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**PHYLOGEOGRAPHY OF THE STRIPED FIELD MOUSE (*APODEMUS AGRARIUS*) THROUGHOUT THE PALAEARCTIC REGION**

Latinne Alice1, Navascues M. 3, Pavlenko Marina2, Kartavtseva Irina2, Rainer U., Catteau Gilles1 , Sakka Hela1, Quere jean-Pierre3, Chelomina Galina2, Bogdanov Aleksey4, Stanko Michal5, Hang Lee6, Neumann Karsten7  Henttonen Heikki8 & Michaux Johan1

1 Laboratoire de génétique de la conservation, Institut de Botanique, Boulevard du rectorat, 27, 4000 Liège, Belgium.

2 Institute of Biology and Soil Science, Far East Branch of Russian Academy of Sciences, Vladivostok, 690022, Russia.

3 INRA, UMR1062 CBGP, Campus international de Baillarguet, Montferrier-sur-Lez, France.

4 Institute of developmental biology RAS, Vavilov str., 26, 119334 Moscow, Russia

5 Slovak Academy of Sciences, Dept. of Vector-Borne Diseases, Slovakia.

6 Program for Veterinary Science, Seoul National University.

7 Institute of Zoology, Martin-Luther-University Halle-Wittenberg, Domplatz 4, D-06108 Halle (Saale), Germany.

8 The Finnish Forest Research Institute, Box 18 (Jokiniemenkuja 1), FI-01301 Vantaa, Finland.

9 Friedrich-Loeffler-Institut, Bundesforschungsinstitut für Tiergesundheit, Federal Research Institute for Animal Health, Südufer 10 | 17493 Greifswald - Insel Riems

Correspondance to: Johan Michaux, laboratoire de génétique de la conservation, Institut de Botanique, Boulevard du rectorat, 27, 4000 Liège, Belgium. Email: Johan.Michaux@ulg.ac.be.

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**ABSTRACT**

**Aim**

The aim of this study is to infer the genetic phylogeography of the stripped field mouse, *Apodemus agrarius*.

**Location**

**Methods**

**Results**

**Main Conclusions**

**Keywords**

*glacial refugia, Palearctic region, Apodemus agrarius, mitochondrial DNA, phylogeography.*

**INTRODUCTION**

Quaternary climatic oscillations have played a major role in shaping the present geographical distribution of both species and their genetic diversity. In the northern hemisphere, this resulted in extinction of the northern populations during ice ages followed by subsequent northward expansion from refugia during interglacials (Hewitt, 1996, 1999, 2000; Taberlet *et al*., 1998). The refuges for European small temperate mammals were mainly located in the Mediterranean, the Urals and the Caucasus/Carpathian regions (Michaux et al., 2003, 2005; Deffontaine et al., 2005, 2009). However, some other studies also proposed that much more Nordic regions such as Western Scandinavia, Southern Great Britain or the Baltic area would have also played the role of additional refuges for some boreal but also temperate mammal species (e.g. lemming, *Lemmus lemmus*; red squirrel *Sciurus vulgaris*) (Stewart & Lister, 2001; Fedorov & Stenseth, 2001; Stewart and Danel, 2008). This hypothesis is based on the absence of signal of post glacial recolonisation for these species or by the discovery of fossil records dated from the last glacial period. Other studies also proposed that Europe was recolonised by mammal populations that survived in Central Asian refuges during the last glacial maximum (i.e. the voles *Myodes glareolus*, Deffontaine *et al*., 2005; *Microtus agrestis*, Jaarola & Searle, 2002; *M. oeconomus*, Brunhoff *et al*., 2003; *Microtus arvalis* , Haynes *et al.,* 2003; the arctic fox, *Alopex lagopus*, Dalen *et al*. 2007 or the lemming, *Myopus schisticolor*, Fedorov *et al*. 2008). Generally, these species were characterised by a lack of phylogeographic structure and a signal of population expansion suggesting their survival in a low number of refuge areas followed by expansions at continental scale.

Finally, recent studies suggested that some mammal species colonised Europe from much more far regions, like the Far East of Russia or China (e.g. the common hamster, *Cricetus cricetus*, Neumann et al. 2005 and the Harvest mouse, *Micromys minutus*, Yasuda et al., 2005). However, these studies were generally developed on a weak sampling, particularly for the oriental populations and many questions still remain concerning the relationships between populations from the Eastern and the Western Palearctic areas: where did they survive during the Quaternary glaciations? How and when did the oriental populations colonise the western regions? During which climatic periods (glaciations? Interglacials?)? Are they characterised by particular ecological habits allowing them to colonise large areas?

In order to better understand such questions, we propose to study the striped field mouse, *Apodemus agrarius* throughout its distribution area. Indeed, this species appears to be a particularly good candidate to better understand the genetic structure of oriental newcomers in Europe.

It is widely distributed all over the Palearctic region, from Central Europe to the Korean Peninsula and the Russian Far East. However, its range is divided into two extended isolated fragments (European–Siberian and Far Eastern–Chinese), which are about 600–700 km apart, the disjunction zone running along Transbaikalia and Mongolia (Fig. 1).

Phylogeographic information based on allozymes (Bogdanov, 2002), karyotype variations (Kartavtseva and Pavlenko, 2000) and RAPD markers (Atopkin *et al*., 2007) showed very weak genetic differences among animals from the two main populations groups, only evidencing that the Far Eastern group seems to be more heterogeneous as compared to the European-Siberian one. These hypotheses were confirmed by a recent study based on sequences of the mitochondrial cytochrome b (Sakka *et al.,* 2010). Moreover, the low karyotype and allozyme differentiation in striped field mouse also suggests a recent and rapid spreading of the species from the East to the West Palearctic. According to Pavlenko (2000), this spreading occurred after the last glaciation, during the humid and warm ecological Holocene optimum (7000–4500 years ago), accompanied by a strong development and growth of forests. However, this assumption is not supported by recent paleontological data which evidenced that *A. agrarius* was already present in South-Western France during the Late Pleistocene (19000 years BP) (Aguilar et al. 2008). Estimation of expansion periods based on molecular markers and analysed following recent statistical methods based on the coalescent theory would be extremely useful to better understand the demographic and expansion history of this species.

According to Atopkin *et al*. (2007), the disjunction of the *A. agrarius* range in Transbaikalia occurred later, during the Holocene, and was associated to a strong dryness period in this region, which caused rarefaction, and in some cases disappearance, of trees and shrubs. However, this hypothesis must absolutely be confirmed by a better sampling throughout the distribution range of the species as well as by the use of more sensitive genetic methods based on rapidly evolving genes.

On the taxonomic point of view, more than 25 subspecies of striped field mouse have been described, mainly based on body size and coat color (Musser & Carleton, 2005). However, variations in these traits are primarily determined by landscape and (or) microclimatic conditions of the population environment. Therefore, many authors consider most striped field mouse subspecies as non-valid, restricting their number to two to ten for this species (Koh et al. 2014). A deep taxonomic revision appears nevertheless essential with the use of a set of diagnostic traits, including genetic ones.

The aim of the present study is to better understand the genetic and phylogeographic structure of the striped field mouse using biological material from the two main distribution isolates of the species and the sequencing of the complete mitochondrial cytochrome b gene and genotyping of microsatellite markers.

**MATERIAL AND METHODS**

**Samples and DNA extraction**

A total of 158 *Apodemus agrarius* have been sequenced for the mitochondrial DNA cytochrome b. Twenty-four cytochrome b sequences from *Apodemus agrarius* available in GenBank were also added to this dataset to cover the entire distribution range of *A. agrarius* (68 localities in 20 countries) (Table 1 & Fig. 1). These specimens were obtained from collaborators, museums and field missions performed by our laboratories.

All samples used in the present study were tissue samples stored in ethanol. GenomicDNA was extracted using the DNeasy™ Tissue kit (Qiagen Inc., Valencia, CA) following the manufacturer’s instructions.

Table 1: Geographic origin of *A. agrarius* samples used in this study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Country | n cytb | n localities cytb | n microsatellites | n localities microsats |
| Austria |  |  | 21 | 7 (AU1-7) |
| Bulgaria |  |  | 8 | 1 (BU) |
| China | 29 | 11 (CH1-11) |  |  |
| Croatia | 5 | 1 (CRO) |  |  |
| Czech Republic | 4 | 1 (CZ1) | 10 | 3 (CZ2-4) |
| Denmark | 5 | 1 (DA1) | 19 | 2 (DA1-2) |
| Estonia | 1 | 1 (EST) | 1 | 1 (EST) |
| Finland | 3 | 3 (FIN1-3) |  |  |
| Germany | 10 | 9 (GE1-9) | 61 | 24 (GE3-26) |
| Hungary | 2 | 1 (HU) | 2 | 1 (HU) |
| Italy | 1 | 1 (IT1) | 1 | 1 (IT2) |
| Kazakstan | 3 | 2 (KAZ1-2) |  |  |
| Korea | 18 | 5 (KO1-5) | 12 | 4 (KO1-4) |
| Lithuania |  |  | 1 | 1 (LIT) |
| Poland | 5 | 1 (PO1) | 31 | 4 (PO1-4) |
| Romania | 4 | 1 (RO1) | 11 | 5 (RO1-5) |
| Russia (Far East) | 52 | 10 (FE1-10) | 68 | 16 (FE1, FE3-5, FE7-18) |
| Russia | 19 | 10 (RU1-10) | 1 | 3 (RU1, RU9-10) |
| Slovakia | 1 | 1 (SLV1) | 79 | 13(SLV1-13) |
| Slovenia | 6 | 3 (SL1-3) | 1 | 1 (SL1) |
| Taiwan | 9 | 3 (TAI1-3) |  |  |
| Turkey | 3 | 1 (TUR) | 1 | 1 (TUR) |
| Ukraine | 2 | 2 (UK1-2) |  |  |

**Cytochrome b amplification**

The mitochondrial cytochrome *b* (*cytb*)gene was amplified using the universal PCR primers L7 (5’-ACCAATGACATGAAAAATCATCGTT-3’) and H16 (5’-ACATGAATYGGAGGY-CAACCWG-3’) (Kocher *et al.*, 1989). Amplifications were carried out following the protocol of Michaux *et al.* (2003) and performed in a Labover PTC100 thermal cycler employing 39 cycles (30 s/94°C, 1 min/52°C, 2 min/68°C) with a final extension cycle of 10 min at 68°C. All the sequencing procedures were performed by Macrogen Inc. (Seoul, Korea). The sequences were aligned using ClustalW algorithm in BIOEDIT 7.0.5.2 (Hall, 1999).

**Microsatellite genotyping**

In order to confirm the results obtained with the mitochondrial marker, we also genotyped 340 *A. agrarius* specimens coming from 88 localities in 17 countries using 9 microsatellites (Table 1 & Fig. 1 ou 2?). These markers were selected from the paper of Makova *et al.* (1998). The amplification protocols followed the recommendations of this last paper. One primer of each of the 9 primer pairs was labelled with one of the fluorochromes used in the ABIGeneScanTM system (ABI). Reaction mixtures contained approximately 100 ng of genomic DNA, 2.5 units of Taq DNA polymerase (Promega), 10 units of Promega buffer, 1.5 mM of MgCl2, 0.6 mM of each primer (labelled and unlabelled), 250 mM of dNTPs (Perkin Elmer), and water to a final volume of 25 mL. Thermal conditions were an initial denaturation for 3 minutes at 94 °C, followed by 35 cycles at 94 °C for 1 min, 30–45 seconds at the annealing temperature, 72 °C for 30–60 seconds, and a final extension for 3 minutes at 72 °C. After amplification, the 9 microsatellite loci for each mouse were analysed on an ABI 3100 automatic sequencer. The 9 loci were analysed in two runs for each animal. Results were compiled and analysed with the GeneScanTM and GenotyperTM softwares (ABI).

**Mitochondrial data analysis**

The final cytb dataset included 182 sequences from *Apodemus agrarius*. Phylogenetic reconstructions were performed using the maximum-likelihood criterion (ML) (Felsenstein, 1981) algorithm implemented in the PHYML program (Guidon & Gascuel, 2003). We used MODELTEST version 3.0 (Posada & Crandall, 1998) to determine the most suitable model of DNA substitution for the *cytb* dataset studied. The robustness of the tree was assessed by 1000 bootstrap resampling (Felsenstein, 1985). A Bayesian phylogeny reconstruction approach (Yang & Rannala, 1997) implemented in MRBAYES 2.01 (Huelsenbeck *et al.*, 2001) was also used. Metropolis-coupled Markov chain Monte Carlo (MCMC) sampling was performed with five chains run for 3 000 000 iterations, using default model parameters as starting values. Bayesian posterior probabilities were picked from the 50% majority rule consensus of trees sampled every 100 generations, discarding the trees obtained before the chains reached stationary distribution ("burn in", empirically determined by checking of likelihood values).

Haplotype networks may more effectively portray the relationships among sequences for populations with low sequence diversity (Crandall & Templeton, 1993), so a Median-Joining Network was also constructed using the software NETWORK 4.5 (Bandelt, Forster, Röhl, 1999) to infer the relationships between haplotypes.

Haplotype (h) and nucleotide (π) diversities (Nei, 1987) and their standard deviations (Tajima, 1993), Fu’s *Fs* and genetic differentiation (using population pairwise Fst) among populations were estimated using ARLEQUIN 3.1 program (Excoffier *et al.*, 2005). Fu’s *Fs* is a powerful tests used to detect population expansion under assumptions of neutrality (Fu, 1997; Ramos-Onsins & Rozas, 2002). These indices were calculated for the two main striped field mice fragments (Eastern and Western Palearctic). Moreover, to assess whether genetic diversity was higher within the potential refuge regions, these two main groups were divided into five regional subgroups: the first one corresponding to the populations from the Russian Far East; the second one to the animals living in Western Siberia (Western side of the Baikal lake, Novosibirsk region, and Altai region) and Kazakhstan; the third one, to the Central Russian populations (from the Ural mountains to the Moscow region) and Ukraine; the fourth one to all the European and turkish populations; the fifth one, to the Korean, Taiwanese and Chinese field mice.

The genetic structure of populations was also examined using an analysis of molecular variance (AMOVA) performed in ARLEQUIN. AMOVA was conducted at three hierarchical levels of population subdivision: among the two main geographic fragments (Eastern and Western Palearctic groups), among regional subgroups within each fragment (Europe + Turkey, Western Siberia, Central Russia, Russian Far East and China + Korea + Taiwan) and within each regional subgroup. The significance of these parameters was estimated by 10,000 permutations of the distance matrix.

Demographic histories of the two main field mice groups (Eastern and Western Palearctic fragments) were inferred using our cytb dataset and an isolation-with-migration (IM) model implemented in the IM program (Hey & Nielsen, 2004). The model uses the coalescent simulation within a Bayesian inference framework to estimate posterior probability distributions for 5 parameters including: contemporary and ancestral effective population sizes, divergence times (*T = t µ*) and rates of gene flow between the Eastern and Western fragments. We assumed equal migration rates in both directions (i.e., just one m) and a HKY model of sequence evolution. We used a burn-in of 200,000 steps followed by a run of 1 million steps. Prior boundaries were empirically determined to ensure that the posterior distributions fell completely within the prior distributions. The modes of the posterior probability distributions were thus taken as the Maximum Likelihood Estimate (MLE) of the parameters. We estimated the credibility intervals as the 90% Highest Probability Density (HPD) intervals (i.e., the shortest span that includes 90% of the probability density of a parameter). To ensure reliable convergence toward the stationary distribution, we monitored multiple independent runs, each with 70 up to 100 independent chains under Metropolis coupling to improve mixing. Mixing properties of the MCMC were assessed by examining the level of autocorrelation between final and initial parameter values and by visual inspection of the parameter trend plots. Analyses were considered to have converged upon the stationary distribution if independent runs generated similar posterior distributions, with each having a lowest effective sample size of 50 for each estimated parameter

To convert parameter estimates scaled by *µ* (i.e., *T* and *θ)* to demographic units, we used a per generation mutation of 2.7 %/MYr as generally used for rodents of the genus *Apodemus* (eg. Michaux *et al.,* 2003; 2005). Assuming a generation time (*G*) for *A. agrarius* of 0.5 year, population divergence time (*T*) can be converted to calendar years (*t* in years) and estimates of population mutation rates (*θ1*, *θ2*, and *θA*) can be converted to estimates of effective population size parameters (*N1*, *N2*, *NA*, respectively, in number of individuals). To integrate the uncertainty related to the mutation rate and the generation time in the estimated parameters scaled by the mutation rate (*T* and *θ*), we converted the parameters using the extreme values of *µ* and *G*. We applied the same conservative approach for the credible intervals, taking the extreme 90% HPD values obtained using the two plausible values of *µ* and *G*.

Migration parameters in the model can be used to obtain population migration rates (i.e., the effective number of migrants per generation), using an estimate of *θ* (i.e., 2*Nm = θm*/2) (21). 2*N1m1* and 2*N2m2* are the effective number of migrants per generation into population 1 and 2 respectively.

We also roughly estimated the timing of demographic expansion of each group and subgroup using the mode of mismatch distribution Tau calculated in DNASP (Librado & Rozas, 2009) and expressed as Tau =2µt, where t is the expansion time in number of generations and µ is the mutation rate for the whole sequence.

**Microsatellite data analysis**

The proportion of null alleles (NA) at each locus and for each population was estimated with FREENA (Chapuis & Estoup, 2007). Genetic diversity was assessed by calculating expected (He) and observed (Ho) heterozygosities with ARLEQUIN over all loci for each group and confirmation of Hardy-Weinberg equilibrium (HWE) was tested using GENEPOP. Multi-locus Fis was calculated for each group with FSTAT 2.9.3.2 (Goudet, 2001). The allelic richness (AR) was calculated using the rarefaction procedure implemented in FSTAT.

STRUCTURE 2.3.1 (Pritchard et al., 2000) was used to infer the number of populations (K) and assign individuals to genetic clusters independently of spatial sampling. Ten iterations were run for each value of K from 1 to 15 using an admixture model with a burn-in of 1x105 and MCMC values of 1x106. We used CLUMPAK to average the results of multiple iterations for a given K and to generate a visual output of STRUCTURE results.

Demographic history was inferred from microsatellite data using an approximate Bayesian computation (ABC) approach via random forests (Marin et al. 2016; Pudlo et al. 2016). In this approach, data is simulated from the demographic model with parameter values taken from prior probability distributions and data is transformed into summary statistics. Random forests are used to learn about the parameters from the simulated summary statistics. The resulting random forests (i.e. sets of decision trees) can then be used to estimate the posterior probability distributions of concurrent models and their parameters from the observed summary statistics. Forty thousand simulations were generated to create the reference table and random forests of 1000 trees for the estimation of parameters and posterior probabilities. Prior error from the ABC-random forests were calculated with an out-of-bag approach (see Marin et al. 2016; Pudlo et al. 2016 for details).

In our analysis, a model of two populations (eastern and western clusters) was evaluated. Each population was characterized by a parameter *θ* (*θ*W=4NWμ and *θ*E=4NEμ, where NW is the effective population size of the western population, NE is the effective population size of the eastern population, and μ is the mutation rate). Western population was founded by individuals from the eastern population at time T=t/4NW (time tF measured in number of generations). Two concurrent models were evaluated regarding the presence or absence of gene flow between the two populations. If gene flow was detected, an additional parameter, the scaled migration rate M=4NWm, was included. Microsatellites were assumed to mutate following a generalized stepwise mutation model (GSM), in which the number of repeat units gained or lost in each mutation is taken from a geometric distribution with parameter PGSM. Data under this model was generated by simulation using coalescent simulator ms (Hudson 2002) with a custom script (see below) to transform its output into microsatellite data. Each simulated data set was summarized by statistics used in population genetics to characterize microsatellite genetic diversity and population differentiation, known to be informative about demography (see Supplementary methods and Supplementary Table S1). Parameter values at each simulation were sampled from prior probabilities distribution specified in table 1. Point estimates of parameters at the natural scale were obtained by using an estimate of NW obtained from *θ*W point estimate and assuming a generation time of 0.5 years and a mutation rate of 5×10-5 per generation. While no estimate of mutation rate is available for *A. agrarius*, Dietrich et al. (1992) estimated a mutation rate around 5×10-5 in *Mus musculus* that would be compatible with the lack of observed mutation in the *Apodemus* pedigrees studied by Baker et al. (1999).

Code in R (R Development Core Team 2009) to perform this ABC analysis (simulation, summary statistics computation and ABC-random forest) is available at http://github.com/mnavascues/microsatABC-IM. It uses functions from pegas (Paradis 2010), mmod (Winter 2012) and adegenet (Jombart 2008) for calculating summary statistics and abcrf (Pudlo et al. 2016) and quantregForest (Meinshausen 2006) for performing random forests analyses.

**RESULTS**

**Mitochondrial DNA analysis**

Phylogenetic and phylogeographic analysis

A total of 117 haplotypes was identified among our cytb dataset. All sequences have been deposited in GenBank (accession numbers….). The complete data matrix comprised these 117 haplotypes as well as two *Apodemus chevrieri* as outgroups. This matrix provided 923 base pairs, of which 208 sites were variable and 127 were parsimony informative. The nucleotide frequencies were 29.2%, 26.7%, 30.4% and 13.6% for T, C, A and G, respectively. ML and Bayesian analyses were performed using the HKY85 + I + Gamma model suggested for the dataset by the Akaike information criterion estimated using MODELTEST, with a proportion of invariable site equal to 0.616 and gamma distribution shape parameter equal to 0.8323.

The phylogenetic trees obtained with the ML and Bayesian analyses were weakly supported and did not show any clear phylogeographic structure. Haplotypes corresponding to animals coming from the whole distribution area of the stripped field mouse were mixed and not associated within supported clades in the tree. However, two genetic groups corresponding to the Western and Eastern Palearctic fragments are evidenced in our median joining network (Fig. 2). Few cytb haplotypes are shared among individuals from Russian Far East and Europe, from Europe and Central Russia and from Western Siberia and Central Russia.

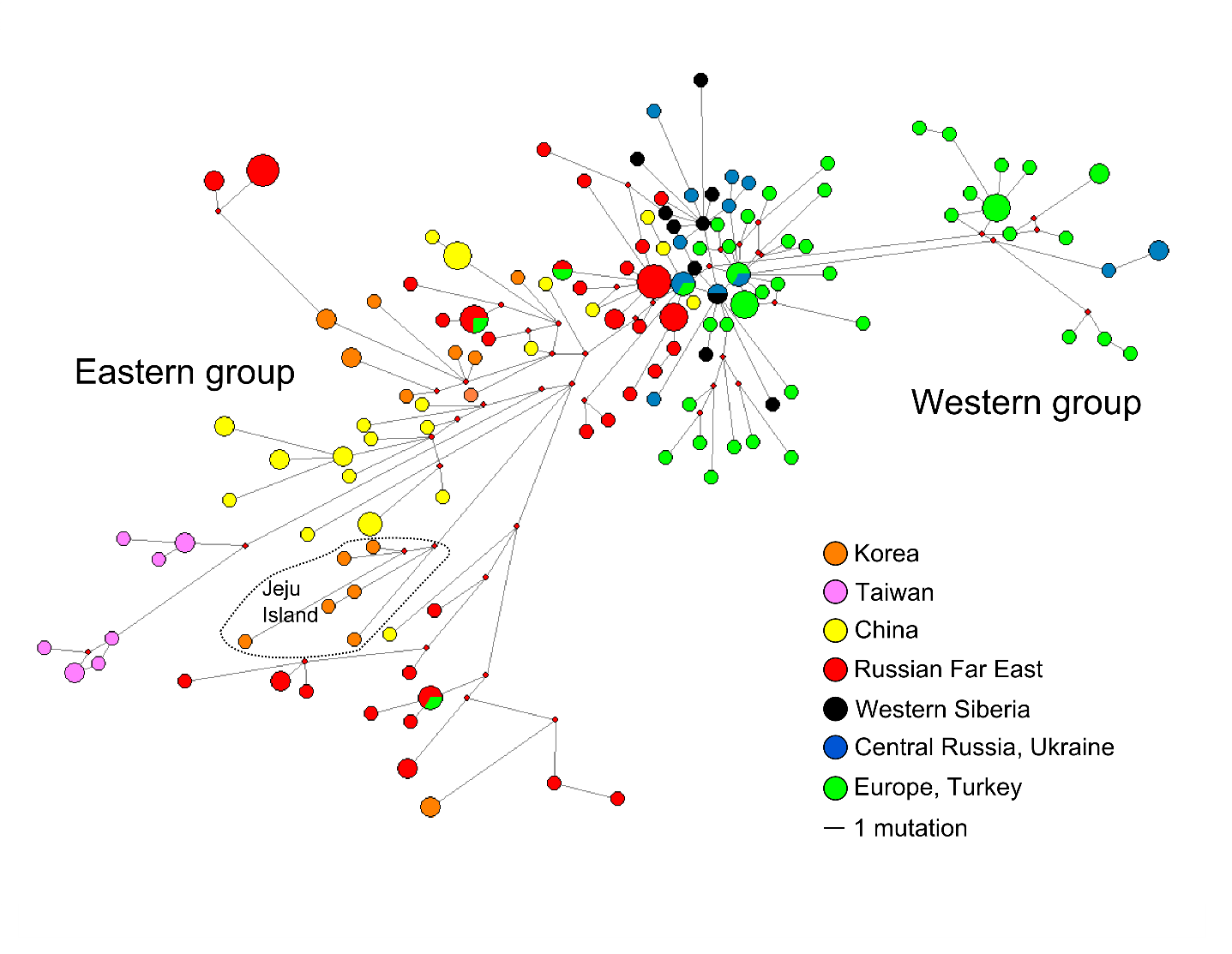


Figure 2: Median-joining network based on cytb dataset. Circles correspond to distinct haplotypes and circle size is proportional to the number of animals sharing this haplotype. Branch length is proportional to the number of mutations between haplotypes.

**Analysis of genetic diversity and differentiation**

We calculated nucleotide and haplotype diversities for the two main striped fieldmice fragments (Eastern and Western Palearctic) and the five regional subgroups. The results of these analyses are summarized in Table 2 and indicate that the populations of the Western Palearctic fragment are characterised by weaker nucleotide diversity values (from 0.0062) as compared to Eastern Palearctic one (0.0159). Haplotype diversity is high and similar in all groups, except in Central Russia where it is lower. The Fu’s *Fs* test of neutrality was significant for all groups (Table 2), which indicate population expansion.

FST estimates among the five main subgroups (Table 3) confirmed the genetic differentiation (FST > 0.20) between eastern and western subgroups.

Table 2: Diversity estimates and expansion times for *A. agrarius* groups and subgroups

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Corresponding localities | N | h ± SD | π ± SD | Fu’s Fs | Tau | Expansion time |
| Overall | All | 182 | 0.9933 ± 0.0016 | 0.0135 ± 0.0068 | **-24.05267** | 0.228 |  |
|  |  |  |  |  |  |  |  |
| Eastern group | CH1-11, TAI1-3, KO1-5, FE1-10 | 108 | 0.9894 ± 0.0033 | 0.0159 ± 0.0079 | **-24.10376** | 7.244 |  |
| Western group | CRO, CZ1, DA1, EST, FIN1-3, GE1-9, HU, IT1, PO1, RO1, SLV1, SL1-3, TUR, RU1-10, UK1-2, KAZ1-2 | 74 | 0.9874 ± 0.0056 | 0.0062 ± 0.0034 | **-25.48372** | 0.108 |  |
|  |  |  |  |  |  |  |  |
| China, Taiwan, Korea | CH1-11, TAI1-3, KO1-5 | 56 | 0.9890 ± 0.0060 | 0.0180 ± 0.0090 | **-16.00178** | 10.299 |  |
| Russian Far East | FE1-10 | 52 | 0.9668 ± 0.0114 | 0.0114 ± 0.0058 | **-8.51826** | 5.264 |  |
| Europe, Turkey | CRO, CZ1, DA1, EST, FIN1-3, GE1-9, HU, IT1, PO1, RO1, SLV1, SL1-3, TUR | 50 | 0.9771 ± 0.0113 | 0.0058 ± 0.0032 | **-25.59017** | 2.014 |  |
| Central Russia, Ukraine | RU1-5, RU7, RU10, UK1-2 | 14 | 0.8901 ± 0.0807 | 0.0051 ± 0.0029 | **-2.84393** | 4.327 |  |
| Western Siberia, Kazakhstan | RU6, RU8-9, KAZ1-2 | 10 | 1.0 ± 0.0447 | 0.0051 ± 0.0029 | **-6.12762** | 2.772 |  |

Table 3: FST among the five subgroups

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | China, Taiwan, Korea | Russian Far East | Europe, Turkey | Central Russia, Ukraine | Western Siberia, Kazakhstan |
| China, Taiwan, Korea |  |  |  |  |  |
| Russian Far East | 0.13 |  |  |  |  |
| Europe, Turkey | 0.29 | 0.23 |  |  |  |
| Central Russia, Ukraine | 0.29 | 0.26 | 0.15 |  |  |
| Western Siberia, Kazakhstan | 0.27 | 0.23 | 0.19 | 0.04 |  |

The AMOVA showed that the majority of the total mtDNA variation (71.7%) was distributed within the regional subgroups whereas a low percentage of this variation (17.4%) was observed between the two defined groups (Eastern and Western Palearctic fragments) and among subgroups within the groups (10.9%).

**Demographic history (IM model)**

The estimated current population size of Eastern lineage is three times larger than that of Western lineage. The divergence time between these two lineages was estimated at 154 kyr (95% CI: 97 kyr–228 kyr) under the IM model (Table 4). The gene flow was estimated at around 4,5 female migrants from East to West and 1,4 migrant from West to East.

Table 4: Parameters converted on a demographic scale assuming a mutation rate of 2.7 % MYr-1, and a generation time 0.5 yr. The length of the usable sequence was 766 bps.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | N1 (inds) Eastern lineage | N2 (inds) Western lineage | N (inds) Ancestral population | T (Yrs) | 2N1m1 (inds) | 2N2m2 (inds) |
| HiSmth | 6 648 293,2 | 2 121 409,9 | 664 829,3 | 154 240,4 | 4,5 | 1,4 |
| HPD90Lo | 4 569 190,6 | 1 468 668,4 | 181 317,1 | 97 186,0 | 1,2 | 0,4 |
| HPD90Hi | 9 162 556,8 | 3 158 543,7 | 1 607 678,2 | 227 734,3 | 19,4 | 6,7 |

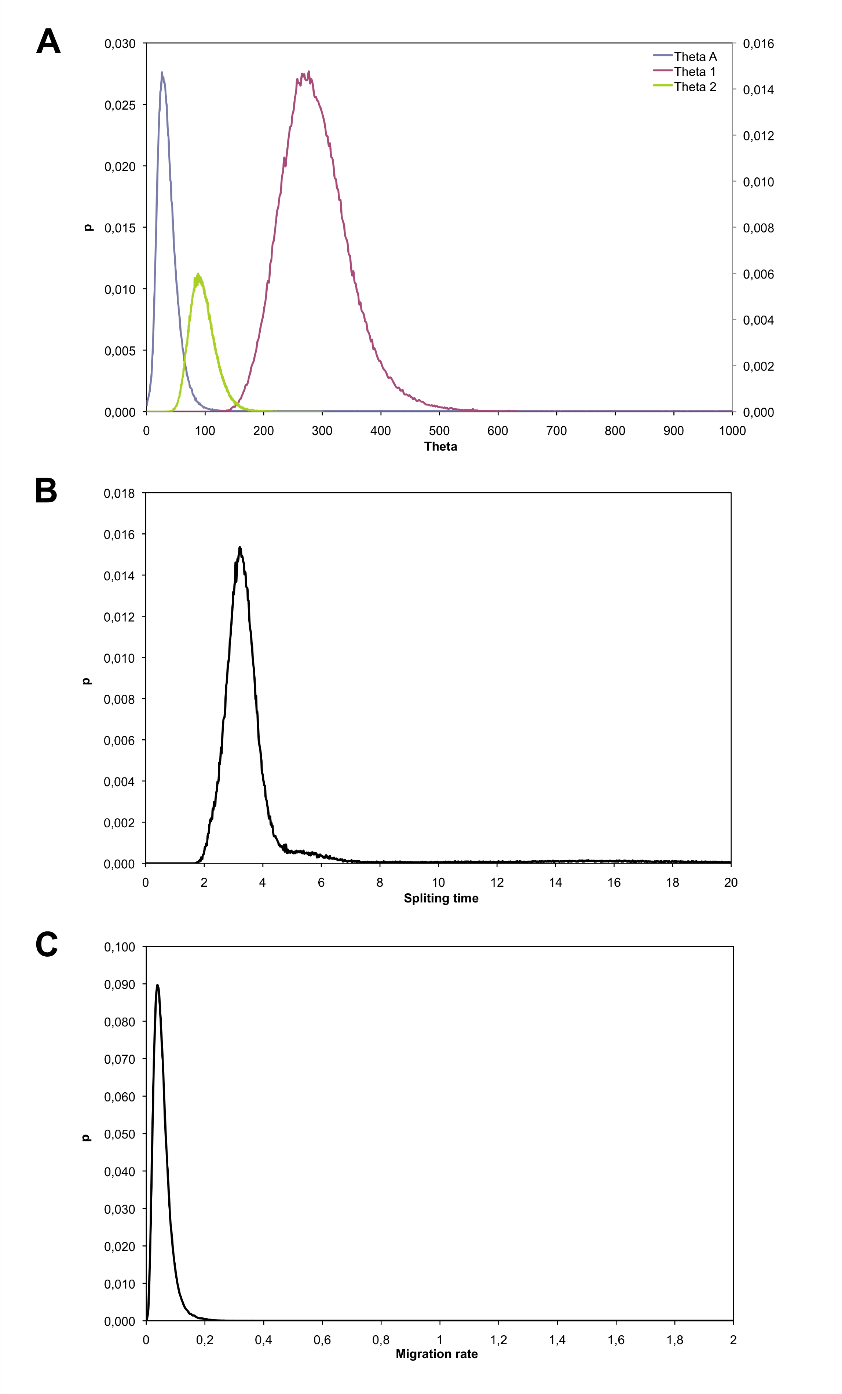
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Figure 3: Plots of posterior probability of parameters estimated with the isolation-with-migration model: (A) Effective population sizes of the Eastern lineage (Theta 1), Western lineage (Theta 2) and ancestral population (Theta A), (B) splitting time between Eastern and Western lineages and (C) migration rate (Nm) between Eastern and Western lineages

**Microsatellite data analysis**

Genetic diversity

The values of NA frequency determined in FreeNA were very low for each locus in each group, except for the locus AGRA11 in Korea and Russian Far East (>10%). Observed heterozygosity and allelic richness are higher in Eastern group and subgroups (Korea and Russian Far East) (Table 5). Tests for HWE showed deviation from the expected frequencies in all groups. All inbreeding coefficient (Fis) were significant (Table 5).

Table 5: Microsatellite genetic diversity within *A. agrarius* groups and subgroups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Corresponding localities | n | Ho | He | Fis | AR |
| Overall | All | 340 | 0.67633 ± 0.12353 | 0.80644 ± 0.10300 | **0.162** | 21.07 |
|  |  |  |  |  |  |  |
| Eastern group | KO1-4, FE1, FE3-5, FE7-18 | 80 | 0.73267 ± 0.10842 | 0.86524 ± 0.05688 | **0.109** | 16.66 |
| Western group | AU1-7, BU, CZ2-4, DA1-2, EST, GE3-26, HU, IT2, LIT, PO1-4, RO1-5, SLV1-13, SL1, TUR, RU1, RU9-10 | 260 | 0.65890 ± 0.15377 | 0.73896 ± 0.16587 | **0.154** | 12.61 |
|  |  |  |  |  |  |  |
| Korea | KO1-4 | 12 | 0.73232 ± 0.18672 | 0.84326 ± 0.05644 | **0.137** | 7.84 |
| Russian Far East | FE1, FE3-5, FE7-18 | 68 | 0.73275 ± 0.10193 | 0.85588 ± 0.06176 | **0.145** | 9.01 |
| Europe, Turkey | AU1-7, BU, CZ2-4, DA1-2, EST, GE3-26, HU, IT2, LIT, PO1-4, RO1-5, SLV1-13, SL1, TUR | 247 | 0.65732 ± 0.15898 | 0.73558 ± 0.17095 | **0.107** | 6.94 |
| Central Russia, Western Siberia | RU1, RU9-10 | 13 | 0.68803 ± 0.13927 | 0.75492 ± 0.11485 | **0.092** | 7.06 |

Population structure

We used the ΔK method described by Evanno et al. (2005) to interpret the STRUCTURE output. The highest ΔK was found at K = 2. For K = 2, the Korean populations clustered with the populations from the Russian Far East (Eastern goup) (Figure 4). The second cluster corresponds to the Western group (European, Turkish, Russian, Ukrainian and Kazak populations). Several individuals from Slovakia and Russia were admixed. The Eastern cluster (Korea + Russian Far East) is recovered until K = 5.

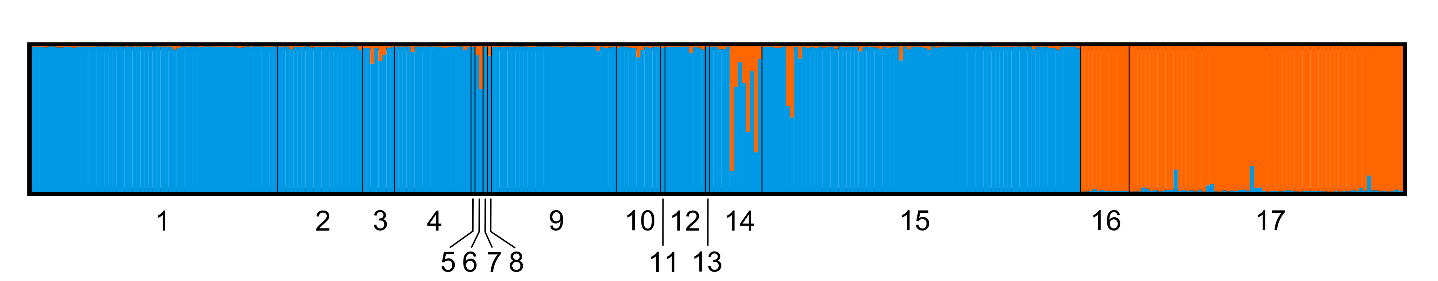


Figure 4: Population structure estimated using STRUCTURE (K=2). Each individual is represented by a vertical line partitioned into K colour segments, the length of each colour being proportional to the estimated membership coefficient. Numbers correspond to sampling countries: 1 = Germany, 2 = Austria, 3 = Bulgaria, 4 = Denmark, 5 = Estonia, 6 = Hungary, 7 = Italy, 8 = Lithuania, 9 = Poland, 10 = Romania, 11 = Slovenia, 12 = Czech Republic, 13 = Turkey, 14 = Slovakia, 15 = Russia (Central Russia + Western Siberia), 16 = Korea, 17 = Russian Far East

Demographic history

Distinguishing between models (migration or pure divergence) was difficult with the ABC-random forest approach, with a prior error rate of 0.42. A model with migration between western and eastern populations was slightly favored over a model of pure divergence with a posterior probability estimated at only 0.54. Because of this low posterior probability, parameters common to both models were estimated from the reference table from both models. Migration rate was also estimated for the isolation-with-migration model. Point estimates (median of posterior probability distribution) and 95% highest posterior density intervals are reported in Table 6 and more detailed description of the posterior distribution presented in the supplementary materials.

Table 6. Parameters (coalescent scale) estimated for the isolation with migration model

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Prior | prior MSE | median | 95%HPD | natural scale |
| θW | Log-uniform(0.1,1000) | 1.30 | 5.25 | 1.86–81.69 | *N*W ~ 26000 individuals |
| θE | Log-uniform(0.1,1000) | 1.05 | 11.86 | 6.70–164.53 | *N*E ~ 59000 individuals |
| *T* | Log-uniform(10-5,10) | 1.67 | 0.17 | 0.03–8.45 | *t* ~ 8900 years |
| *M* | Log-uniform(10-5,100) | 973.82 | 4.96×10-3 | 1.24×10-5–3.64 | m < 3.47×10-5 |
| *P*GSM | Uniform(0,1) | 6.39×10-3 | 0.50 | 0.09–0.64 |  |

MSE: mean squared error

The estimated effective population size of the Eastern group (θE) is 2.3 times higher than the one of the Western group (θW). The estimated divergence time between the Eastern and Western groups is 8900 years.



**Discussion**

Origin of the fragmented distribution area of *Apodemus agrarius*

The distribution area of *A. agrarius* is divided into two main and geographically well isolated parts. The first one corresponds to China, Korea and the Russian Far East and the other comprises a large region starting from the Western part of the Baikal Lake to Central Russia, Europe and Turkey. An important question concerns the genetic relationships between populations of these two distribution ranges: are these populations genetically related with frequent gene flow between them or have they been separated for a long time? What is the region of origin of *A. agrarius*? What are their demographic histories?

Our findings based on cytochrome b sequences and microsatellites lead to the following scenario for the evolutionary history of *A. agrarius*: this speciesappeared around 5 Myrs ago (Michaux *et al*., 2002; Suzuki *et al.,* 2003) in the Asian Far East and probably in China (higher genetic and nucleotide diversities for cytochrome b; higher allelic richness for microsatellites, signal of more stable populations in this region). Later, it would have expanded in other Extreme East Asian areas, such as the Ussuriland (Russian Far East). Indeed, the Median Joining Network, the Fst analyses and the microsatellite results evidenced close relationships between populations from both regions. The origin of *A. agrarius* in Far East Asia is also corroborated by effective population size estimations (cytochrome b sequences and microsatellites), which evidenced a population size around three times higher on the Eastern range part as compared to the Western one.

Around 150 000 years ago, as suggested by the IM analyses, *A. agrarius* would have been able to colonise the Central Palearctic region, probably via Far East populations. Indeed, the network evidenced closer relationships between these last populations. This result is similar to others results previously obtained using cytochrome b sequences (Sakka *et al.* (2010) . In contrast, it is different to those obtained by proteins and RAPD-PCR methods (Atopkin *et al*., 2007), which proposed a closer relationship between Western and chinese populations. However, as observed in several other organisms (Stakel, 1998), a western colonisation via the Chinese striped field mouse appears unlikely as important biogeographic barriers, such as the Himalayan Mountains or the Gobi desert, surround this region. The precise origin of first colonisers to the West is therefore likely the Far East of Russia.

From this period, the Central-Western Palearctic populations (Western group) started to differentiate from the Russian Far East and Chinese ones even if some gene flow continued happening between animals from both distributions ranges as suggested by microsatellite data. This gene flow seemed to be higher from East to the West than the contrary.

Our dating estimation for the disjunction of the *A. agrarius* ranges appear much older as compared to those proposed by Atopkin *et al*. (2007). Indeed, they estimated that this separation occurred later, during the Holocene, and that it was associated to a strong dryness period in this region, which caused rarefaction, and in some cases, the disappearance of trees, shrubs and grasslands. However, other similar climatic events would have happened around 150 000 years ago and would have led to similar isolation. Indeed, our estimations correspond to the end of the Riss ice age, which was characterized by particularly cold and dry climates.

Later, the Central-Western populations progressively increased and expanded throughout Central Asia to colonise finally the Western European region, around 19 000 years ago (Aguilar *et al.* 2008). This scenario is corroborated by other paleontological studies, which confirm the assumption that *A. agrarius* is an Asiatic immigrant and a relatively new member of the European fauna (Kowalski, 2001; Martín Suárez and Mein, 1998). This Western colonisation would have been favoured during the last Quaternary ice ages, as some habitats corresponding to the habitat preferences of the stripped field mouse (e.g. meadows, grasslands) were largely spread during glacial phases in large parts of Central and Western Asia (ref. to add. To ask to our Russian colleagues). According to the low levels of nucleotide diversities as well as to the signal of recent expansion observed with the Fu’s Fs index and the star like topology observed in the Median Joining network, this expansion would have occurred relatively quickly. Moreover, the low karyotype and allozyme differentiation in striped field mouse also suggest a recent and rapid spreading of the species from the East to the West Palearctic (Bogdanov, 2002; Kartavtseva and Pavlenko, 2000). Such kind of colonisation process of western regions from the far East of the Palearctic is quite rare for mammals. To our knowledge, this patterns was only observed on the Harvest mouse (*Micromys minutus*) (Yasuda et al. 2005). This study evidenced a close genetic relationship between Western and Eastern Palearctic populations and a recolonization process of Europe from refugia situated in the Central to East Asian region. A similar signal seems to exist on the Roe deer (*Capreolus pygargus*) (Lorenzini *et al*. 2013). Indeed, populations from Lituania and Poland appears genetically closely related to animals from Central and Far Asia, suggesting a recent colonisation of Europe from these last regions.

**Genetic structure and refuge areas**

*Apodemus agrarius* showed a very complex genetic structure within the Eastern group. China, the Russian Far East and Korea seem to represent important centres of diversification for this species as the levels of genetic diversity (particularly the nucleotide diversity for the cyt b) are significantly higher within these regions as compared to the other ones. This diversification could be the result of the past isolation of several populations during the Quaternary ice ages. They led to allopatric differentiation processes, which led themselves to the appearance of a large set of haplotypes, that gradually differentiated over time.. Indeed, during these periods, the cooler climate events allowed the extension of the Gobi desert to the Pacific areas. According to Zhou *et al*. (2004), the extension of the arid zones during the ice ages was probably linked to an important discordant state of the mode of monsoons. They probably led to the isolation of the Russian Far East (Primorye and Khabarovsk regions), different Chinese regions (Zhang et al. 1997) as well as of the Korean peninsula populations (Harrison *et al*., 2001; Zhou *et al*., 2004; Zhang *et al*. 2008; Koh et al. 2014; Kim & Park, 2015). This last region, characterised by south temperate mountain climate was not deeply affected by the global Quaternary climate changes (Liu and Li, 1996; Kim & Park, 2015) and therefore, could have allowed many organisms to survive, even during the coldest phases. They would have therefore played the role of glacial refugia where different genetic lineages appeared and survived.

The Russian Far East could have also been a potential Quaternary refuge for *A. agrarius.* This result is corroborated by the high values of genetic, haplotype and nucleotide diversities observed for this region (Table 2). This result confirmed those of other studies based on RAPD-PCR markers (Atopkin *et al.* 2007; Dokuchaev *et al*., 2008). The same tendencies (Table 2) were observed in China suggesting that this region was probably also a refuge for the striped field mouse during the Quaternary glaciations, as for *A. draco* and *A. latronum* (Sakka *et al.* 2010). However, our sampling does not allow to precisely and clearly locate the Chinese refuges. These hypotheses follow the results obtained in other studies carried out on the Asian *Apodemus* species (Suzuki *et al*., 2003).

Concerning the Western group, our analyses performed on the cytochrome b gene evidenced a signal of star like topology in the Median Joining network, as well as a level of genetic diversity significantly lower as compared to the Eastern populations. The same low level of genetic diversity is also confirmed using the microsatellite markers.

This lower genetic diversity would be the result of founder events associated to the colonisation of Western regions from a low number of colonisers coming from the East, followed by a recent population expansion. This hypothesis is corroborated by demographic analyses based on microsatellite markers, which evidenced that the founder population was almost six times lower than its estimated current effective population size. However, this signal could be also explained by a strong population decrease associated to the last glacial Quaternary events. Indeed, as the colonisation of Western Siberia is estimated to be around 150 000 years ago, these populations would also have suffered to the last Quaternary glaciations. However, these events would also have been positive for the spread of this species, by the opening of habitats and the extension of grassland areas in Central and Western Asia (see above).

Taxonomic implication

Corbet (1978) classified *A. agrarius* populations from Europe and western and central Asia as the subspecies *A. a. agrarius*. In contrast, populations from Eastern Asia were considered as the subspecies *A. a. ningpoensis*. However, more recent studies based on morphometric (Koh and Tikhonova, 1998), allozymes (Bogdanov, 2002), karyotype variations (Kartavtseva and Pavlenko, 2000) or genetic markers (Atopkin *et al*., 2007, Suzuki et al. 2008, Sakka et al., 2010, Koh et al. 2014) did not evidence any distinction between both subspecies.

Our cytochrome b sequence analyses also evidenced a close connection between populations from both distribution ranges and the precise analysis of all these data rather confirms a relatively recent origin of Western populations from Eastern ones and therefore a strong relationship between them. In contrast, microsatellite markers evidenced a clear distinction between both distribution ranges. Considering the high evolutionary rates of these markers, this result would represent a recent separation between both *A. agrarius* groups, and which would not be totally complete as we also evidenced the existence of relatively frequent gene flow among them.

According to these findings, only one subspecies, *A. a. agrarius,* would be recognised for all Palearctic continental populations. However, some morphological (Jones and Johnson, 1965) and genetic studies (Koh *et al*., 1999) suggested that the striped field mice from the Korean peninsula could be differentiated from the other Far East populations and proposed to consider them as two particular subspecies: *A. a. pallescens* in South Korea and *A. a. corea* in central Korea. Our results do not really confirm this hypothesis, as microsatellite markers did not evidence any difference between the Korean animals and the other populations from the Far East. Moreover, the network based on cytochrome b sequences did not evidence any clear separation of the Korean animals. This confirm the conclusions of Koh et al. (2014), which proposed to invalidate these last two subspecies and to consider all continental Eurasian form of stripped field mice as belonging to *A. a. agrarius*. In contrast, following Koh *et al*. (2014), some differentiation would exist on the insular populations from Taiwan and the Jeju island. This result was also observed by Sakka *et al.* (2010) as well as by our present study . Koh *et al*. (2014) therefore proposed to consider them as two different subspecies, respectively, *A. a. insulaemus* and *A. a. chejuensis*. However, these taxonomic status will have to be confirmed by a better sampling from these two islands.

Conclusion

Our study gave for the first time a whole idea of the evolutionary and demographic history of the stripped field mouse throughout the Palearctic region. According to our results, this speciesappeared around 5 Myrs ago in the Asian Far East and probably in China. Around 150 000 years ago, it has been able to colonise the Central Palearctic region, probably from a low number of founders from the Russian Far East. From these regions, the species progressively increased and expanded relatively quickly throughout Central Asia to finally colonise the Western European region, around 19 000 years ago. *A. agrarius* would therefore be an Asiatic immigrant and a relatively new member of the European fauna. The study of this biological model enhanced the importance of Far East Asian regions as a point of origin and diversification for several European species and as a source for the European biodiversity. Such example evidenced the complexity of the origin of the existing European fauna, many species having survived to the Quaternary glaciations in European refugia, but several of them coming from much more distant origins like Central Asia (e.g. *Microtus arvalis*, Haynes *et al*. 2003 ; *M. oeconomus*, Brunhoff *et al*., 2003, *Cricetus cricetus*, Neuman *et al.* 2005…) or even Far East Asia (e.g. *Micromys minutus*; Yasuda *et al*., 2005; *A. agrarius*, present study).

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Bibliograph:

Beaucoup des réf citées sont dans notre papier Sakka et al. 2010.

J’ai rajouté une série d’autres plus bas et si tu ne trouves pas certaines, dis les moi et je te les retrouverai !

C’est parfait !

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