

Causes and consequences of reciprocal translocations on sex chromosomes

Michael F Scott

UCL Genetics Institute, Department of Genetics, Evolution and Environment, University College London, Gower Street, London WC1E 6BT.
m.f.scott@ucl.ac.uk

Under XY sex determination, the Y chromosome is only inherited via males, whereas the X is predominantly found in females. Thus, it is favourable when alleles with high male fitness become associated with the Y chromosome and when alleles with high female fitness become associated with the X chromosome. These favourable associations can be strengthened through linkage. Re-arrangements, such as inversions and sex chromosome-autosome fusions, can increase linkage and thereby become favoured (Charlesworth, 2017). In a From the Cover article in this issue of *Molecular Ecology*, Toups *et al.* (2019) present the first genomic analysis of a sex chromosome reciprocal translocation, a particularly dramatic chromosomal re-arrangement that modifies linkage with the sex chromosome. As a result of reciprocal translocation, one studied population of the common frog (*Rana temporaria*, Figure 1) displays a remarkable sex-determining system in which there are two physically unlinked sex chromosomes that are exclusively co-transmitted (Figure 2A).

After reciprocal translocation, both chromosomes that carry a segment of the ancestral-Y become co-inherited Y chromosomes. One might expect these new physically unlinked Y chromosomes to become dissociated from one another during meiotic segregation. However, segregation patterns that result in aneuploidy (duplications and deletions of segments) will typically result in gametes or zygotes that are inviable (Hartl & Ruvolo, 2012). Therefore, surviving lineages only result from 'alternate' segregation, in which two unlinked X chromosomes and two unlinked Y chromosomes are transmitted together (Figure 2B).

The genomic data presented by Toups *et al.* (2019) supports the presence of a reciprocal translocation between the ancestral sex chromosome (chromosome 1) and an autosome (chromosome 2) in a *R. temporaria* population in Ammarnäs, Sweden. Gene trees on both chromosomes have Y chromosome clades that are found only in males and have topologies that are consistent with one another, indicating co-inheritance. Toups *et al.* (2019) also develop a coalescent model to explore how homologues on the sex chromosomes are expected to diverge following reciprocal translocation. They find that X-Y differentiation peaks within the Sex-Determining Region (SDR) and declines with distance into regions that recombine on either side. The translocation breakpoint links the segregation of the two Y chromosomes and is therefore the centre of differentiation on the new Y chromosome that does not carry the SDR. On chromosomes 1 and 2 in Ammarnäs, Toups *et al.* (2019) observe patterns of male-female F_{ST} that are consistent with these predictions.

A Y chromosome reciprocal translocation brings a large number of previously autosomal loci into full- or partial-linkage with the SDR. Linkage may become particularly strong in *R. temporaria* because recombination rates are low in males (Rodrigues *et al.*, 2018). If any linked loci experience sexually-antagonistic selection, they can develop favourable associations with the SDR. That is, alleles beneficial in males (females) become associated with the Y (X). By increasing linkage and strengthening these associations, a reciprocal translocation can spread (Charlesworth, 2017). Although there are no direct data on sexually antagonistic selection in *R. temporaria*, Touns *et al.* (2019) measure expression in males and females. They find that chromosome 2, which became linked to the SDR in the Ammarnäs population, is also enriched for genes with female-biased expression in a different population of *R. temporaria* where chromosome 2 is autosomal. One hypothesis is that a number of loci on chromosome 2 experience sexually antagonistic selection, which can favour sex-biased expression (Mank, 2017). Such loci could have driven the spread of the reciprocal translocation in the Ammarnäs population.

Carriers of reciprocal translocations typically suffer from semisterility because they produce aneuploid gametes. This fertility cost can be severe and should slow or prevent the spread of a reciprocal translocation; about 50% of gametes are expected to be aneuploid through 'adjacent' segregation (Hartl & Ruvolo, 2012). However, the frequency of 'alternate' segregation can be strongly influenced by the relative positions of the centromere, translocation breakpoint, and chiasmata. Recombination is restricted to the chromosome ends in *R. temporaria* males. Intriguingly, this is a common recombination pattern in species where (autosomal) translocation heterozygotes are maintained (Holsinger & Ellstrand, 1984) and may encourage 'alternate' segregation (Hejnowicz & Feldman, 2000), greatly reducing fertility costs. Unlike reciprocal translocations between autosomes, the Y chromosome reciprocal translocation in *R. temporaria* is only found in males. Males could suffer a relatively small fertility cost from adjacent segregation because they typically produce many more sperm than are necessary to fertilize all eggs. However, this hypothesis requires that inviability due to aneuploidy occurs during the gametic stage (as is typical in plants) and not after zygote formation. Future investigations in *R. temporaria* could target the frequency of different segregation patterns and/or the stage at which inviability occurs to investigate how a reciprocal translocation was able to spread despite fertility costs.

Loci in close linkage with the SDR on the Y chromosome are expected to experience 'degeneration'. That is, deleterious mutations accumulate because, once lost, mutation-free Y chromosomes cannot be recovered through recombination (Charlesworth & Charlesworth, 2000). In mammals, this process is thought to have caused the extremely reduced size and gene content of Y chromosomes. In the Ammarnäs *R. temporaria* population, both Y chromosomes should degenerate because recombination rates with both X chromosomes are low in males. However, Touns *et al.* (2019) find that loci on both Y chromosomes have expression levels, dN/dS ratios, and numbers of large deletions that are comparable to those of the autosomes. One explanation is that the recombination rate in males is not low enough to cause detectable degeneration. Another is that there has been insufficient time for deleterious mutations to accumulate after the acquisition of the SDR and/or reciprocal translocation. Finally, it could be that significant recombination occurs between X and Y chromosomes in occasional 'sex-reversed' females that have an XY genotype (Perrin, 2009). Sex reversed *R. temporaria* females have been observed in natural

populations and exhibit recombination rates that are higher and more uniformly distributed along the chromosome than in males (Rodrigues *et al.*, 2018).

Recombination between X and Y chromosomes, especially in 'sex reversed' females, allows new chromosomal arrangements to be generated. For example, recombination between the ancestral X (X_{Anc}) and homologous Y chromosome (Y_1) could occur in-between the SDR and the translocation breakpoint. This restores a Y chromosome with a male-determining allele and a full complement of genes from the ancestral sex chromosomes but with some X_{Anc} alleles. Thus, the stable maintenance of the sex determination system in Figure 2 requires that these recombination events are either very rare or deleterious due to selection against linked alleles that are adapted to males/females.

On both sex chromosomes and autosomes, structural re-arrangements provide important tests for predictions about the evolution of recombination and its effect on molecular variation. With the adoption of new sequencing technologies and methodologies (Tattini *et al.*, 2015), structural variants are likely to be identified with increasing frequency and confidence in non-model organisms. Toups *et al.* (2019) present the first genomic analysis of the uniquely extensive structural variation on sex chromosomes in *R. temporaria*. They find that new sex-linked regions become differentiated but do not find evidence of neo-Y chromosome degeneration. Aside from the reciprocal translocation in Ammarnäs, another one of the three studied populations displayed evidence of a putative translocation/fusion with a different autosome. Across populations, this system therefore presents an opportunity to investigate whether the hypothesised costs and benefits of re-arrangements vary, e.g., male/female fitness of different karyotypes, male fertility costs from aneuploidy, and the frequency of sex reversal. An ongoing goal is to firmly link such fitness data with genomic data on re-arrangements to explain when and why structural variants spread.

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Figure 1 *Rana temporaria* female basking in the sun. Photo provided by Christophe Dufresnes.

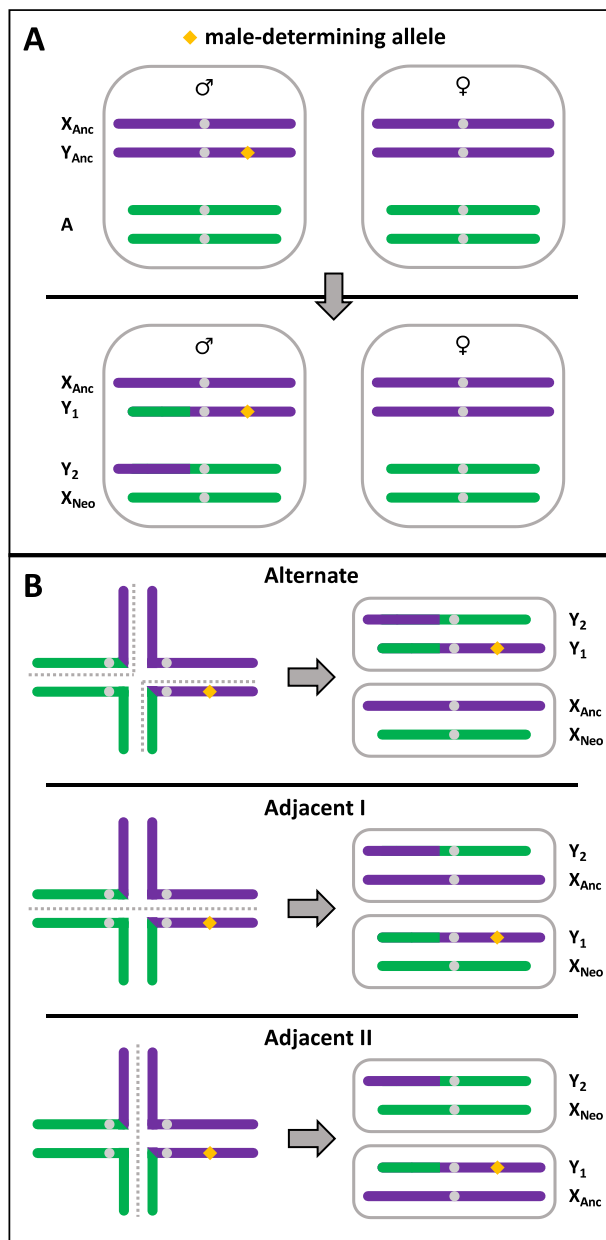


Figure 2 Reciprocal translocation resulting in unlinked sex chromosomes that are co-transmitted. (A) Reciprocal translocation between a segment of the ancestral Y chromosome, Y_{Anc} , and an Autosome, A, (above) results in two new Y chromosomes, Y_1 and Y_2 , and a new X chromosome, X_{Neo} (below). (B) Segregation of quadrivalents (left) formed during meiosis I in males carrying the reciprocal translocation. In the 'Alternate' pattern of segregation, both gamete types (right) have the full haploid set of homologous sequences. Under 'Adjacent I' and 'Adjacent II' segregation, gamete types have segments that are duplicated and deleted.