Genetic distinctiveness of a village population of house mice: relevance to speciation and chromosomal evolution

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SUMMARY

A population of house mice, *Mus musculus domesticus*, from the village of Migiondo was found to be genetically distinct from nearby populations in Upper Valtellina (Italian Alps). At the supernatant malic enzyme locus, *Mod1*, the only alleles found in Migiondo (*c* and *n2*) were virtually absent from the other populations in the valley, which were characterized by allele *a*. The extraordinary genetic distinctiveness of the Migiondo population is apparently the result of genetic drift, perhaps coupled with a founder event, and attests to the existence of nearly impenetrable geographic barriers around the village isolating it from other settlements only a few hundred metres away. The *Mod1* features of the house mice in Migiondo are reminiscent of the characteristics of house mice on maritime islands. The genetic confirmation of the geographic isolation of Migiondo is of interest because there is evidence that this village may have been the site of recent speciation and extinction events. The data are also of significance given the phenomenal chromosomal variation in house mice from the vicinity of the Alps. It has frequently been proposed that genetic drift/founder events are of importance in the fixation of chromosomal rearrangements; this study provides the first direct evidence for their occurrence in alpine mouse populations.

1. INTRODUCTION

House mice, *Mus musculus domesticus*, from the Swiss 'Val Poschiavo' and the Italian 'Upper Valtellina', adjoining alpine valleys, have long attracted considerable interest. Poschiavo mice first drew attention due to their unusually dark coloration and were described as a separate species, *Mus poschiavinus*, by Fatio (1869): the 'tobacco mouse' (so called because of their association with kilns for drying tobacco). Exactly 100 years later, Gropp *et al.* (1969) discovered that the Poschiavo mice had a chromosome number of $2n = 26$, strikingly different from the standard 40-chromosome karyotype. This first demonstration for wild house mice of Robertsonian fusion mutations (the joining together of pairs of the standard acrocentric chromosomes at their centromeres to form metacentric chromosomes) heralded the start of important evolutionary studies (reviewed by Boursot *et al.* (1993); Sage *et al.* (1993); and Nachman & Searle (1995)) and biomedical investigations making use of Robertsonian chromosomal markers (e.g. Gropp & Kolbus 1974; Herbst *et al.* 1981; Cattanach & Kirk 1985). Mice from Val Poschiavo and Upper Valtellina have also been sources of critical genic markers for studies of mammalian sex determination (Eicher *et al.* 1982; Eicher 1994).

Subsequent to the demonstration of the unusual karyotype in house mice from Val Poschiavo, reduced chromosome numbers attributable to Robertsonian fusions were found in other populations in Italy and Switzerland (Capanna *et al.* 1976) and further afield (Adolph & Klein 1981), and some of these 'karyotypic races' were also shown to hybridize freely with standard mice in nature (Capanna *et al.* 1977; Adolph & Klein 1983). With regard to the 26-chromosome tobacco mice, it was demonstrated early on (Gropp *et al.* 1969) that they could be crossed with standard 40-chromosome laboratory mice in captivity, and it was through further backcrosses and intercrosses that stocks of mice homozygous for each of the seven individual Robertsonian metacentrics were isolated for biomedical studies (Cattanach & Moseley 1973; Ford & Evans 1973). However, in nature, the situation is rather complex. It was demonstrated by Gropp, Capanna and co-workers that in addition to the 26-chromosome form in Poschiavo there is a 24-chromosome form in Upper Valtellina (Capanna & Corti 1982; Gropp *et al.* 1982). Both forms were found together at high frequencies (60%: 40%) in the Upper Valtellina village of Migiondo, but despite a large sample of 150 mice from the settlement, no hybrids

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were found (Capanna & Corti 1982; Mainardi *et al.* 1986). As a result of the chromosomal differences between the Poschiavo and Upper Valtellina forms of house mice, hybrids would have been expected to form a chain-of-five configuration at the first division of meiosis (Hauffe & Searle 1993). The existence of such a configuration, instead of the normal situation of just bivalents, leads to aberrations in the meiotic division, abnormal or absent gametes and, ultimately, reduced fecundity (see reviews by Gropp & Winking (1981); Redi & Capanna 1988; Searle 1993). It was therefore possible that hybrids were originally produced on contact of the Poschiavo and Upper Valtellina karyotypic forms, but that, because of their unfitness, natural selection favoured assortative mating (Capanna & Corti 1982), i.e. the process of reinforcement (Dobzhansky 1940; Butlin 1987; Howard 1993) may have occurred.

That was the situation in Val Poschiavo/Upper Valtellina in the early 1980s. We started our study in the region in 1989. Although we have failed to find any house mice at all in Val Poschiavo, they are very numerous in the villages and hamlets along the 20 km of the River Adda, which comprises Upper Valtellina; they are apparently rather strictly associated with houses and farms in this area (Hauffe & Searle 1993; H. C. Hauffe, unpublished data). Along this short stretch of river valley, we have not only found the Upper Valtellina and Poschiavo karyotypic forms, we have also located the previously described 22-chromosome Lower Valtellina form (Gropp *et al.* 1982), the 40-chromosome standard race and a new 24-chromosome 'Mid Valtellina' form (Hauffe & Searle 1993). From the karyotypes that we have observed in the field, it is evident that, within the valley as a whole, all the karyotypic forms are hybridizing with each other (in fact we consider the Mid Valtellina form a product of hybridization; Hauffe & Searle 1993). The tobacco mouse coloration was recorded on mice of a variety of karyotypes (Hauffe 1993) and is known to merely reflect a single dominant allele (E^{tob}) at the extension locus (Lyon *et al.* 1996). Thus, like Gropp *et al.* (1982), we consider it appropriate that the karyotypic forms within Val Poschiavo/Upper Valtellina should be classified as 'karyotypic races' (Poschiavo, Upper Valtellina, Lower Valtellina, Mid Valtellina and standard races; Hauffe & Searle 1993) and that the designation '*Mus poschiavinus*' for the Poschiavo race is inappropriate.

The fact that we found hybrids between the Poschiavo and Upper Valtellina races in villages close to Migiondo, supports the scenario that these races were previously able to hybridize in that village too, and that reproductive isolation arose by reinforcement (Hauffe & Searle 1992). However, when we surveyed Migiondo itself during 1989–92, instead of the two karyotypic races (Upper Valtellina and Poschiavo) recorded by Capanna and colleagues ten years earlier, we found only one (Poschiavo). Apparently, therefore, the Upper Valtellina race had gone extinct within the village. Hence our description of the situation as 'a disappearing speciation event' (Hauffe & Searle 1992).

Within Upper Valtellina, although the village of Migiondo is only a few hundred metres from other settlements, it is surrounded by rather severe physical barriers: a deep gorge to the north and steep cliffs to the south and east. Also, there is little movement of agricultural material (which may harbour mice) to and from the village (E. Olandi, personal communication). Therefore we have suggested that both the supposed reinforcement event and the extinction event were favoured by the fact that the mouse population in Migiondo was rather small and geographically isolated from others in the valley (Hauffe & Searle 1992). Reinforcement is more likely in an isolated population because there will be no gene flow from 'pure race' populations swamping the effects of selection within the hybridizing population (Howard 1993). Clearly, extinction events are more likely if populations are small (MacArthur & Wilson 1967).

We decided to use allozyme markers to test whether the house mice in Migiondo display features that might be expected of a small, isolated population. Among 23 allozyme loci screened, five were polymorphic. At 22 of these loci the mice from Migiondo showed characteristics similar to nearby populations that comprised some combination of Upper Valtellina, Poschiavo or Mid Valtellina race mice. However, the allelic variation at the supernatant malic enzyme locus (*Mod1*, E.C. 1.1.1.40) was far more informative. This paper describes how this variation clearly supports our perception of the Migiondo mouse population as small and geographically isolated.

2. MATERIALS AND METHODS

Specimens were collected in Upper Valtellina during autumn 1989, 1990 and 1991, as described in Hauffe & Searle (1993). The mice were collected from 17 distinct villages/settlements, with 1–5 houses/farms sampled per village (four houses in the case of Migiondo). A large proportion of the individuals caught were karyotyped at a laboratory base in the valley (Hauffe & Searle 1993) and, for all individuals, freshly frozen tissue samples were brought back to Britain on dry ice for long-term storage at −80 °C. Treatment of the tissue samples and the cellulose acetate electrophoresis followed the methodology in Searle (1985). To visualize supernatant malic enzyme, liver or kidney samples were used and the electrophoretic running buffer was 40 mM Tris–10 mM citrate, pH 7.6. The stain was applied as an agar overlay. Approximate final concentrations of histochemicals on the gels were as follows: 71 mM Tris-HCl, pH 8.0, 0.23 mM NADP, 0.19 mM PMS, 0.57 mM MTT, 12 mM $MnCl_2$, 59 mM malate, pH 8.0. To identify the genotype of each individual, use was made of tissue samples from mouse inbred strains known to carry $Mod1^a$ and $Mod1^b$ (Lyon *et al.* 1996; all allozyme nomenclature follows the standardized system described in this reference).

3. RESULTS

Three *Mod1* alleles were identified in mice from Upper Valtellina:

(i) $Mod1^a$, previously described in inbred strains and wild mice (Shows & Ruddle 1968; Lyon *et al.* 1996);

(ii) $Mod1^c$, which generates a product that runs anodal to MOD1A and is thought to be equivalent to

Table 1. *House mice from Upper Valtellina: number of individuals with various* Mod1 *genotypes*[a]

village	coordinates (km)[b]	predominant karyotypic races present at site[c]	no. mice screened at *Mod1*	*a/a*	*a/c*	*c/c* or *c/n2*	*n2/n2*
Sondalo	5131.8 N 1602.0 E	POS, UV	11	11	0	0	0
Sommacologna	5131.6 N 1600.7 E	POS, UV	11	10	1	0	0
Migiondo	5130.8 N 1600.5 E	POS	22	0	0	18	4
Sontiolo	5130.3 N 1600.6 E	UV	4	4	0	0	0
Tiolo	5129.5 N 1600.3 E	UV	7	7	0	0	0
Lago	5128.7 N 1599.4 E	UV	2	2	0	0	0
Grosio	5127.4 N 1597.8 E	MV	9	9	0	0	0
Grosotto	5126.0 N 1597.0 E	POS, MV, LV	16	13	2	1	0
Farm Via Prada	5124.6 N 1596.3 E	MV	5	5	0	0	0
Vione	5124.1 N 1596.2 E	POS	3	3	0	0	0
Mazzo	5123.3 N 1597.0 E	AA	12	12	0	0	0
Vervio	5122.8 N 1595.5 E	AA	1	1	0	0	0
Tovo S. Agata	5121.9 N 1596.0 E	AA	13	13	0	0	0
Nova	5121.4 N 1594.6 E	AA	2	2	0	0	0
Lovero	5120.6 N 1595.0 E	AA, UV	4	4	0	0	0
Sernio	5119.9 N 1592.6 E	UV	5	5	0	0	0
Biolo	5119.3 N 1593.4 E	?	2	2	0	0	0

[a] Among those individuals collected at Migiondo and classified as $Mod1^c/Mod1^c$, an unknown proportion were actually $Mod1^c/Mod1^{n2}$: see text.

[b] The coordinates are presented according to the Gauss-Boaga system.

[c] Data on karyotypic races follow Hauffe & Searle (1993): AA, all acrocentric standard race; POS, Poschiavo race; UV, Upper Valtellina race; MV, Mid Valtellina race; LV, Lower Valtellina race. Hybrids were common; sometimes the races recorded as present in a site were only represented by hybrids.

the Mod^c described by Selander *et al*. (1969) in wild *Mus musculus musculus* (see also She *et al*. (1990)) and by Berry & Peters (1977) in wild *M. m. domesticus* (see also Britton-Davidian *et al*. (1989));

(iii) $Mod1^{n2}$, a null allele.

A null allele ($Mod1^{n1}$) has previously been described as a spontaneous mutant in the C57BL/6J inbred strain (Johnson *et al*. 1981), but the allele we identified must have had a different origin and it is the first time, to our knowledge, that a null allele at the *Mod1* locus has been found in wild mice. $Mod1^{n2}/Mod1^{n2}$ homozygotes were scored readily because of the complete absence of MOD1 activity, despite normal activity for all the other 22 isoenzymes screened. At Migiondo, the only village where $Mod1^{n2}/Mod1^{n2}$ homozygotes were detected, there were also some individuals that could clearly be scored as $Mod1^c/Mod1^{n2}$ heterozygotes, due to the presence of a single faint MOD1C band. However, there were other individuals caught at Migiondo where it was uncertain whether the faintness of the single MOD1C band was a consequence of heterozygosity for the null allele, or the result of sample-by-sample variation in enzyme activity. (Our protocol is primarily designed for detecting mobility variants and will only reveal gross differences in enzyme activity.) Therefore, at Migiondo, we have not tried to calculate separately the frequency of $Mod1^c/Mod1^c$ and $Mod1^c/Mod1^{n2}$ individuals. At sites other than Migiondo, there were no $Mod1^{n2}/Mod1^{n2}$ homozygotes, nor any unequivocal heterozygotes for the null allele. It is assumed, therefore, that the $Mod1^{n2}$ allele is limited to Migiondo.

Altogether 129 house mice from 17 villages in Upper Valtellina were scored for *Mod1* genotype. Table 1 presents the frequency data. At this locus, Migiondo stands out as being completely different from all other settlements. Not only is it the sole site where the $Mod1^{n2}$ allele has been recorded, it is also the only site where allele $Mod1^a$ was not found. Apart from Migiondo, $Mod1^a$ completely dominates Upper Valtellina: 103 out of 107 mice collected were $Mod1^a/Mod1^a$ homozygotes. Even villages a few hundred metres from Migiondo, such as Sommacologna, Sontiolo and Tiolo, are dominated by $Mod1^a$ (table 1). In Migiondo, it is allele $Mod1^c$ that is the most common, but with the null allele $Mod1^{n2}$ also present at fairly high frequency. Allele $Mod1^c$ has also been found at low frequency in two other villages—Sommacologna and Grosotto—both characterized by individuals homozygous or heterozygous for the Poschiavo race karyotype (table 1), which is, of course, the only karyotype found in Migiondo.

4. DISCUSSION

(*a*) *A village as an 'island'*

On the basis of extensive surveys of *M. m. domesticus* in Britain, Western Europe and the Mediterranean basin, especially by Berry and Peters (1977) and Britton-Davidian and co-workers (Britton-Davidian *et al*. 1989; Navajas y Navarro & Britton-Davidian 1989; Britton-Davidian 1990; Said & Britton-Davidian 1991), the common alleles at the supernatant malic enzyme locus are $Mod1^a$ and $Mod1^b$ (also recorded as alleles '120' and '100', respectively; J. Britton-Davidian, personal communication). However, in a few populations in Tunisia, Egypt, Southern Germany, Northern Spain, Corsica and, most significantly, Northern Italy, a third allele '140' has been recorded at low frequency (Britton-Davidian *et al*. 1989; Navajas

y Navarro & Britton-Davidian 1989; Britton-Davidian 1990; Said & Britton-Davidian 1991). This allele is almost certainly the same as the *Mod1*^{c} allele reported in the present study and by Selander *et al*. (1969).

Thus the high frequency of the *Mod1*^{c} allele in Migiondo may reflect either a founder event or genetic drift, whereby an allele that is normally rare in *M. m. domesticus* has increased to a very high frequency within a particular population. Furthermore, the high frequency of the previously undescribed null allele in Migiondo, *Mod1*^{n2}, can most reasonably be considered to be a *de novo* mutation that has increased in frequency by genetic drift. There is no reason to suspect some selective advantage associated with either rare allele in Migiondo. Indeed, on the basis of the previously described null allele, *Mod1*^{n1}, there is, if anything, an expectation of a disadvantage associated with *Mod1*^{n2} (Johnson *et al*. 1981).

Therefore, the genetic distinctiveness of the Migiondo mice with respect to the *Mod1* locus, is consistent with this population being small and geographically isolated, perhaps founded by a small number of individuals and/or subject to population bottlenecks. All these features are reminiscent of a population on a small maritime island. Indeed, to our knowledge, it is only island/island or island/mainland comparisons in the house mouse that have previously revealed such dramatic frequency differences at allozyme loci between geographically close populations. Most pertinent are the comparisons between islands of the Faroe archipelago, where populations on different islands were found to be fixed for different alleles at certain loci (Berry & Peters 1977). In particular, while the populations on Hestur and Sandøy are polymorphic for alleles *Mod1*^{a} and *Mod1*^{b}, the population on Fugløy is monomorphic for the *Mod1*^{c} allele, which otherwise has not been described on Faroe, Orkney or Shetland (Berry & Peters 1977). The similarity between Fugløy and Migiondo mice is striking, but it must be remembered that Migiondo is a mainland village only a few hundred metres from other villages with more typical *Mod1* characteristics.

Clearly, while the complete absence of the *Mod1*^{a} allele indicates no recent movement of house mice into Migiondo, the occurrence of the *Mod1*^{c} allele in Sommacologna and Grosotto suggests occasional migration of individuals out of Migiondo. On the basis of karyotype (H. C. Hauffe, unpublished data), the Sommacologna mouse carrying the *Mod1*^{c} allele could have been the progeny of a migrant from Migiondo, while those in Grosotto could have been the progeny (one mouse) or grandprogeny (two mice). They could also, of course, be more distantly related to Migiondo mice.

(*b*) *Speciation by reinforcement in Migiondo?*

There has been much discussion in recent years about the likelihood that speciation may occur by the reinforcement process (Howard 1993; Liou & Price 1994; Kelly & Noor 1996). The case that we have presented (Hauffe & Searle 1992) for such a reinforcement event in Migiondo was that: (*a*) in the early 1980s the Poschiavo and Upper Valtellina races were found together in the village at high frequencies without hybrids (Capanna & Corti 1982), suggesting assortative mating; (*b*) we found that the races interbreed elsewhere in the valley (Hauffe & Searle 1993), and so it may be presumed that the races were able to hybridize on first colonization of Migiondo; (*c*) our laboratory studies have demonstrated that Poschiavo X Upper Valtellina hybrids suffer reduced fertility on cytogenetic grounds (Hauffe 1993), indicating a potential selection pressure for assortative mating; and (*d*) there is only one type of hybrid produced on contact of the Poschiavo and Upper Valtellina races and a reasonable likelihood that crossover suppression may promote linkage disequilibrium between an assortative mating locus and the chromosomes involved in hybrid unfitness (Hauffe & Searle 1993). Thus, we envisaged that the Poschiavo and Upper Valtellina mice colonized Migiondo and produced unfit hybrids, and that natural selection then favoured the evolution of assortative mating, made possible by the cytogenetic system (Hauffe & Searle 1992). We also considered that the geographic barriers around Migiondo were a feature that may have favoured speciation by reinforcement (Hauffe & Searle 1992, 1993). We reasoned that the barriers would reduce the flow of genes from 'pure race' populations; if such gene flow had been substantial it could have disrupted the effects of selection in the village (see Howard (1993)).

In the present study we have demonstrated a complete absence of the *Mod1*^{a} allele in Migiondo, despite its substantial dominance elsewhere in the valley. This provides clear evidence that Migiondo is indeed remarkably insulated from incoming gene flow. Thus, there is even more reason to be convinced that conditions in Migiondo were particularly favourable for a reinforcement event.

(*c*) *The extinction event in Migiondo*

We have described the situation in Migiondo as a 'disappearing speciation event' (Hauffe & Searle 1992). Although the Poschiavo and Upper Valtellina karyotypic races were present and reproductively isolated in the early 1980s (Capanna & Corti 1982; Mainardi *et al*. 1986), only the Poschiavo race was found ten years later (Hauffe & Searle 1992, 1993). It appears that the Upper Valtellina race, which was already decreasing in numbers through the late 1970s–early 1980s (Capanna & Corti 1982; Mainardi *et al*. 1986), became extinct between 1983 and 1989 (Hauffe & Searle 1993).

Such an extinction event is more likely in a population that is small and isolated (MacArthur & Wilson 1967); the allozyme data are consistent with such characteristics for the house mouse population in Migiondo.

(*d*) *The fixation of chromosomal rearrangements*

The evidence from *Mod1* that genetic drift, perhaps coupled with a founder event, has occurred in the house mouse population in Migiondo is interesting in

another respect. It has long been argued that genetic drift and/or founder events may be of importance in the generation of karyotypic races, which requires fixation of chromosomal rearrangements often in the face of heterozygous disadvantage (Wright 1941; Lande 1979). In the house mouse, genetic drift and founder events are still considered two of a number of potentially important processes in the fixation of Robertsonian fusions (see Nachman & Searle (1995) for a recent review). The fact that a founder event/genetic drift should have been demonstrated in a village in Northern Italy is of particular significance as this is within a region (S. Germany/E. Switzerland/N. Italy) where 21 karyotypic races and 38 distinct Robertsonian fusions have been described in the house mouse (Hübner 1992). Migiondo is a remarkably isolated place, which may appear, at first sight, to be totally unrepresentative. However, over the 4000 years that house mice are thought to have occupied the Alps (Auffray *et al*. 1990), there may have been a large number of situations where founder events/genetic drift could have occurred, leading to the fixation of at least some of the Robertsonian fusions currently found in this region.

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