

## Glossary

**Assortative mating** Mating that takes place between individuals with similar phenotypes more often than expected under random pairing in the population. Conversely, disassortative mating is the preferential mating between individuals with dissimilar phenotypes.

**'Classical' mouse inbred strains** Mouse strains established in the first three decades of the twentieth century. Some of these strains have become the standards in mouse research (e.g., C57BL/6J, C57BL/10J, BALB/cJ, A/J, C3H/HeJ, 129/SvJ, DBA/2J, CBA/CaJ). Unfortunately, rather than genetically pure representatives of individual house mouse subspecies, these inbred strains are complex mixtures of their genomes (with prevalence of the *Mus musculus domesticus* genome).

**Cline** A smooth gradient in a character (e.g., allele frequency or the mean of a quantitative trait) across a spatially continuous habitat.

**Commensalism** In ecology, a type of relationship between two organisms where one organism benefits from the other, while the opposite relationship is neutral (i.e., the other organism poses no benefit or harm to its counterpart). The house mouse is considered commensal in relation to humans (hence can be regarded as a synonym for synanthropy, that is, life ecologically associated with humans).

**Haldane's rule** According to this principle, if the offspring of two different populations or taxa suffers greater viability or fertility, it is the heterogametic sex.

**Inbred strain** A line of an organism generated and maintained by inbreeding. A strain is considered inbred if it has been bred by the strict brother–sister mating for at least 20 generations. At this point, 98.7% of loci in each animal's genome should be homozygous. At each subsequent generation, heterozygosity is reduced by 19.1% so that at 30 generations 99.8% of the genome will be homozygous.

**Introgression** Invasion of foreign genetic material into a genome. A gene flow from the gene pool of one species into the gene pool of the other through repeated backcrossing of hybrids with one of the parental species.

**Large X-effect** A hypothesis that genes having a large effect on postzygotic isolation are often presented on the X chromosome.

**Parapatry** Occurrence of two species or populations in areas that are immediately adjacent to each other; where the two distribution areas abut a narrow contact zone may be formed.

**Reinforcement** The strengthening of postzygotic isolation as a result of emergence of prezygotic barriers. According to this hypothesis, strong selection against hybrids supports any mutation that causes preference of a sexual partner of the same species in the area of sympatry.

**Reproductive character displacement** Reinforcement of reproductive barriers; a pattern of increased prezygotic isolation in sympatry (i.e., when two populations occur in the same area) compared with allopatry (i.e., when two populations occur in different areas so that their ranges do not come into contact).

## What Is a Hybrid Zone?

There are various notions of what constitutes a hybrid zone, but most often it is defined as an area where genetically distinct populations meet, mate, and leave offspring of mixed ancestry. Hybrid zones can be maintained by various kinds of natural selection, for example, by balancing selection favoring hybrid individuals within an area of intermediate habitat ('bounded hybrid superiority'), or they may have a spatially complex structure formed by different, patchily intermingled habitats (mosaic zones). However, the majority of hybrid zones are maintained by a balance between dispersal and selection. This selection can be extrinsic or intrinsic. In the former case, different alleles are adapted to different habitats while being selected against in a foreign habitat so that the hybrid zone is located at a particular point along an environmental gradient. In contrast, intrinsic selection negatively affects alleles appearing on a foreign genetic background and so is independent of a particular environment. The zone can move across geographic space due

to demographic differences between populations or as a result of asymmetric selection until it is 'trapped' at a region of the lowest population density ('density trough'). This kind of hybrid zone is called tension zone because it tends to minimize its length as a consequence of differential dispersal and is probably the most frequent though in many cases both extrinsic and intrinsic selection participate in maintaining a particular zone.

## Tension Zones

Tension zones are formed after secondary contact of two populations or species diverged in allopatry. Upon contact, allele frequency gradients or clines are clustered at the same position (they are 'coincident') and have the same, 'concordant', width. With passing time, concordance of clines diminishes as some genes pass through the zone relatively freely, whereas transition of others is strongly impeded. Cline widths are proportional to

the characteristic scale of selection,  $\frac{\sigma}{\sqrt{s}}$ , where  $\sigma$  is the dispersal (defined as the standard deviation of the distance between parent and offspring) and  $s$  is the selection against admixture. Thus, in principle, the relationship between cline shape and selection is straightforward: the stronger the selection against an allele at a locus, the narrower the cline for this locus.

In a typical case, a cline for a trait can be modeled with a simple sigmoid function, which can be used for a number of hybrid zone types (tension zones, zones maintained by extrinsic selection, or selection acting on quantitative traits). However, selection usually acts at more than one locus and tension zones are thus characterized by increased associations between loci in the center. These linkage disequilibria cause the effective selection maintaining the barrier to gene flow to be stronger than it would be if it affected each locus independently. From estimates of linkage disequilibria, dispersal, and cline shape parameters, we can estimate the strength of selection, the number of selected genes, or the mean fitness of hybrids.

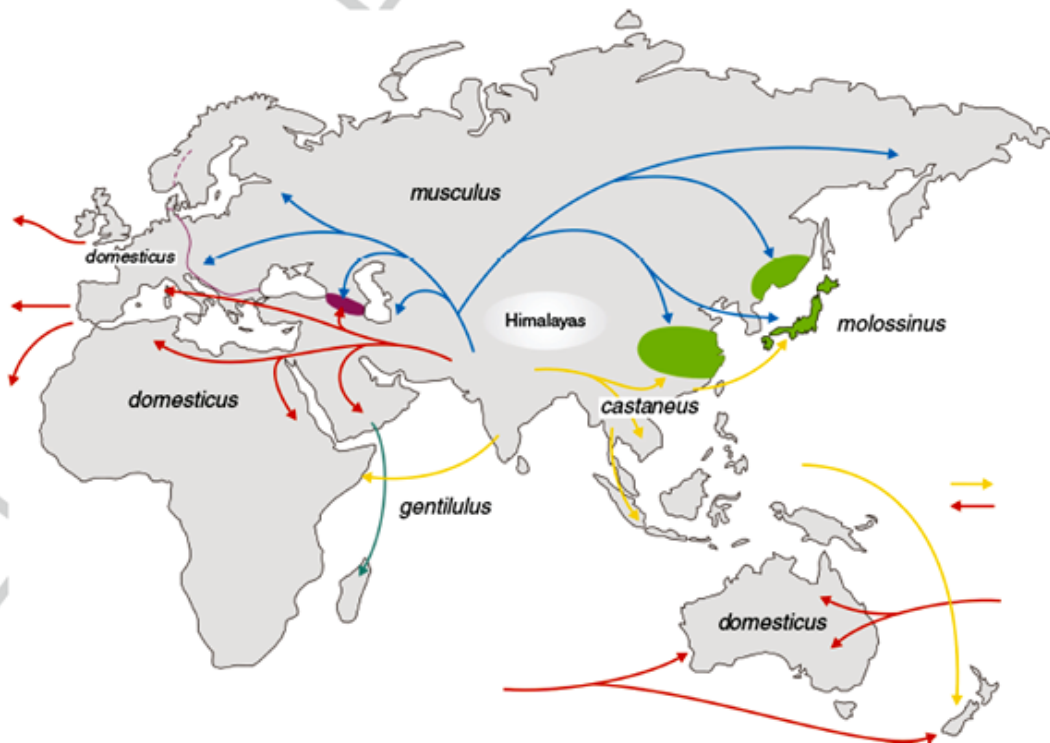
### A Case Study: The House Mouse

Among the best-studied hybrid zones are zones of secondary contact between the house mouse subspecies. House mice (*Mus musculus*) are supposed to have originated about 500 000 years ago in the northern part of the Indian subcontinent. From this 'cradle', individual subspecies have spread, mostly due to their

commensal life, to their current ranges. Three of these subspecies have reached wide distribution: *musculus* occurs from Central and Northern Europe to the Far East; *castaneus* occurs in Southeastern Asia; *domesticus* lives in Western and Southern Europe, the Middle East, and Northern Africa, and it has also been introduced to the Americas, Australia, and Africa south of the Sahara. In Japan, the Russian Far East, and part of China, *M. m. musculus* and *M. m. castaneus* hybridize across a vast area giving rise to a hybrid taxon described as a distinct subspecies *M. m. molossinus* (Figure 1).

There is a wide agreement that no extant house mice occupied western Eurasia before the end of the last glaciation. The mouse progression has followed two colonization routes consistent with human historical patterns: *M. m. domesticus* has arrived from Asia Minor along the Mediterranean Basin, whereas *M. m. musculus* followed a pathway north of the Black Sea. The two subspecies meet along a narrow zone running through Norway and Denmark and from the Baltic coast to the Black Sea (Figure 2). Though the exact dating of the contact is still debated, the zone is supposed to have formed progressively from the Balkans northwards. There is evidence that Scandinavia has been colonized from East Holstein (northern Germany) by a small group of hybrid mice. The hybrid origin of the founders resulted in a peculiar genetic mosaic with the *musculus*-type nuclear genome and *domesticus* mitochondrial DNA (mtDNA).

The European house mouse hybrid zone consists of a mixture of multiple filial and backcross generation hybrids. F<sub>1</sub> hybrids are missing or extremely rare and for most markers the zone structure is unimodal, with predominately



**Figure 1** Colonization routes of house mouse subspecies starting from northern parts of Indian subcontinent. Arrows indicate movements of the *castaneus* (yellow), *domesticus* (red), and *musculus* (blue) subspecies; *gentilulus* (green) refers to an mtDNA lineage found in Yemen and Madagascar. Mice of the Americas, Australia, and Africa south of the Sahara have been imported by humans. Hybridization between *M. m. musculus* and *M. m. castaneus* has resulted in the formation of a hybrid taxon (*M. m. molossinus*) in Japan, China, and the Russian Far East (green). Hybrid zones between *M. m. musculus* and *M. m. domesticus* in Europe and Transcaucasia are depicted in purple.





**Figure 2** The course of the *M. m. musculus*/*M. m. domesticus* hybrid zone in Europe with hitherto studied transects in Denmark (A), northern (B) and eastern Germany (C), northeastern Bavaria (Germany) and Czech Republic (D), southern Germany (E), and Bulgaria (F). The position of the zone in Norway is tentative only (dashed line). As shown by the light-blue arrows, *domesticus* mice colonized the continent from the Middle East through Asia Minor and along the Mediterranean, whereas *musculus* mice followed the route north of the Black Sea. From this scenario, it follows that the hybrid zone is older in southern parts than in northern parts, with the most recent contact in Denmark and Norway. Note that colonization of Scandinavia by a few hybrid individuals from East Holstein has led to a mosaic genome of Scandinavian mice with nuclear *M. m. musculus* genome and mtDNA of *M. m. domesticus*.

intermediate genotypes and phenotypes in the center. Assuming dispersal estimates of around 1 km, molecular clines suggest the fitness of the hybrids to be ~50% relative to the fitness of both parental populations for autosomal loci and ~30% for X-chromosome loci. Estimates of the number of genes under selection range between 46 and 120 and the effective selection pressure maintaining the zone is 3–9% for autosomes and ~25% for the X chromosome. However, in spite of long-standing efforts, the genetic basis of reproductive isolation between the two subspecies is still largely unknown. Laboratory crosses between the wild-derived *M. m. musculus* inbred strain PWD and the 'classical' strain C57BL/10 carrying predominantly *M. m. domesticus* alleles yield sterile male  $F_1$  hybrids, in agreement with Haldane's rule. The locus causing hybrid male sterility in this cross (hybrid sterility 1, *Hst1*) is the first described mammalian 'speciation gene' and recently has been identified with the *Prdm9* gene. Moreover, backcross data suggest interactions with at least two other loci. Nevertheless, studies of wild populations suggest that sterility alleles are either absent or segregating in the European house mouse hybrid zone and the genetic basis of reproductive isolation in the house mouse is thus likely to be more complex than previously envisaged.

It has been suggested that mouse hybrids suffer from an increased intestinal parasite burden, this effect being caused by the breakdown of coadapted immune system gene complexes due to recombination in  $F_2$  or backcross generations. However, some experiments shed doubt on recombination as a cause of pinworm susceptibility, and experimental infections by other

parasites have yielded varying results. Moreover, recent large-scale parasitological analyses of the Central European portion of the hybrid zone show a contradictory picture, with hybrids harboring fewer parasites than pure *M. m. musculus* and *M. m. domesticus*.

Since the work of Darwin, the puzzling question about how hybrid sterility or inviability can arise in a population in the face of natural selection has remained. According to a model proposed independently by T. Dobzhansky and H. Muller, postzygotic barriers may come about through accumulation of different mutations at two or more loci after an ancestral population has been split by a geographic barrier. Emerging alleles are perfectly compatible with the parental genetic background but incompatible with mutations fixed in the other population, resulting in reduced fertility or viability after their secondary contact. Although the Dobzhansky–Muller model has become a cornerstone of the genetics of speciation, there is growing evidence that intrinsic postzygotic isolation may also arise through selection on selfish genetic elements, rather than through Darwinian adaptation to the external environment and/or random drift. Thus, incompatibilities are accumulated due to an 'arms race' within the genome in allopatry. Upon contact, differently adjusted conflict systems are likely to be mutually incompatible, leading to hybrid dysfunction.

In addition to postzygotic isolation, barriers between hybridizing taxa can also be mediated through preferential mating between individuals of the same population. This assortative mating can be established in allopatry as a by-product of natural or sexual selection or upon secondary contact between two diverged populations with incomplete postzygotic isolation. In the latter case, selection will favor any mutation leading to avoidance of detrimental heterosubspecific matings, thus reinforcing the barrier. For example, one of the genes coding for an alpha subunit of salivary androgen-binding proteins (ABPs; *Abpa27*) was found to possess three alternative alleles, each fixed in one subspecies (the *a* allele in *domesticus*, *b* in *musculus*, and *c* in *castaneus*). In addition, inbred strains derived from the former two subspecies displayed preference for saliva containing a product of the own subspecies' *Abpa* allele, suggesting that this gene could be involved in prezygotic isolation. A similar tendency to consubspecific preferences, based on urinary cues, was shown for males and females of *M. m. musculus*, whereas *M. m. domesticus* displayed no preference. However, transitions of markers located within or very close to genes encoding salivary ABPs and major urinary proteins (MUPs) across the hybrid zone are not significantly steeper than clines for loci presumed to be neutral or nearly neutral, calling into question the role of these proteins in prezygotic isolation. In contrast, recent analyses suggest stronger consubspecific preferences in parapatry than in allopatry, a phenomenon known as reproductive character displacement.

Studies on the nature of the reproductive barrier between *M. m. musculus* and *M. m. domesticus* carried out on various portions of the zone have shown a remarkably consistent picture of steeper transition of sex chromosomes relative to autosomal markers, in agreement with the large X-effect of Haldane's rule (see Glossary). However, several recent findings have suggested that introgression patterns for diverse genes may be quite complex or that they can differ for the same locus between various parts of the zone. For example, an

unexpectedly extensive introgression of the *musculus* Y into *domesticus* territory was revealed in western Bohemia (Czech Republic) and northeastern Bavaria (Germany), accompanied by a perturbation of the census sex ratio. This astonishing pattern was explained as a result of genetic conflict between loci involved in sex ratio distortion. In this case, the *musculus* Y is successful on the naive *domesticus* background so that it can spread across the zone at the expense of the *domesticus* Y. Thus, here, genetic conflict leads to decay in the barrier to gene flow between *M. m. musculus* and *M. m. domesticus*, which is the opposite to the predictions of the mutual destruction hypothesis described above. A similar introgression of *musculus* loci into *domesticus* territory in the same area was also revealed for mtDNA and several X-linked loci. Finally, recent whole-genome data indicate that the zone may have been moving.

Given that diverse and rich data are now available from several geographically separated portions of the zone, along with the fact that the house mouse is a model species with known sequence of its genome and huge databases of suitable molecular markers, the European house mouse hybrid zone becomes a paramount tool for genetic and evolutionary studies.

**See also:** Hybrid Sterility, Mouse (00753); Hybridization, Organismal (00759).

## Further Reading

- Barton NH and Hewitt GM 1985. Analysis of hybrid zones. *Annual Review of Ecology and Systematics* 16: 113–148.
- Boursot P, Auffray J-C, Britton-Davidian J, and Bonhomme F (1993) The evolution of house mice. *Annual Review of Ecology and Systematics* 24: 119–152.
- Britton-Davidian J and Searle JB (2005) The genus *Mus* as a model for evolutionary studies. *Biological Journal of the Linnean Society* 84(a special issue).
- Harrison RG (1993) *Hybrid Zones and the Evolutionary Process*. New York; Oxford: Oxford University Press.
- Macholán M, Baird SJE, Munclinger P, and Piálek J (in preparation) *Evolution of the House Mouse*. Cambridge Series in Morphology and Molecules. Cambridge: Cambridge University Press.
- Otte D and Endler JE (1989) *Speciation and Its Consequences*. Sunderland, MA: Sinauer Associates, Inc.

## Relevant Websites

- <http://www.blackwellpublishing.com> – Evolution, meiotic drive.
- [http://en.wikipedia.org/wiki/Haldane%27s\\_rule](http://en.wikipedia.org/wiki/Haldane%27s_rule) – Haldane's rule (including dominance theory and large X-effect).
- [http://en.wikipedia.org/wiki/House\\_mouse](http://en.wikipedia.org/wiki/House_mouse) – House mouse.
- [http://en.wikipedia.org/wiki/Hybrid\\_zone](http://en.wikipedia.org/wiki/Hybrid_zone) – Hybrid zone.
- [http://en.wikipedia.org/wiki/Intragenomic\\_conflict](http://en.wikipedia.org/wiki/Intragenomic_conflict) – Intra-genomic conflict.
- <http://bio4esobill2009.wordpress.com> – Prezygotic and postzygotic reproductive isolation.
- [http://en.wikipedia.org/wiki/Reproductive\\_isolation](http://en.wikipedia.org/wiki/Reproductive_isolation) – Reproductive isolation.
- <http://science.jrank.org/pages/48540/Hybrid-Zones.html> – Science encyclopedia.