A CRITICAL REVIEW OF LONG-DISTANCE GENE MIGRATION IN HOUSE MICE DEDUCED FROM THE GEOGRAPHIC DISTRIBUTIONS OF GENETIC MARKERS

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Dedicated to the memory of my father, Morton Joseph Miller

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ABSTRACT: Many genetic markers of commensal house mice have limited geographic ranges. Stowaways may cause sharing of identical genetic markers by geographically-isolated populations that are connected by transport routes. Confirming identity by descent through stowaways requires a knowledge of transport routes and genetic screening methods maximizing variation of putative "foreign" genetic markers, such as sequencing, high-resolution restriction mapping, and microsatellite loci, which are listed in descending order of usefulness. Additional genetic screening can refute alternative causes of "foreign" genetic markers, such as convergence to the same genotype and inaccurately known geographic ranges. Methods and problems in detecting long-distance gene migration of any species are illustrated by examples from commensal house mice. The strongest examples of "foreign" genetic markers are mice in geographically disjunct sites having the same DNA sequences or sharing multiple "foreign" genetic markers. The longterm genetic impact of stowaways can be estimated by resampling sites receiving infrequent shipments.

INTRODUCTION

Stowaways traveling in transported goods is the accepted cause of the worldwide distribution of commensal house mice (Mus musculus domesticus) (Agulnik et al. 1993; Auffray et al. 1990b; Bauchau 1990; Boursot et al. 1993; Horiuchi et al. 1992; Marshall 1977; Mathias and Mira 1992; Michaux et al. 1990; Navajas y Navarro and Britton-Davidian 1989; Nishioka 1992; Ryan et al. 1993; Van de Kamp-Hilt and Van Bree 1964; Wheeler and Selander 1972; Winking et al. 1988). Their rapid spread with modern transportation poses potential health hazards (Morse 1993). The taxonomic status of commensal house mice remains controversial (M. domesticus (Prager et al. 1993; Sage et al. 1993) vs. M. musculus domesticus (Bonhomme et al. 1989; Boursot et al. 1993; Bonhomme et al. 1994; Boursot et al. 1996; Din et al. 1996). Whereas fertile hybrids occur between M. m. musculus and M. m. domesticus and between M. m. musculus and M. m. castaneus, each subspecies has alternative alleles for some genetic markers. Mice from Iran, Pakistan, and India are the "missing link" between M. m. musculus and M. m.domesticus, having genetic markers characteristic of M. m. musculus, M. m. domesticus, M. m. castaneus, and M. m. bactrianus.

Traits that house mice share with many successful invaders include abundance, commensality, wide diet and habitat breadth, short generation time, high genetic variability, and pregnant colonisers (Ehrlich 1987). Stowaways entering existing populations may fail to mate or have genomes failing to integrate with residents' genomes. However, experimental introductions show these problems can be overcome (see below INTRODUCTIONS). In contrast, stowaways colonizing new populations may have a greater genetic impact, if simulations of colonization during range expansion (Nichols and Hewitt 1994; Ibrahim et al. 1996) are realistic models for house mouse populations. Loss of feed and shelter create many opportunities for extinctions and colonization by house mouse metapopulations (AEM Baker Submitted). Survival of "foreign" genetic markers depends on successful breeding by descendants of stowaways and on genetic drift and selection. Longevity of different "foreign" genetic markers can be examined at sites receiving infrequent feed shipments. Contributions of this critical review include a survey of methods and problems in detecting long-distance gene migration of any species and a summary of putative examples of the genetic impact of stowaway house mice.

TRANSPORTED GOODS. Published examples of house mouse stowaways include 64 house mice trapped on two Japanese overseas cargo ships (Suzuki 1980); two escaping during forklifting dry dogfood from a semi-truck; one buried alive in poultry feed; four escaping during unloading of hay, a transport rate of 10^{-5} mice/ kg hay; and seven recently-dead and one still alive on a feedmill grain

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cleaner, a transport rate of 10^{-6} mice/ kg grain (Baker 1994). Multiplying these transport rates by the worldwide volume of transported feed and hay (e.g., United States Department of Agriculture 1988) implies contemporary transport of thousands of stowaway house mice. If experimental introductions accurately model the genetic impact of stowaways (Bennett 1978; Baker 1981; Berry et al. 1990, 1991; see INTRODUCTIONS below), some stowaways breed with residents.

GENETIC MARKERS. Each geographically isolated population is expected to have a unique "genetic signature", a combination of alleles, haplotypes and karyotypes (Lewontin 1985; Schmidt 1995). Many genetic markers of house mice have restricted geographic distributions (Berry 1981; Sage 1981; Sage et al. 1986a, b, 1993; Boursot et al. 1984, 1993; Britton-Davidian 1990; Potter et al. 1986; Berry and Corti 1991; Vanlerberghe et al. 1986, 1988a, 1988b). These restricted geographic distributions could be the consequence of long distance gene migration by colonists during range expansion (Nichols and Hewitt 1994; Ibrahim et al. 1996; Richard A. Nichols, personal communication). The unique genetic signatures of stowaways's "foreign" genetic markers can remain for thousands of generations, dependent on the number of colonists's descendants. Alternatively, restricted geographic distributions of genetic markers demonstrate the minimal impact of long distance gene migration (J. Britton-Davidian personal communication).

Genetic signatures can be distinguished by genetic screening techniques maximizing the number of polymorphisms, such as microsatellite loci (Dietrich 1992,1994; Dallas et al. 1995; Schmidt 1995), high-resolution restriction mapping, sequencing (Prager et al. 1993; Nachman et al. 1994) , and cluster analysis (see CHOICE OF GENETIC MARKERS below). Whereas convergence of one genetic marker might occur by mutation, mutations causing convergence of multiple loci are unlikely. Stowaways have the greatest chance of detection when alternative alleles occur at many genetic loci, such as long distance gene migration by congeneric species. However, more selection against the introgression of stowaway's genetic marker occurs between than within species. For example, across house mouse hybrid zones, sex chromosome DNA morphs introgress minimally (Dod et al. 1993: Tucker et al. 1992: Vanlerberghe 1986, 1988a, 1988b); whereas an introduced Y chromosomal moprh survived when mice carrying the morph were introduced into a conspecific population (Berry et al. 1991).

INSIGHTS FROM HYBRID ZONES AND EXPERIMENTAL INTRODUCTIONS

Limited insights on survival of "foreign" genetic markers carried by stowaways can be gained from analyses of genetic markers in hybrid zones and in experimental introductions. Large populations of two species occur in hybrid zones, whereas rare stowaways carry "foreign" genetic markers into large "host" populations. The rarity of stowaways decreases the survival of the stowaways's "foreign" genetic markers compared to that of genetic markers in hybrid zones. Genomes of introduced mice and their host populations are very similar because introduced mice usually originate within 20 km. Nearby populations are less likely to have differentiation of loci affecting viability, which promotes survival of introduced genomes. In contrast, stowaways and their "host" populations may be further apart. Usually few mice were introduced, and often, only one sex. Studies of lab mice provide models for examining survival of "foreign" genetic markers (after Sokal et al 1974), such as examining the influence of introducing particular chromosomes or genes into different genetic backgrounds (personal communication, Xavier Montagutelli).

HYBRID ZONES. A variety of genetic markers have been examined in Danish, German, and Bulgarian hybrid zones between M. m. domesticus and M. m. musculus (Hunt and Selander 1973; Schnell and Selander 1981; Sage 1981; Boursot et al. 1984; Sage et al. 1986a, 1986b, 1990; Vanlerberghe et al. 1986, 1988a, 1988b; Dod et al. 1993; Tucker et al. 1992; Boursot et al. 1993). Whereas many allozyme and genetic markers for morphometric traits move freely across hybrid zones, others fail to cross some hybrid zones, such as mitochondrial, Y, and X chromosomal DNA, Robertsonian fusions, malate dehydrogenase, and malic enzyme, (Dod et al. 1993; Tucker et al. 1992).

INTRODUCTIONS. Experimental introductions of mice carrying "foreign" genetic markers occurred into established populations on Gull Island; three New York poultry barns; the Isle of May; an outdoor enclosure in Australia; and simulated homes in France and Italy. Extinction of "foreign" genetic markers occurred at all sites except where large numbers were introduced on the Isle of May. The isolation of Isle of May from other sources of mice and the absence of deleterious genetic markers may be the main reason for the lack of extinction.

Few +/t males (N = 7, 8) were released on Gull Island (Anderson et al. 1964; Bennett 1978), after which genetic screening of trapped mice occurred for 15 y. The introduced t lethal haplotype went extinct after 12 y. Selection against t lethal homozygotes, which die prenatally, and genetic bottlenecks in population size probably contributed to t haplotype extinction.

Larger numbers of mice from Eday Island (N= 42 males, N= 35 females; Berry et al. 1991) were introduced onto the Isle of May, where a resident population of 1 000 mice was estimated at the time of introduction (Berry et al. 1990). At the last sampling, 8 y after the introduction, increases in frequencies occurred for most introduced genetic markers, which included mitochondrial (mt) DNA, Y chromosomal DNA, Robertsonian fusion, and alleles detectable by starch gel electrophoresis (hemoglobin, carbonic anhydrase, adenosine deaminase, guanine deaminase, esterase-3, and esterase-10). Genetic markers with the highest frequencies at introduction retained the highest frequencies. The four times greater incorporation of introduced Y than mtDNA implies more breeding by introduced males than females, which could result from a harem breeding structure. Y chromosomal DNA is paternally inherited, whereas mtDNA is inherited through the maternal line.

Few females (N=7, 3, 4) were released into three poultry barns (Baker 1981). The introduced hemoglobin allele Hbb^s declined to a low frequency (p=0.02) in these poultry barns when sampled 1 to 2.5 y later. Genetic bottlenecks associated with cleaning poultry barns contributed to the decline (Berry et al. 1992). Selection at the hemoglobin locus may have caused the decline (Berry and Murphy 1970; Berry and Peters 1977; Myers 1974; Newton and Peters 1983; Petras and Topping 1983), though the Hbb^s allele occurred naturally in most nearby populations (Baker 1981).

Three introductions of mice totaling 14 males and 30 females carrying t semilethal haplotypes (+/t^{w2} and t^{w2}/t^{w2}) occurred in an enclosure holding a +/+ resident population (Pennycuik et al. 1978). Introduced females successfully bred. At the first genetic screening of mice, two years after the introduction, 20 males sired a few +/t pups, whereas 40 sired only +/+ pups. As the usual criterion for scoring a male as +/t is the male's siring 5 to 7 +/t pups, the exact frequency of +/t mice is unknown.

Two introductions of individually-marked trapped mice, totaling 21 males and 23 females in France and 18 males and 18 females in Italy, occurred into two sets of three 15-20 m square boxes connected to adjacent farmland (Auffray et al. 1990a). Trapping prior to introductions yielded no mice in Italy, though no comparable data were reported for France. The nearest source of commensal mice was a farm 820 m from the Italian site and a home 650 m from the French site. Introduced mice were homozygous at three loci in France, amylase-1, glucose phosphate isomerase-1, and the beta chain of hemoglobin, and at six loci in Italy, carbonic anhydrase, mannose phosphate isomerase, nucleoside phosphorylase, amylase-1, glucose phosphate isomerase-1, and the beta chain of hemoglobin. Genetic monitoring occurred for 4 mo in Italy and 10 mo in France. Heterozygotes for the introduced loci were trapped near or in the boxes. As no prescreening of resident mice occurred before the introduction, heterozygotes could be progeny of the introduced mice or immigrants from nearby farms. With addition of prescreening and of introducing large numbers (N>100), repeating this study could determine the duration of introduced "foreign" genetic markers within resident populations.

Introductions without monitoring genetic markers have also been done. Extinction is the most likely outcome when house mice are introduced on islands where no conspecifics occur (reviewed in Berry et al. 1982). Five introductions totaling 454 male and 442 female house mice occurred from 1973 to 1978 on two Shetland islands, Linga and Oxna (Berry et al. 1982). Introduced mice included 405 males and 405 females, which were 6 to 8 wk old F1 hybrids between inbred mouse strains CBA and C57BL, and 49 male and 37 female mice trapped on Skokolm, a Welsh island. The importance of abundant food for survival is implicated by finding descendants of mice released on Linga in 1973, when imported grain provisioning started, and none in 1975, when provisioning stopped. Mice released on Oxna in l977 and l978 failed to breed and none survived more than a few weeks despite imported grain provisioning in 1978. Possible causes of these extinctions include minimal availability of mouse food on both islands; presence of a potential predator or competitor, Rattus norvegicus, on Oxna; laboratory genomes of introduced mice, which were ill-suited for survival; and the failure to find mates when juveniles dispersed. Of three introductions to sites that had been mined 8-y earlier, 2% of the house mice remained more than 69 days (Fox and Twigg 1991). Low recapture rates were also reported for females introduced onto "highway cloverleaf grass islands" (Vandenbergh and Coppola 1986). Recapture rates were higher for mice introduced as male-female pairs than for single-sex introductions (Nelson 1992).

POSSIBLE EXPERIMENTS WITH LAB MICE. Mouse strains could be used to study which "foreign" genetic markers survive in coadapted genomes (after Sokal et al. 1974; Xavier Montagutelli personal communication). This work is important for the insights about long distance gene migration and about coadaptation, which is rarely tested experimentally. If the duration since the establishment of a strain is directly related to the degree of coadaptation of a genome, then newly developed strains are expected to tolerate more "foreign" genetic markers than older strains. Newly developed strains are models for commensal populations that are frequently disrupted, such as populations at grain elevators, hay wholesalers, or commercial poultry egg farms. Holding genetic background constant while varying genetic markers can determine which "foreign" genetic markers influence various traits that confound

these experiments, such as fecundity, mate choice, longevity, age at first reproduction, and sexual selection.

UNDERESTIMATION. The total number of stowaway events is likely to be underestimated. Stowaways transported from areas with few unique genetic markers go undetected. "Foreign" genetic markers will be lost during population bottlenecks. Selection may act against mice carrying certain "foreign" genetic markers, such as M. m. domesticus-specific alleles on a M. m. musculus genetic background (Vanlerberghe et al. 1988; Boursot et al. 1993).

IMPLICATIONS. The successful introduction of 77 Eday mice to the Isle of May implies that simultaneous arrival of large numbers of stowaways are likely to have a lasting genetic influence on the gene frequencies of their host populations. Large numbers overwhelm the ability of residents to exclude introduced mice. When eight males and eight females, were introduced simultaneously, in five replicates, 23% died (Reimer and Petras 1967). When two males and two females were introduced simultaneously, 50% died (Andrzejewski et al. 1963). Whether introductions of large numbers would be as successful in mainland populations, which are surrounded by populations having alternative alleles, must be tested experimentally.

If "foreign" genetic markers occur at low frequencies, most will be lost from commensal populations that frequently bottleneck in size. By chance, some "foreign" genetic markers will increase in frequency. If sufficient genetic markers are screened, it should be possible to find "foreign" genetic markers. Alleles favored by selection have a better chance of increasing in frequency, though these too could be lost during population bottlenecks. The ability of genetic markers to become incorporated into foreign genomes will vary. For example, the M. m. domesticus-specific Esterase-2 allele occurred in M. m. musculus populations from Yugoslavia, Romania, Bulgaria, and Austria (personal communication, Francois Bonhomme).

ALTERNATIVE HYPOTHESES

"Foreign" genetic markers can be identified as occurring in populations along transport routes. Four explanations for the presence of "foreign" genetic markers in geographically isolated populations are: (a) identical by descent; (b) identical by convergence; (c) identical by descent from escaped laboratory mice; and, (d) representatives of markers with inaccurately known geographic ranges. Most available data, which are based on single trapping periods and on genetic screening techniques with unknown error rates, are insufficient to determine which explanation is correct. DNA sequences can distinguish between identity by descent and identity by convergence (Lewontin 1985). Mice that were genetically screened included trapped mice, laboratory-born descendants of trapped mice, and laboratory-born descendants of trapped mice that were crossed to laboratory mice.

IDENTITY BY DESCENT. As DNA sequences can distinguish identity by descent with a high degree of reliability, the strongest example is mitochondrial DNA sequences for mice from geographically-isolated pairs of European countries (Table 1) (Prager et al. 1993). Nuclear loci in which recombination occurs, are less valuable in distinguishing identity by descent. The other strong examples for the genetic impact of stowaways include mice with multiple "foreign" genetic markers. It is unlikely that all loci would be the same as those in populations where stowaways originated (Baker et al. 1989; Corbet 1990; Baker and Palumbi 1994; Shaw et al. 1988; Scribner et al. 1994; Simon et al. 1994). However, recombination over generations will decrease the number of "foreign" genetic markers. In a sense, this is an analysis of gene trees (sensu Pamilo and Nei 1988), in which genes vary in degree of informativeness. Examples from populations with two or more of the same genetic markers in geographically-isolated populations follow (Table 1). Geographically-isolated Italian mice from Orobie and Molise share two Robertsonian chromosomes and Y chromosomal DNA (probe YB10) (Tucker et al. 1989). Two mice trapped in Sofia, Bulgaria, which is within the range of M. m. musculus, each carried five of six M. m. domesticus genetic markers; ten mice trapped in other eastern European populations within the range of M.m. musculus had two or more M. m. domesticus genetic markers (Francois Bonhomme unpublished data). Mice from geographically-distant sites of Zadar, Yugoslavia and Palermo, Sicily each share three Robertsonian fusions (Rb6.12, Rb8.17, Rb10.14), whereas mice from Faray and Eday Islands share three other Robertsonian fusions (Rb3.14, Rb4.20, Rb9.12) (Winking et al. 1988). These mice included 15 of 16 mice trapped in Zadar and F1 progeny of mice trapped in Palermo and lab mice. The Faray and Eday example is weakened by the possibility of a recent land bridge between these islands. The following mice shared t and histocompatability haplotypes: Temuco, Chile and New York City (H2 w31, tw5); Ann Arbor, Michigan and Haifa, Israel (H2 w2, twSL); and Paris, France and Clinton, Montana (H2 w28, tw12) (Nizetic et al. 1982). Though some recombination occurs, inversions suppressing recombination between t and H-2 complexes weakens these examples. Unique haplotypes at the t complex occur in mice from such disjunct locations as Algeria and Yugoslavia (mosaic 1) and Michigan, Bulgaria, Egypt,

Spain, and Chile (mosaic 8) (Table 4 of Erhart et al. 1989). Mice from Lake Casitas California and Japan share a gene for genetic resistance to a retrovirus and the same alleles at isocitrate dehydrogenase and nucleoside phosphorylase (Gardner et al. 1991; Rice et al. 1980; Bonhomme et al. 1984; Bonhomme and Guenet 1990). However, these strong examples must be confirmed by eliminating other causes of foreign genetic markers, such as identity by convergence and inaccurate geographic boundaries.

IDENTITY BY CONVERGENCE. Independent evolution may cause identity of two genetic markers. For example, in isolated subpopulations, gene amplification repeatedly evolved to cause genetic resistance to poisons (Schimke 1988). Strong evidence for convergence includes slight differences between genetic markers of resident mice and putative descendants of stowaways at one or two hypervariable loci, such as mitochondrial (mt) type 28 DNA (p. 118 and other examples in Prager et al. 1993). Putatively identical bands on electrophoretic gels can be checked for identity using other screening protocols, which separate alleles by charge or size (Bonhomme and Selander 1978), including high resolution restriction mapping (Prager et al. 1993; Berry and Kreitman 1993) or sequencing (Raymond et al. 1991; Prager et al. 1993; Baker and Palumbi 1994). Sequencing provides the least equivocal data. Multiple alternative phylogenetic trees may also provide insights (Edwards 1993). Crosses of mice carrying particular genetic markers can be made to laboratory lines so that electrophoretic mobility of alleles can be compared to the defined genetic markers of laboratory lines (Tibby Russell, personal communication).

Environment may change phenotypes. Though rearing temperature influences tail length (Thorington 1970; Barnett 1965; Barnett et al. 1975), some workers continue using tail length to distinguish M. m. musculus and M. m. domesticus. Compared to mice reared outdoors, mice reared in heated houses are expected to have longer tails. Though young mice have shorter tails than older mice, young mice have the same number of tail vertebra as older mice (Prager et al. 1993). In contrast to environmental influences on tail length, laboratory-raised descendants of trapped mice retained the same number of tail vertebrae as their trapped ancestors (Prager et al. 1993). However, rearing temperature influenced tail vertebral number in some inbred strains (Barnett 1965).

ESCAPED LABORATORY MICE. Laboratory mice may escape from their cages or be released outdoors (AEM Baker personal observation). Long standing strains of lab mice are hybrids between Asian M. m. musculus and M. m. domesticus (Bonhomme et al. 1987). Foreign genetic markers can enter a population when escaped lab mice or stowaways breed (Van De Kamp-Hilt and Van Bree 1964; Berry et al 1981). Discriminating between descendants of stowaways and escaped lab mice will be difficult because recombination, selection, and genetic drift will obscure the "genetic signature" of escaped lab mice. Additional circumstantial data, such as location on a transport route or location near a university, may help in discrimination. What is more interesting is the duration of these "foreign" genetic markers, whatever their origin, in populations.

INACCURATE GEOGRAPHIC RANGE. Exact geographic boundaries of genetic markers are usually unknown. Sites where Bonhomme et al. (Table 1) reported "foreign" genetic markers, such as Ljubljana and Sofia, are near hybrid zones (personal communication, Roland Hubner). These sites warrant further systematic trapping to determine their distances from hybrid zones.

Lake Casitas, California mice, which share genetic resistance to a virulent murine leukemia retrovirus with Japanese populations, is another example requiring more population screening to strengthen the case for the genetic contribution of stowaways. All other populations near Lake Casitas were genetically sensitive, lacking the gene for genetic resistance. Genetic screening of more populations near Lake Casitas could further pinpoint the center of genetic resistance and strengthen this example. Finding more genetic markers diagnostic for Japanese mice in Lake Casitas mice would also strengthen the argument.

CHOICE OF GENETIC MARKERS

Properties of genetic markers useful in assessing the genetic impact of stowaways follow: (1) small fragmented geographic ranges, each having different polymorphisms, such as mtDNA; (2) selectively neutral to eliminate selection as a cause for a genetic marker (e.g., Schimke 1988), such as some DNA introns where no selection occurs (personal communication, George Roderick); (3) low mutation and recombination rate (e.g., Green et al. 1993) to increase the chance of detecting genetic markers over generations, such as ribosomal RNA, Y chromosomal DNA, and t complex DNA; (4) unambiguous scoring of genotypes, using techniques such as high resolution restriction mapping or sequencing (e.g., Raymond et al. 1991; Berry and Kreitman 1993; Prager et al. 1993); (5) many unlinked genetic markers for independent confirmation of the genetic impact of stowaways and as a way to discriminate a mouse with a mutation from a stowaway (Dietrich et al. 1992, 1994) . A mouse with a mutation will be similar to host mice at all loci but the mutated locus (after Baker et al. 1989; Corbet 1990; Karl and Avise 1992;

Baker and Palumbi 1994); (6) mtDNA, which is inherited through the maternal line, or Y chromosome DNA to determine the influence of stowaway's sex on gene migration (e.g., Berry et al. 1991; Tucker et al. 1989; Dod et al. 1993); (7) markers that can quickly increase in frequency in small populations to counter chance loss, such as t haplotypes, HSR, and Rb fusions, which are favored by transmission distortion or meiotic drive. However, t lethal haplotypes, were lost within 12 y of introduction on Gull Island (Anderson et al. 1964; Bennett 1978); whether these results are pertinent to continental populations, which have the potential to have larger effective population size (after Nunney and Baker 1993), is unknown. (8) markers with many alleles per locus, such as microsatellite loci, which differ among populations (Dallas et al. 1995; Blouin et al. 1996; Schmidt 1995). If simulations accurately reflect house mouse populations (Slatkin 1995; Goldstein et al. 1995; Di Rienzo et al. 1994; Weber and Wong 1993; Schlotterer and Tautz 1992; Valdes et al. 1993), individuals in a line of descent differ by a few repeat units, which has a large sampling variance (Slatkin and Hudson 1991; Richard A. Nichols personal communication). This means mice with similar length microsatellite alleles may have the same origin. The weakest data are morphometric traits, which are influenced by many genes and by the environment.

"FOREIGN" GENETIC MARKERS WITH DISJUNCT GEOGRAPHIC DISTRIBUTIONS

M. m. domesticus-specific genetic markers occurring within the range of other Mus subspecies or within the range of other M. m. domesticus populations include mt DNA, enzyme loci, a genetic resistance locus, t and histocompatability (H-2) haplotypes, homogeneously-staining region (HSR), Robertsonian fusions (Rb), and morphometric characters, which are divided in Table 1 into strong and weak examples of the genetic impact of stowaways. Controls for accurate genetic screening and error rates in genetic screening were usually unstated in the original articles. A minimal standard for future studies is crossing each putative descendant of stowaways to a standard lab strain and rescoring the genetic marker in relation to the well-studied allele of the lab strain (personal communication, Tibby Russell). Rb is the most common "foreign" genetic marker.

MITOCHONDRIAL DNA (mtDNA). MtDNA haplotypes are inherited through the maternal line. Their relatively small geographic ranges probably reflect the small home ranges of female mice. Some mtDNA haplotypes intogress across hybrid zones. For example, M. m. domesticus mtDNA haplotypes introgress into the range of M.m. musculus, though different mtDNA haplotypes occur north and south of the hybrid zone (Vanlerberghe et al. 1988). The importance of intensive sampling to detect genetic variants is exemplified by a study where 16 mt DNA haplotypes occurred in an eggplant field in which 412 mice were sampled, whereas 8 mtDNA haplotypes occurred in a poultry barn where 18 mice were sampled (Ritte et al. 1992).

For 171 mice trapped in Japan, Korea, China, Taiwan, Philippines, Indonesia, and Malaysia, within the ranges of M. m. musculus and M. m. castaneus, mtDNA haplotypes were found by digesting each DNA with one of 13 restriction enzymes, end-labeling, electrophoresis, and autoradiography. One or two mice were trapped at most sites, the maximum mice per site was 37. Of three males with M. m. domesticus mt DNA haplotypes, two were from one Japanese seaport (Ogasawara) and another from a seaport near a USA Army base (Yonekawa et al. 1988). Other genetic markers characteristic of M. m. domesticus also occurred at Ogasawara (Robertsonian fusion; allozyme loci; Bonhomme et al. 1989). An alternative explanation for the presence of these M. m. domesticus haplotypes is their retention as ancestral haplotypes. However, ancestral haplotypes are expected to be widespread, rather than being present in only two seaport populations.

When high resolution restriction mapping and sequencing or sequencing alone were used to find PCR-amplified mtDNA haplotypes of 217 house mice, the same haplotype occurred in disjunct locations, including type 1 (7 mice from England, Germany), type 2 (5 mice from England, Germany, Denmark), type 27 (84 mice from Finland, Sweden, Denmark, Germany), type 28 (36 mice from Sweden, Germany) and type 36 (4 mice from Sweden, Germany) (Prager et al. 1993).

Y CHROMOSOMAL DNA. Many Y chromosomal restriction fragment length polymorphisms (RFLP) exist, including differences between Mus subspecies and populations within the same subspecies (Tucker et al. 1989). The mice used for Y DNA studies were descendants of trapped mice, which had been karyotyped and crossed to lab mice. Of 255 mice that were hybridized to Y chromosome probe pYB10, four mice from two geographically-isolated Italian towns, Orobie and Molise, shared two Rb and Y chromosomal DNA . Of 16 mice that were screened with the Y chromosome probe 145SC5, six from Quebec, California, Maryland, and Delaware shared the same Y chromosomal DNA (Nishioka 1992). The geographic boundaries of each Y chromosomal DNA morph must be known to make these data convincing examples of the genetic impact of stowaways.

ENZYME LOCI. Most geographic surveys of enzyme loci had few examples of the same genetic marker occurring in geographically-disjunct populations. Two mice trapped in Sofia Bulgaria each had M. m. domesticus

Table 1. Breeding by stowaways deduced from disjunct geographic distributions (locations 1 and 2) of genetic markers. More locations were listed in the original references than are included in Table 1. Strong examples (I) include mice from geographically disjunct populations with the same DNA sequences or mice sharing more than one genetic marker, whereas weak examples (II) include mice sharing one genetic marker.

Marker	Location 1	Location 2	Comment and References
		I. STRONG EXAMPLES	
Mitochon-drial DNA	England	Germany	DNA sequenced: type 1 (7 mice)
	England	Denmark	type 2 (5 mice)
	Finland	Germany	type 27 (84 mice)
	Finland	Germany	type 28 (28 mice)
	Sweden	Germany	type 36 (4 mice) (Prager et al. 1993); what are the geographic boundaries of these mtDNA morphs?
	Ogasawara, Japan	?	M. m. domesticus haplotype found in two males trapped near this Japanese seaport (Yonekawa et al 1988); other M. m. domesticus markers include a Robertsonian fusion and glucose phosphate dehydrogenase allele; has a rare amylase allele; populations with the highest heterozygosity of any Japanese mice (Bonhomme et al. 1989)
Y chromo-somal DNA	Orobie, Italy	Molise, Italy	mice have the same two Robertsonian (Rb) fusions and Y chromosomal DNA (YB10 sequence; Tucker et al. 1989)
Enzyme loci	Sofia Bulgaria; Ljubljana Yugoslavia; Braila,Romania Ilmitz,Austria	western Europe	M. m.domesticus alleles found in mice trapped in cities within the range of M. m. musculus; two from Sofia each had five alleles; ten each had two or more alleles; esterase-1, esterase-2 alleles; glucose phosphate isomerase, indophenol oxidase, mannose 6 phosphate isomerase, nucleoside phosphorylase, phospoglucomutase (Francois Bonhomme unpublished); is long distance gene flow underestimated by selection against M m.domesticus alleles?
Genetic resistance to retrovirus	Lake Casitas, California	Japan	genetic resistance gene maps to same location in Lake Casitas and Japanese mice (Gardner et al. 1991); Lake Casitas, Japanese, and Indonesian mice share the same markers at isocitrate dehydrogenase and nucleoside phosphorylase (Rice et al. 1980; Bonhomme et al. 1984; Bonhomme and Guenet 1990); what is geographic distribution of resistance? do Lake Casitas and Far Eastern mice share other markers, such as Aat-2, Sod-1, Es-10, Aat-1, Gdc-1, Es-3, Es-2, Np-1, Pk-2, Gpd-1, Pgm-1?
Rb3.14 Rb4.10 Rb9.12	Faray Island	Eday Island	each mouse had the same 3 Rb; Caithness has Rb 4.10, 9.12 (Winking et al. 1988); a 1 km land bridge may occur between Faray and Eday
Rb6.12 Rb8.17 Rb10.14	Zadar Yugoslavia	Palermo Sicily	each mouse had the same 3 Rb (Winking et al. 1988)

II. WEAK EXAMPLES

Mitochondrial DNA haplotype	Sasaguri, Japan	?	one male trapped near a Japanese seaport and USA army base (Yonekawa et al 1988)
Y chromosomal DNA	Quebec	Maryland, Delaware, California	mice share same repetitive DNA sequence, probe 145SCS, Q12 pattern (Nishioka1992); mice caught at McGill University = escaped lab mice? what is the geographic distribution of each haplotype?
Enzyme loci	Ljubljana Yugoslavia; Braila Romania; Ilmitz Austria	western Europe	M. m. domesticus alleles found in 30 of 65 mice trapped in cities within the range of M. m. musculus; 25 of the 30 mice had the M. m. domesticus Es-2 allele, whereas other M. m. domesticus alleles occurred in 4 or 5 mice; esterase-1, esterase-2, glucose phosphate isomerase, indophenol oxidase, mannose 6 phosphate isomerase, nucleoside phosphorylase, phospoglucomutase (Francois Bonhomme unpublished)
	Binasco, Bergamo Italy	Tubingen Germany; Barcelona, Spain	each mouse had the same rare transferrin allele Trf110 (Britton-Davidian et al. 1989)
	Hawaii	western Europe	five polymorphic loci in Hawaiian mice have alleles absent in North American mice- hemoglobin, esterase-1, esterase-2, esterase-3, esterase-5; five loci screened in 670 mice trapped on six islands; 28 mice examined for alcohol dehydrogenase, lactate dehydrogenase, malic enzyme, malate dehydrogenase, glucose-6-phosphate dehydrogenase, esterase-2, 6-phosphogluconate dehydrogenase, isocitrate dehydrogenase, phosphoglucomutase, phosphoglucose isomerase (Wheeler and Selander 1972)
	"Big Island" Hawaii; Enewetak and Medren Islands	Japan	Hawaiian, Enewetak, and Japanese mice share one isocitrate dehydrogenase allele; Hawaiian, Enewetak, Medren, and Japanese mice share one mannose 6-phosphate isomerase allele and glutamate oxaloacetate transaminase-1 allele (Bonhomme et al. 1984); 10.9 to 16.6% mean heterozygosities per locus interpreted as moderate climate (minimal selection); sorbitol dehydrogenase, malate dehydrogenase, malic enzyme, isocitrate dehydrogenase, purine nuceloside phosphorylase, glutamate oxaloacetate transaminase, glutamate oxaloacetate transaminase mitochondrial, esterase-1, esterase-3, aconitase, mannose phosphate isomerase, glucose phosphate isomerase,, hemoglobin (Berry et al. 1981); escapees from >3000 lab mice used in atom bomb testing on Marshall Islands?
Complexes H2- t:			each mouse had same haplotype at H2 and t complexes (Nizetic et al. 1982); haplotypes in linkage disequilibrium (Hammer et al. 1989), though some recombination occurs; what is the geographic distribution of these haplotypes?
w31-w5	Temuco, Chile	New York	
w2-SL	Haifa, Israel	Ann Arbor, Michigan	
w28-12	Paris, France	Clinton, Montana	

H2 complex:			
w30	Buin, Chile	New York	
w29	Paris	New York	
t complex:			Classes of mosaic t haplotypes
1	Algeria	Yugoslavia Bulgaria	(Table 3 of Erhart et al. 1989)
8	Michigan	Egypt, Spain Buin Chile	(Table 4 of Erhart et al. 1989)
HSR single-band	Georgia	Switzerland, Germany, Scotland, Tunisia	Homogeneously staining region (HSR) detected by C banding of chromosome I; a single band in 108 of 146 M. m. domesticus examined; Georgian mice are within the range of M. m. musculus but share the single band characteristic of M. m. domesticus;
double-band	Oland Island, Sweden	eastern Europe, Asia	double-band characteristic of M. m. musculus (Agulnik et al. 1993)
Rb 1.3	Olympia, Greece	Migiondo, Orobie, Rovedero	Robertsonian (Rb) metacentric chromsomes primarily in coastal regions; other Italian sites shared Rb chromosomes, but are omitted here because all sites may be within the same Rb race (Winking et al. 1988; Bauchau 1990); populations in Spain and Denmark, at the periphery of Rb populations, probably have independent origins (personal communication, Jeremy Searle); what is the geographic range of each Rb fusions?
Rb 1.11	Zadar, Yugoslavia	Monastir, Tunisia;	
Rb 1.12	Lipari Island	Ancarano	
Rb 2.5	Olympia	Tubingen	
Rb 2.15	Palermo, Sicily	southern Germany	
Rb 3.6	Milan	southern Germany	
Rb 3.8	Luino	southern Germany,	
Rb 4.6	Bergamo	Monastir	
Rb 4.12	Alpine valleys	southern Germany	
Rb 5.12	Amoudia	Thebes	
Rb 5.13	Palermo	southern Germany	
Rb 5.14	Lipari	southern Germany, Monastir	
Rb 5.15	Zadar	Cremona, Gallarate, Bergamo, southern Germany, Barcelona	
Rb 6.9	Denmark	Thebes	
Rb 6.10	southern Germany	Barcelona	
Rb 6.13	Cittaducale	Caithness	
Rb 7.18	southern Germany	Monastir, Cremona	
Rb 8.12	Lipari	Sondalo	
Rb 8.17	Palermo	southern Germany	
Rb 9.12	Orkney Island	Caithness	
Rb 9.14	Milano	southern	

Rb 9.16	Olympia	Germany Palermo, Molise	
Rb 10.14	Palermo	southern Germany	
Rb 11.13	Cremona	southern Germany	
Rb 11.14	Caithness	Milan	
Rb 13.15	Monastir	Olympia, Kastritstis	
Rb 13.16	Barcelona	Mesolcina, Ibiza	
Rb 8.14	Calcutta	Italy	Rb interpreted as identity by convergence (Sage 1981)
Tail length/ total length	Berlin	western Europe	longer ratio characteristic of M. m. domesticus; same pelage as M. m. domesticus (Zimmerman 1949); environmentally-determined phenotype?
Skull shape, pelage	Thailand, Bombay, Indonesia, Rangoon, Calcutta	?	M. m. castaneus skull shape; rare, local populations limited to port cities (Marshall 1977); though now M. m. castaneus are known to occur more widely (Bonhomme et al. 1989, 1994; Din et al. 1996); environmentally-determined phenotypes?

alleles at five of six loci. A total of 30 of 65 mice trapped within the range of M.m. musculus carried M. m.domesticus alleles (Francois Bonhomme unpublished data). Of these 30, ten had two or more M. m. domesticus alleles, whereas 25 had M. m. domesticus alleles at the Esterase-2 (Es-2) locus. Es-2 is a selectively-neutral genetic marker or has many different alleles all migrating to the same position on a starch gel. Another survey showed a rare transferrin allele (Trf10) occurred at four disjunct European sites (Binasco and Bergamo Italy; Tubingen, Germany; Barcelona, Spain) (Britton-Davidian et al. 1989).

Hawaiian and other Pacific Islands were surveyed intensively by two groups (Wheeler and Selander 1972; Berry et al. 1981). Both groups surveyed some of the same loci and some of the same sites, but reached different conclusions. After assessing 670 mice for five enzyme loci and 28, for 14 loci and finding alleles present in the six Hawaiian islands but absent from populations in North America and Denmark, Wheeler and Selander (1972) concluded the extra alleles were brought by stowaways because house mice lived in Hawaii for too short a period (200 y) to accumulate mutations. After assessing 300 house mice for 36 enzyme loci and finding very high mean heterozygosity on the "Big Island" Hawaii (16.6% per locus) and Enewetak (11.4%) and Medren (10.9%) atolls, Berry et al. (1981) concluded that a mild climate was responsible. Large genetic distances occurred between these islands and Asian mice, M.m. castaneus, M. m. musculus, and M. m. molossinus (0.181 - 0.276 (Berry et al. 1981). Finding large genetic distances may mean that most genetic markers of stowaways were lost. Berry et al. (1981) stated 3 000 caged laboratory mice occurred during atom bomb testing on the Marshall Islands, which were included in their survey; whether laboratory mouse genomes occur in their survey is unknown.

Later surveys by Bonhomme et al. (1984) showed Hawaiian, Japanese, and Indonesian mice shared an allele at isocitrate dehydrogenase, whereas Hawaiian, Enewetak, Medren, and Japanese mice shared alleles for mannose-6- phosphate isomerase and glutatamate oxaloacetate transaminase-1. Mice from India, which are considered part of the "missing link" as genetic intermediates among domesticus, musculus, castaneus, and bactrianus, have higher heterozygosities than those reported for Hawaii, Enewetak, and Medren by Berry et al. (1981) (Bonhomme et al. 1994, Din et al. 1996). These Indian mice heterozygosity data imply that genes from Asian Mus populations introgressed into populations of Hawaii, Medren, and Enewetak. Mice from Ogasawara, Japan are also recent admixtures of M. m. domesticus, M. m. musculus, and M. m. castaneus. For example, they carry genetic markers characteristics of M. m. domesticus , such as a Robertsonian fusion and a glucose phosphate dehydrogenase allele.

GENETIC RESISTANCE. Genes for a retroviral envelope sequence responsible for genetic resistance to a virulent murine leukemia mapped to the same locus in mice from Lake Casitas, a California squab farm (Fv-4) and from Japan (M. m. castaneus) (Akvr-1) , which implies the same gene

occurs in both populations. Japanese immigrants probably transported stowaways to their California squab farm. Mice trapped within 33 km of the farm lacked genetic resistance (Gardner et al. 1991). Across studies on genetic resistance, sample sizes were large but variable, such as 263 to 5427 mice. The genetic distance, based on enzyme loci, between mice on this squab farm and on another farm 66 km away was 0.019, comparable to that within Danish M. m. musculus or M. m. domesticus (Rice et al. 1980). Further support for the hypothesis that Japanese stowaways are responsible for the genetic resistance is mice from Lake Casitas, Japan, and Indonesia sharing the same markers at isocitrate dehydrogenase and nucleoside phosphorylase (Rice et al. 1980; Bonhomme et al. 1984; Bonhomme and Guenet 1990). Traits dependent on selection, such as genetic resistance, may be poor choices for studies of long-distance gene migration. Independent evolution of genetic resistance occurs (Schimke 1988). Genetic resistance genes may be lost or evolve independently if selection varies geographically.

HISTOCOMPATABILITY (H-2) AND t COMPLEX HAPLOTYPES. At different geographic sites, certain bacteria and viruses may select for particular H-2 haplotypes, which causes a more uniform geographic distribution of H-2 haplotypes than enzyme polymorphisms (Nadeau et al. 1988). H-2 haplotypes probably have the greatest genetic diversity of any gene complex. Most mice are heterozygotes for H-2 haplotypes. The H-2 and t complexes map to overlapping regions on chromosome 17 where four inversions suppress recombination, though some recombination occurs (Silver 1993). The t complex influences male fertility, fetal development, genetic recombination, and transmission of the t chromosome. About half the populations tested have t haplotypes, with a mean frequency less than 7% (Ardlie 1995). +/t males preferentially transmit the t chromosome, denoted transmission ratio distortion.

Mice living in geographically-distant locations that share the same H-2 and t complex haplotypes include one mouse from Temuco, Chile and two from New York City (H-2 w31, tw5); one from Ann Arbor, Michigan and one from Haifa, Israel (H-2 w2, twSL); one from Paris, France and one from Clinton, Montana (H-2 w28, tw12) (Nizetic et al. 1982). Descendants of lab mice crossed to trapped mice were each assessed for t haplotypes and histocompatability haplotypes. Assessment of H-2 haplotypes included crossing mice to lab lines carrying different H-2 haplotypes. H-2 haplotypes were determined by antigen testing, whereas t haplotypes, by crossing trapped mice to different tester stocks. Mice living in geographically-disjunct locations that share the same "mosaic" t complex haplotypes include those living in Algeria and Yugoslavia (mosaic 1) and Michigan, Bulgaria, Egypt, Spain, and Chile (mosaic 8) (Table 4 of Erhart et al. 1989). Mosaic t haplotypes were screened using probes for different parts of the t complex, including some probes from outside the area of recombination suppression. These examples may be compromised by selection for particular H-2 haplotypes and by the unknown geographic boundaries of these haplotypes.

HOMOGENEOUSLY STAINING REGIONS (HSR). The one HSR band on chromosome 1 of M. m. domesticus is distinguishable from the two HSR bands of M. m. musculus (Agulnik et al. 1993). The size of the HSR band varies among populations, occurring in heterozygotes and homozygotes. Most populations lack HSR. Meiotic drive favors HSR in some female heterozygotes. Some HSR homozygotes have reduced female fertility and viability. Of 146 mice trapped in Tunisia, Scotland, and continental Europe including (USSR) Georgia, 108 shared single-banded HSR. The Georgian mice occur within the range of M. m. musculus and are M. m. musculus - M. m. domesticus hybrids.

ROBERTSONIAN (RB) FUSIONS. When two acrocentric chromosomes join at the centromere, they form a Rb fusion. All but sex chromosomes occur in Rb fusions, which have been most intensively studied in Europe. Chromosome banding techniques distinguish individual chromosomes. Meiotic drive favoring the Rb fusion may occur (Britton Davidian et al. 1989). Fertility remains high when Rb and nonRb mice mate (Nachman et al. 1994). The formation of Rb races is a model for speciation (Hauffe and Searle 1993). Arguments for mutations causing Rb identity by convergence include the greater genetic similarity of Rb and adjacent nonRb populations compared to that among all Rb populations; and the unique set of Rb fusions in each population (Britton-Davidian et al. 1989; Nachman et al. 1994). However, Bauchau (1990) claimed Britton-Davidian et al. 's conclusion was based on a small sample of Rb populations. When more Rb and nonRb populations were sampled by sequencing their mtDNA , Rb populations occurred in several clades (Nachman et al. 1994). Finding Rb in several clades implies identity by convergence of mutations in geographically-isolated populations. However, Nachman et al. sequenced mtDNA of only two mice per site, which may be insufficient because 8 and 16 mtDNA haplotypes occurred in two populations (Ritte et al. 1992).

Strong evidence for the genetic impact of stowaways includes mice from Zadar, Yugoslavia and Palermo, Sicily, which each share three Rb 6.12, 8.17, and 10.14 (Winking et al. 1988; Bachau 1990). Mice from Eday and Faray Islands also share Rb (Bachau 1990; Berry et al. 1992). However, these islands are <1 km apart and were probably connected when the sea level dropped (Jeremy Searle personal communication). Each of 23 Rb occurred at two or more geographically-isolated sites (Winking

et al. 1988; Bachau 1990). The lack of a direct commercial transport connection between Calcutta and Italy implies that a shared Rb has independent origins (Sage 1981), which is supported by a positive correlation between geographic air distance and the probability that two populations share a common Rb by chance (Bauchau 1990).

MORPHOMETRIC CHARACTERS. Morphometric characters were the original characters used to distinguish Mus subspecies. Though morphometric characters are the product of many genetic loci and are influenced by environmental variates, they are still used to distinguish subspecies (Marshall and Sage 1981; Auffray et al. 1990b; Gerasimov et al. 1990). For 1650 European mice, the ratio of lengths of tail to head and body is greater for M. m. domesticus (0. 92 to 1.06) than M. m. musculus (0.82 to 0.86; Zimmerman 1949). Berlin mice (N=375) live within the geographic area of M. m. musculus, but their mean ratios were similar to those of M. m. domesticus, from 0.95 to 1.27 (Zimmerman 1949). Recently more accurate estimates of tail length were based on number of tail vertebrae, a trait with non-overlapping distributions between pure populations of M. m.domesticus and M. m. musculus (Prager et al. 1993). Tail vertebral number and length correlate (r=0.76, N=52, Prager et al. 1993). The range of tail lengths for mice with the same number of vertebra can be substantial (tail lengths of mice with 30 tail vertebra - 47 to 74 mm; 34 tail vertebra - 73 to 88 mm).

Populations started by stowaways might be expected to be rare and local. Marshall (l977) trapped rare, local populations of M. m. castaneus in warehouses, homes, and other buildings of Asian port cities and centers of commerce, such as Bombay, Calcutta,and Rangoon. Away from the port cities and trade centers, other rodent species were found. However, M. m. castaneus was later found in Taiwan, Philipines, and Malaysia (Bonhomme et al. 1989; Bonhomme et al. 1994; Din et al. 1996).

PREDICTIONS

Most of the reviewed examples of long distance gene migration by stowaways are ambiguous because one marker was sampled and genetic screening techniques with unknown error rates were used. If these same populations are resampled using sequencing, high resolution restriction mapping, or multiple genetic markers, such as microsatellites, some predictions distinguishing the genetic impact of stowaways might be tested:

(1) Discriminability of stowaways is expected to be inversely related to the number of generations since the arrival of stowaways and directly related to minimum size of the host population. With succeeding generations after the arrival of stowaways, recombination and genetic drift decrease linkage disequilibrium and the proportion of "foreign" genetic markers in descendants of stowaways.

(2) Resampling can distinguish foreign genetic markers persisting over several generations, which have a greater genetic impact, than those quickly going extinct. Persistence is most accurately checked in populations having long intervals between shipments, such as feedlots with nine months between shipments.

(3) If genomes of stowaways predominate in host populations, low F_{st} values should occur for populations from stowaways's origins and destinations.

(4) Compared to genomes of mice in isolated populations, genomes of mice living in populations on established transport routes are expected to be in greater flux. Historical worldwide transport routes have been published (Franck and Brownstone 1984), whereas commerce indexes provide contemporary data. More alleles occur in larger populations. Therefore minimum population size and frequency of population bottlenecks are important covariates.

(5) The number of repeats at microsatellite loci of mice living in populations on established transport routes are expected to be significantly different from those of nearby populations. In contrast, the number of repeats at microsatellite loci of mice living in populations far from established transport routes are expected to be similar to those of nearby populations.

CONCLUSIONS

Finding the same genetic marker in mice from geographically distant populations that are connected by transport implies long distance gene migration. DNA sequences are the strongest examples of long distance gene migration. Other strong examples include mice with multiple "foreign" genetic markers. Repeated trapping and genetic screening on known transport routes terminating at sites with abundant shipments of feed and hay, such as grain elevators, feedstores, and feedlots, can document the longterm genetic impact of stowaways. The following criteria maximize the chance of documenting long distance gene migration:

(1) The same DNA sequences or multiple "foreign" genetic markers are expected to occur in

descendants of putative stowaways and in their populations of origin.
(2) Genetic screening methods that maximize detectable genetic variation should be used.
(3) Intensive trapping and genetic screening must document geographic boundaries of genetic markers to show these genetic markers are truly "foreign".

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