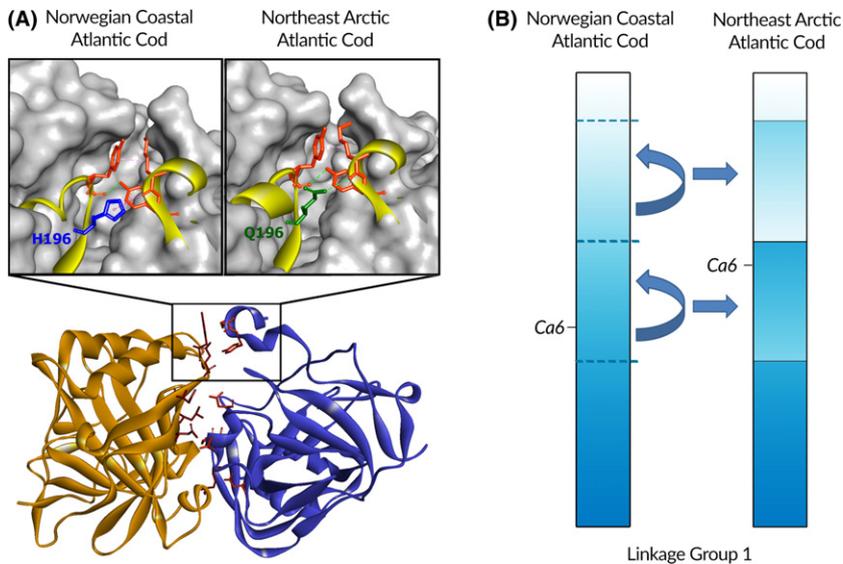
The authors next wanted to know whether the inversions they found were a quirk of their mapping population, or a *bona fide* genetic difference in wild populations. To do this, they set out to examine the frequency of the inversions in wild populations of NCC and NEAC fish. The authors obtained close to a 1000 individuals from 14 separate locations in the North Atlantic and genotyped each using their SNP array. They then found markers that were diagnostic of the inversions and examined the frequency of these markers in each population. As expected, the inversions were completely fixed in wild populations of NEAC fish, confirming that the genetic mapping populations were a good proxy for wild variation.

The next two findings by Kirubakaran *et al.* (2016) weighed in on two important unresolved questions about inversions. First, what evolutionary forces are responsible for maintaining polymorphism for inversions in natural populations (Kirkpatrick 2010)? As part of their survey of natural populations, the authors also found the NEAC inversions to be segregating at low frequencies in nearby



**Fig. 1** During the traditional ‘Lofotfishing’, migratory and stationary populations of Atlantic cod are caught at the spawning grounds on the west coast of northern Norway and end up as Bacalhau (salted and dried cod). Photograph kindly provided by Lofoten Photograph Gallery.

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**Fig. 2** (A) The carbonic anhydrase isoform 6 (Ca6) plays a key role in the maintenance of neutral buoyancy by providing protons for blood acidification and gas secretion into the swim bladder. Atlantic cod exhibits two Ca6 variants, and the Gln196His substitution is predicted to reduce the enzyme activity in stationary NCC by decreasing the interactions at the dimeric surface of the enzyme. (Models kindly provided by Maria Cristina De Rosa). (B) The two adjacent inversions on LG1 comprise 763 genes, including Ca6, that are protected from recombination in NEAC × NCC hybrids.

NCC populations, dropping off with geographic distance. This suggests that there may be sufficient gene flow to maintain the NEAC inversions in NCC populations in spite of any countervailing selection and/or loss by genetic drift. Thus, the results presented here by Kirubakaran *et al.* (2016) provide good evidence that the balance between gene flow and selection/drift likely maintains polymorphism for the inversions in the NCC populations. Secondly, how fast do inversions evolve in different lineages? As an addendum to their main results, the authors also applied phylogenetic comparisons to infer the age of the NEAC inversions. They found that the inversions probably arose around 1.6–2 Ma, for a rate of around 2.78 inversions per million generations. How does this compare to other taxa? Assuming that these are the only inversions found between the two forms and that cod have a generation time of around 5 years, this estimate on the slow side compared to rates of inversion evolution in sunflower (5.5 inversions per million generations), but comparable than those estimated for finches (2.23 per million generations) (Burke *et al.* 2004; Hooper & Price 2015).

The final piece of the puzzle was associating the inversions with differences in migratory behaviour – a link in the much sought-after genotype/phenotype-fitness chain (Dalziel *et al.* 2009). In an ideal world, the authors could have derived a behavioural assay for migratory behaviour and used hybrid intercrosses to search for QTLs related to this phenotype. This approach has been, for example, successfully applied in migratory three-spined stickleback (Kitano *et al.* 2012). In lieu of this, the authors took a candidate gene approach, with a twist. The authors first annotated the inversions to identify (by homology) the genes they contained. They then identified gene candidates that were functionally related to the different in migratory behaviour. One excellent example of this was

the enzyme *Ca6*, which (in fish) is involved in the regulation of blood pH associated with changes in depth pressure. Using predictive modelling of this protein, the authors found that the NEAC fish have a high-efficiency variant of this protein (Fig. 2), which likely aids them in deep-water feeding. Overall, while this approach was largely observational, the authors uncovered a rich suite of genes in the inversions which will serve as strong hypotheses for further work.

There are still a huge number of unanswered questions about the role of structural variation in evolution, but studies like Kirubakaran *et al.* (2016) are the key to answering them. Perhaps, the most interesting (and difficult to answer) of these is the chicken-and-egg-esque: Do inversions only fix if they happen (by chance) to capture adaptive alleles, or are inversions themselves adaptive because they maintain LD between sets of adaptive alleles? More work is sorely needed on this front. That said, while our understanding of these questions is still undeveloped, a fascinating picture is emerging in which the physical structure of the genome provides a rich playground for the forces of evolution.

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