Speciation, Chromosomes, and Genomes

Jeremy B. Searle

Department of Biology, University of York, York YO1 5YW, UK

Speciation, the formation of species, is an elusive yet vitally important process for evolutionary biologists to understand. Its elusiveness stems from three factors. First, a lack of agreement as to what we mean by species, which continues to cause no end of confusion; Trémaux's statement in 1865 that "of definitions of species there are as many as there are naturalists" remains largely true (Nelson 1989). Second, speciation is a difficult or near impossible process to study directly (depending on the definition of species adopted). Third, in most cases, we know very little about the genetic basis of species formation.

What relevance then does such a woolly and poorly understood process have to genome biologists? My aim is to show that an appreciation of speciation is important for a full understanding of genomes. I will discuss speciation in relation to a familiar animal model: the house mouse (Western subspecies, *Mus musculus domesticus*), which has become a key system because of its phenomenal tendency to undergo chromosomal rearrangement in nature. The extent of this extraordinary genome repatterning was highlighted recently by Garagna et al. (1997), which is the latest in an extensive series of studies on chromosomal variation in wild house mice dating back nearly 30 years (Gropp et al. 1969).

What Is a Species?

In this paper, I follow a modern version of Mayr's (1963) Biological Species Concept that a species consists of a network of populations through which genes can potentially flow because of reproductive *compatibility*. Chromosomal rearrangements may be important in speciation because they can contribute to reproductive *isolation* between populations. If

a species becomes subdivided into two geographic forms, one of which becomes characterized by a series of chromosomal rearrangements, hybrids between these geographic forms would be expected to suffer reduced fertility due to meiotic difficulties caused by heterozygosity for the rearrangements. Any genetic exchange between the geographic forms would have to occur via the hybrids. Thus, chromosomal rearrangements could be the sole agent of speciation in this case if they disturb hybrid meiosis so much that the hybrids are sterile. If the influence on hybrids is less extreme, the chromosomal rearrangements may promote or combine with genic differences to block gene flow between the geographic forms.

"Karyotypic Races" in the Mouse

In the house mouse, the standard chromosome complement consists of 40 acrocentric chromosomes, but there are at least 40 local "karyotypic races" dotted over West Europe and North Africa characterized by a reduced chromosomal number, down to $2n = 22$ in the most extreme examples (Nachman and Searle 1995). Each step in the reduction of chromosome number is attributable to the fusion of a pair of acrocentric autosomes at their centromeres to generate a metacentric and subsequent fixation of that metacentric within the population in which it occurs. The mutation involved is known variously as a Robertsonian translocation, Robertsonian fusion, or centric fusion. Each karyotypic race is characterized by its own particular combination of metacentrics. Clearly, this difference between races may reflect fixation of different Robertsonian fusions. Also, one race may evolve from another by fixation of whole-arm reciprocal translocations (WARTs), the swapping of chromosome arms between metacentrics or between metacentrics and acrocentrics (Hauffe and Piálek 1997).

How do metacentrics accumulate in the house mouse? Data on wild-caught mice suggest little meiotic abnormality connected with heterozygosity for a single metacentric, so that fixation may occur relatively easily, for example, by genetic drift in small isolated populations (Fraguedakis-Tsolis et al. 1997). Accumulation of metacentrics within a race presumably reflects a high mutation rate (Nachman and Searle 1995) and sequential fixation of metacentrics (Capanna et al. 1977). When two karyotypic races have both accumulated large numbers of metacentrics, with very few or none in common, they can be reproductively isolated from each other on chromosomal grounds (Baker and Bickham 1986). Although the interaction of such massively divergent karyotypic races is poorly studied in wild house mice, they have been hybridized in the laboratory, and the chromosomes are found to form very complex configurations at meiosis (Gropp et al. 1982). In the presence of these configurations, it is virtually impossible for hybrids to produce viable and chromosomally balanced gametes.

Races and Species

Thus, the house mouse has been important in demonstrating empirically that accumulation of chromosomal rearrangements may lead to reproductive isolation between populations. This is relevant to other mammals, such as the muntjac deer, where closely related species differ enormously in chromosomal complement, but for which the involvement of chromosomal rearrangements in speciation has not been well-substantiated. However, even though reproductive isolation between karyotypic races has been demonstrated in house mice, strictly we are not observing speciation in this species. Probably all metacentric races in the house mouse can reproduce with the standard 40-chromosome race (e.g., Said et al. 1993) and

Corresponding author.
E-MAIL jbs3@york.ac.uk; FAX 44 1904 432947.

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so genes can potentially flow between one metacentric race and another via the standard race. Hence, the whole population network of *Mus musculus domesticus* consisting of the standard race and all the various metacentric races should be considered part of a single species on the Biological Species Concept. Many of us, including Garagna et al. (1997) and myself (Haufler and Searle 1992), have failed to distinguish between the house mouse as an excellent model of the processes involved in speciation (which it is) and as an organism undergoing speciation according to the Biological Species Concept (which, to my knowledge, it is not). The misconception extends to inappropriate Linnean names. Thus, the first-discovered 26-chromosome metacentric race of house mouse (Gropp et al. 1969) is still being described as a separate species *Mus poschiavinus* in Lyon et al. (1996; see Fraguadakis-Tsolis et al. 1997). Similarly, the Western house mouse *Mus musculus domesticus* and Eastern house mouse *Mus musculus musculus* are often called *Mus domesticus* and *Mus musculus*, respectively, even though gene flow is clearly possible between them (Hunt and Selander 1973). Of course, people making these species designations may not wish to follow the Biological Species Concept (the species concept most widely used for mammals), but this is rarely, if ever, made clear.

Speciation and Genome Evolution

Let us now turn from a discussion of speciation from the viewpoint of an evolutionary biologist to that of a genome biologist. I believe that the application of the Biological Species Concept is also desirable in genome research of mammals and other sexually reproducing animals because at the moment that two forms become separate species on this definition, there is no possibility of genetic interchange between them. Thus, their genomes will, from that moment, evolve completely independently. At all regions of the genome we should expect nucleotide differences between the species to accumulate. This is clearly a pivotal point in genome evolution.

Even though speciation is a pivotal moment in terms of what is possible with regard to genetic interchange, divergence of the two incipient species may start long before the time of speciation. This divergence will involve the

Figure 1 When a karyotypic race of house mouse defined by a particular metacentric makes geographical contact with the ancestral acrocentric race, three types of individual are expected: (A) homozygous metacentric; (B) heterozygous; and (C) homozygous twin-acrocentric. Here, the chromosomes that define the karyotypic races are shown diagrammatically, with centromeres represented by yellow circles. The metacentric shown here is red short arms and blue long arms, which would have been produced by Robertsonian fusion of the acrocentrics red and blue. Such a geographic contact between races where heterozygotes are formed is known as a hybrid zone. Any genetic exchange between the acrocentric and metacentric races occurs within the hybrid zone via the heterozygotes. If crossing-over in the vicinity of the metacentric centromere at meiosis is suppressed in heterozygotes, then genes will not be exchanged between the races for this chromosomal region.

whole genome if the incipient species are isolated geographically from each other for a period before the speciation event. However, divergence for part of the genome may occur even when the incipient species are making contact and hybridizing.

Let us consider a karyotypic race defined by Robertsonian fusions that will ultimately become a separate species. The centromeric region of a metacentric that defines that race may start to diverge from the equivalent centromeric regions of the homologous acrocentrics at the moment that the metacentric is formed. Heterozygotes for such meta-

centrics may show crossover suppression in the vicinity of the metacentric centromere (Davisson and Akesson 1993). The presence of such crossover suppression means that there will be no genetic exchange between the metacentric and homologous acrocentrics for this chromosomal region, during the process of fixation of the metacentric. Also, the centromeric region of the metacentric will be isolated genetically from the homologous acrocentrics, whenever the karyotypic race characterized by the metacentric comes in contact with the ancestral acrocentric race. At such a contact, hybridization would

be expected, and the area of hybridization is known as a hybrid zone (Fig. 1). The recognition that hybrid zones are sites of only partial genetic exchange between races, because of chromosomal rearrangements and gene loci under selection, has led to hybrid zones being described as “semipermeable barriers to gene exchange” (Harrison 1990).

This semipermeability may be very important to evolutionary biologists because of the possibilities that it may allow in development of reproductive isolation (see Hauffe and Searle 1993 in the context of karyotypic races of the house mouse). For the genome biologist, it is important to realize that genetic exchange between incipient species may occur shortly before speciation for some regions of the genome but cease much earlier for others.

Differences between regions of genomes such as those outlined above are only likely to be detectable between recently separated species. However, there is much to be gained from studies of such closely related forms. Genome researchers have much to contribute to our understanding of speciation through such studies. Imaginative investigations involving crosses and genome manipulation have already begun on reproductive isolation between closely related species of *Drosophila* (Orr et al. 1997). For mammals it is necessary to rely more on direct genome comparisons. Such comparisons have started for Y-specific sequences potentially important in speciation (Tucker and Lundrigan 1993), but far, far more remains to be done.

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