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Rb(7.17), a rare Robertsonian fusion in wild populations of the house mouse

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Summary

Robertsonian (Rb) translocation is the largest source of chromosomal diversity in the western European house mouse (*Mus musculus domesticus*). Recently, the fusion Rb(7.17) was found in the chromosomal polymorphic zone of this subspecies in the north-east of the Iberian Peninsula. This fusion has not been reported in any other European population. Here we give data on the distribution and frequency of this mutation in this region. Results revealed that Rb(7.17) is restricted to a small geographic area, and that, in comparison with other fusions in this polymorphic zone, it occurs at low frequencies. We suggest some possible explanations for the distribution of this translocation.

1. Introduction

A good model in which to study chromosomal speciation is the house mouse (*Mus musculus*), since much information regarding both its genome constitution and the diversity of its chromosomal races is available (Dietrich *et al*., 1996; Mouse Genome Sequencing Consortium, 2002; Piálek *et al*., 2005). The standard karyotype of *M. musculus* has 40 acrocentric chromosomes (19 pairs of autosomes and the sex chromosomes); nevertheless, wild populations of the western European house mouse (*M. musculus domesticus*) show high karyotype diversification due to Robertsonian (Rb) fusions, i.e. centric fusion between two non-homologous acrocentric chromosomes to form a metacentric. This diversification seems to have been occurring in the 3000 years since the arrival of house mouse in Western Europe (Cucchi *et al*., 2005). Although the geographic distribution of the house mouse includes much of the world, these centric fusions have been reported only in some populations from the Orkney Islands (Scotland) to the North African coast and the Middle East, and they produce karyotypes with diploid numbers ranging from 22 to 39 (for review see Piálek *et al*., 2005). Up to now 97 metacentric populations have been recorded and, among all the 171 possible acrocentric combinations, 102 have been reported in wild populations (Piálek *et al*., 2005; Sans-Fuentes *et al*., 2005). The high Rb chromosomal variation in the house mouse can be explained by high mutation and/or high fixation rates (see White, 1978; Winking, 1986; Capanna & Redi, 1995; Nachman & Searle, 1995).

Chromosomal polymorphism in the vicinity of Barcelona is found in one of the well-characterized regions containing Rb populations. This area was first described by Adolph & Klein (1981), who reported the fusions Rb(4.14), Rb(5.15), Rb(9.11), Rb(12.13) and Rb(6.10), and animals with a diploid number ranging between 30 and 40. Later, Gündüz *et al*. (2001) described a new Rb translocation in this area [Rb(3.8)], and hypothesized the presence of a new race (as defined by Hausser *et al*., 1994) with chromosomes Rb(3.8), Rb(4.14), Rb(5.15), Rb(6.10), Rb(9.11) and Rb(12.13) in the homozygous state and with a diploid number of 28. The main characteristics of this area are: (i) it is geographically widespread (5000 km^2), (ii) staggered clines for Rb chromosome have been described (Gündüz *et al*., 2001) and (iii) until now, no

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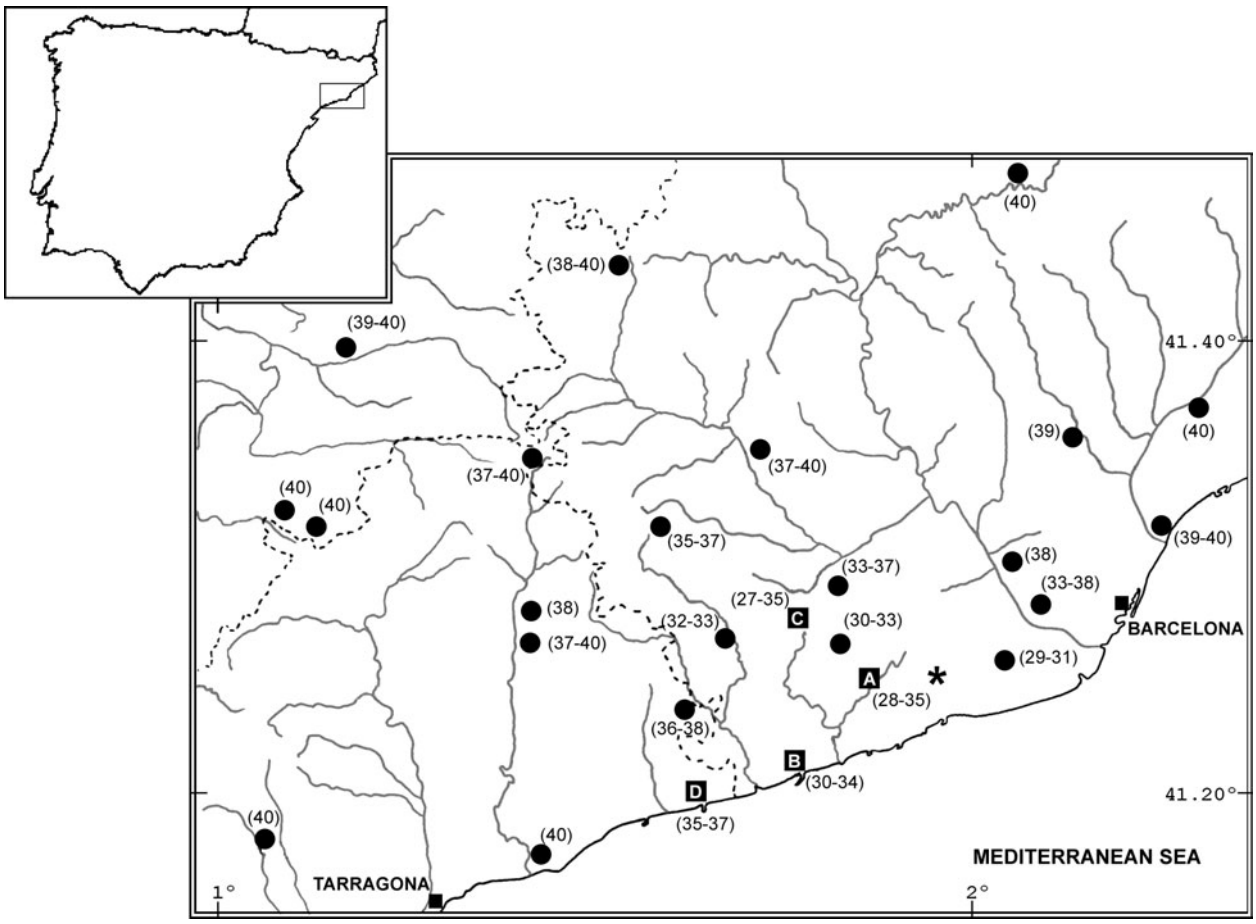

Fig. 1. Known geographic area of the Barcelona Robertsonian polymorphism zone of *M. m. domesticus*. Localities sampled for this study are labelled by a letter (for the names see Table 1). The localities sampled in previous studies are shown by circles (for details see Gündüz *et al*., 2001). The diploid number range for each locality is shown in parentheses. The star indicates the centre of Barcelona Rb Polymorphism area according to Gündüz *et al*. (2001).

chromosomal race has been found. Our surveys in this geographic region revealed a new fusion, Rb(7.17), whose presence has been mentioned in previous studies (Muñoz-Muñoz *et al*., 2003, 2006; Sans-Fuentes *et al*., 2005) but the geographic distribution and frequency of which have never been reported. This fusion is of special interest for several reasons: (i) two chromosomes of very different sizes are involved; (ii) chromosome 7 has been found fused with only a few other chromosomes (Piálek *et al*., 2005); (iii) chromosome 7 is rich in imprinted genes (Coan *et al*., 2005); and (iv) chromosome 17 harbours the t-complex, related to the impairment of fertility in mice (Lyon, 1991; Ardlie, 1998). Here we report data on the distribution and frequency of this fusion.

2. Materials and methods

In this study we report data for 134 mice trapped between 1998 and 2002 in four localities from the Barcelona polymorphic Rb area: Garraf, Vilanova i la Geltrú, La Granada and Calafell (Fig. 1). This sample is part of a wider study that is being conducted in the Barcelona Rb polymorphic area, and corresponds to the sites where animals with Rb(7.17) were detected. Data reported by previous studies in this area for these localities were also included in the analyses ($n = 23$; table 1 in Gündüz *et al*., 2001). It is worth mentioning that in this previous study Rb(7.17) was not detected.

Metaphase karyotypes of mice were prepared following Ford (1966). Slides with spreads were incubated for 12 h at 37 °C. After this period, metaphases were stained using Wright staining for G bands (Mandahl, 1992). On the basis of the analysis of 10 metaphase spreads per animal, chromosomes were identified, following the Committee on Standardized Genetic Nomenclature for Mice (1972).

Since some localities were sampled over several years (La Granada in 1998, 1999, 2000, 2002; Garraf in 1998, 1999), Fst (Wright's fixation index) was calculated for these sites to measure temporal differentiation (Weir & Cockerham, 1984). To test whether Fst values differed significantly from zero, 10 000 genotype permutations between samples were performed. This is a powerful method for detecting

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temporal differences among populations (Goudet *et al*., 1996; Lugon-Moulin *et al*., 1999). We postulate that temporal differentiation was not found, thus samples from the same locality were pooled in subsequent analyses. These analyses were obtained with FSTAT v2.9.3.2 (Goudet, 1995, 2001).

Mean diploid number was calculated for each locality. Metacentric frequencies and mean heterozygosity were also calculated for each locality using BIOSYS-2 (updated version of BIOSYS-1; Swofford & Selander, 1981). To evaluate deviations from Hardy–Weinberg (H-W) equilibrium of each metacentric, an exact probability test was performed for each sample. This test avoids the difficulties of the χ^2 distribution for small samples (Haldane, 1954; Guo & Thompson, 1992). The *P* value was calculated using the complete enumeration method described by Louis & Dempster (1987). H-W equilibrium deviations for the set of all metacentrics in each sample were studied by the Fisher method (Raymond & Rousset, 1995). When multiple tests were used in an analysis, significance levels were adjusted by Bonferroni sequential correction (Rice, 1989). All these tests were performed on minimum samples of five mice using GENEPOP v3.4 (Raymond & Rousset, 1995).

It has been pointed out by some authors that the transmission rate in progeny is related to both total length and arm length ratio of the Rb chromosomes (White, 1973; King, 1993; Castiglia & Capanna, 2000). Therefore, for each metacentric, both length and arm length ratio were estimated. For this purpose we used the chromosome lengths expressed as a percentage of the haploid female complement provided by the Committee on Standardized Genetic Nomenclature for Mice (1972). Total length was estimated as the sum of the lengths of each acrocentric, and the arm length ratio was estimated as the percentage of the shorter arm relative to the longer one. The latter is a measure of the difference in size between the acrocentrics involved in an Rb fusion. For example, an arm length ratio of 50% for Rb(a.b), means that arm 'b' is half the size of arm 'a'. An arm length ratio of 100% indicates that the two arms are the same size.

3. Results and discussion

Of the 134 animals karyotyped, we obtained full data on 120 mice (Fig. 1, Appendix). The remaining 14 animals provided only information on the diploid number (see Table 1 for details). No deviations from H-W equilibrium expectations were detected. The chromosome number of animals from these sites ranged from 27 to 37 (Fig. 1, Appendix). The animals with the lowest diploid number (2n = 27) were found in La Granada (C in Fig. 1), and carried the fusions Rb(3.8), Rb(4.14), Rb(5.15), Rb(6.10), Rb(7.17), Rb(9.11) and Rb(12.13) (Fig. 2). The metacentric with the lowest frequency was Rb(7.17), with values ranging between 0·02 and 0·14 (Table 1). No other metacentric in the Barcelona Rb polymorphic area with such a low frequency range has been reported (table 1 in Gündüz *et al*., 2001). Moreover, Rb(7.17) was distributed in a restricted area. The fusion Rb(7.17) was detected in four localities up to 32 km from the centre of the polymorphism area, located by Gündüz *et al*. (2001) between Garraf and Viladecans (Fig. 1). Although the fusions Rb(3.8) and Rb(6.10) also showed a small geographic distribution in this area, their frequencies were higher than those of Rb(7.17), both reaching values of 0·7. The fusions Rb(4.14), Rb(5.15), Rb(9.11) and Rb(12.13) presented a wider distribution (for details see table 1 in Gündüz *et al*., 2001).

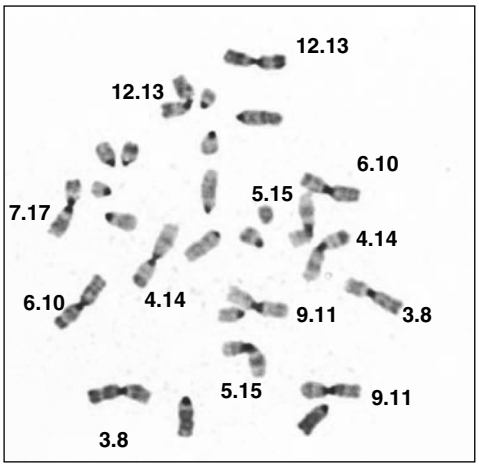

Fig. 2. G-banding staining of metaphase chromosomes of bone marrow cell from a specimen with 2n = 27. All the Rb fusions are shown.

These new samples complement the data reported by Gündüz *et al*. (2001) and suggest the lack of a chromosomal race in the Rb polymorphism zone of Barcelona. The combination of the specific Rb metacentrics observed near Barcelona has not been reported in any other population of *M. m. domesticus* (for review see Piálek *et al*., 2005). Specifically, fusions Rb(7.17), Rb(9.11) and Rb(12.13) have been described only in this area, and therefore this polymorphism is likely to have a partially independent origin. Nevertheless we can not exclude the fact that the others fusions [Rb(3.8), Rb(4.14), Rb(5.15), Rb(6.10)] could have been introduced.

Three of the four localities shown in this study were previously sampled by Gündüz *et al*. (2001) with no report of Rb(7.17). This could be due to the sample size for these sites (table 1 in Gündüz *et al*., 2001). Although the restricted distribution of this mutation observed from these new data could be attributable to a biased sampling, it does not seem likely. The sample size of localities analysed here is higher than that in

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Table 1. *Collection sites corresponding to localities where mice with Rb(7.17) have been captured and its chromosomal characteristics*

Site	km	Latitude/ Longitude	*N*	Mean 2n	H	Frequency of metacentric chromosome 3·8	4·14	5·15	6·10	7·17	9·11	12·13
A. Garraf	7·4	41°17′N, 1°50′E	**7**, 27,(12)[a]	30·2	1·85	0·69	0·87	0·78	0·72	0·07	0·97	0·79
B. Vilanova i la Geltrú	18·6	41°14′N, 1°43′E	**7,(4)**[b], 11,(2)[c]	31·8	1·32	0·11	0·90	0·76	0·21	0·13	0·97	0·95
C. La Granada	21·2	41°22′N, 1°43′E	67	30·9	1·79	0·45	0·99	0·90	0·35	0·14	0·84	0·99
D. Calafell	32·0	41°13′N, 1°34′E	**5**, 15	36·0	1·30	0·00	0·75	0·15	0·00	0·02	0·18	0·90

For sample size (*N*), bold numbers correspond to data from Gündüz *et al*. (2001). Numbers in parentheses indicate animals for which only diploid number is known; these specimens were used only to calculate mean 2n. H, mean number of heterozygote metacentrics per individual.

[a] The number in parentheses corresponds to 1 animal with 2n = 28, 3 with 2n = 29, 3 with 2n = 30, 3 with 2n = 31, 1 with 2n = 32 and 1 with 2n = 33.

[b] The number in parentheses corresponds to 1 animal with 2n = 30, 1 animal with 2n = 31 and 2 animals with 2n = 32.

[c] The number in parentheses corresponds to 2 animals with 2n = 32.

previous studies, and the re-sampling of some of the surroundings localities did not reveal the presence of this mutation (data not shown).

The information available does not allow us to give an accurate explanation of the restricted geographic distribution and low frequency of Rb(7.17), but it is possible that it is the result of the combined action of several factors, such as a recent mutation event and a transmission ratio distortion (TRD) due to the specific characteristics of this metacentric. As for the first concern, data available on laboratory strains suggest that Rb translocations appear spontaneously at high frequency (Nachman & Searle, 1995). Although this hypothesis seems the most plausible, forces acting against fixation can not be excluded *a priori*. Morphological characteristics might be important in the distribution and frequency of the fusions. Thus, the length of the metacentrics has been claimed as possible cause of TRD. For example, Castiglia & Capanna (2000) found a higher transmission rate in the progeny for smaller metacentrics in heterozygous hybrids between Ciuttaducale (2n = 22) and standard races (2n = 40) in the centre of Italy. The total lengths of the metacentrics of the Robertsonian polymorphic area of Barcelona were: Rb(3.8), Lm. 11·10%; Rb(4.14), Lm. 10·20%; Rb(5.15), Lm. 9·59%; Rb(6.10), Lm. 10·45%; Rb(7.17), Lm. 9·17%; Rb(9.11), Lm. 9·01%; Rb(12.13), Lm. 9·97%. Taking into account these values and the frequency of distribution of the metacentrics in this area (see also Gündüz *et al*., 2001), it seems that in this polymorphic zone the total length of these chromosomes is not directly related to their transmission rate. On the other hand, a heterozygous metacentric formed by two chromosomes of very different size may be affected by spatial orientation impairment during meiosis, thereby increasing the probability of malsegregation (White, 1973; King, 1993). The arm length ratios for the metacentrics of the Robertsonian polymorphic area of Barcelona were: Rb(3.8), 81·97%; Rb(4.14), 73·17%; Rb(5.15), 71·90%; Rb(6.10), 85·94%; Rb(7.17), 68·88%; Rb(9.11), 93·35%; Rb(12.13), 94·60%. Since Rb(7.17) is the metacentric in which the two contributing acrocentrics differ most in size (lowest arm length ratio), the arm length ratio may contribute to the low frequency and uncommon occurrence of Rb(7.17).

Other causes related to the low frequency of this fusion could be the genomic characteristics of the chromosomes involved in Rb(7.17). Mouse chromosome 7 is rich in imprinted genes (Coan *et al*., 2005). Some authors have suggested the possibility that some of these genes may fail to be expressed properly in the Rb chromosomes, affecting their segregation (for details see Underkoffler *et al*., 2005). This could be the reason why chromosome 7 has been found fused with only a few different chromosomes (Piálek *et al*., 2005), and why Rb(7.17) occurs in low frequency in Barcelona polymorphic area. Additionally, t-haplotypes, which are variants of chromosome 17 consisting of four non-overlapping inversions in the proximal third of this chromosome, are frequent in house mice and result in different degrees of sterility and often embryonic lethality of both sexes (Hammer *et al*., 1989; Lyon, 1991). Complete t-haplotypes have been detected in standard mice in two localities close to Barcelona (Silver *et al*., 1987), and partial t-haplotypes in mice from Barcelona city, located in the Rb polymorphic area (Figueroa *et al*., 1988). Since Rb fusions show a reduction of recombination in the pericentromeric area (Davisson & Akeson, 1993), the presence of a partial t-haplotype linked to the fusion Rb(7.17) is likely. If so, both the limited geographic distribution of Rb(7.17) and the predominance of the heterozygous state for this fusion (only one animal

showed the translocation in a homozygous state) could be indicative of the presence of a partial t-haplotype linked to this fusion, resulting in the low frequencies for this metacentric. In the light of the available information on the Robertsonian polymorphic area of Barcelona, further studies, both mating and molecular, are needed to investigate these hypotheses.

Appendix. Karyotype characteristics for all mice trapped between 1998 and 2002 in the four localities studied

Location, sex (f, female; m, male), diploid number (2n) and metacentric state (M, homozygote metacentric; H, heterozygote metacentric; A, homozygote acrocentric) are reported.

			Robertsonian translocations						
Locality	Sex	2n	3.8	4.14	5.15	6.10	7.17	9.11	12.13
Garraf	2f, 2m	28	M	M	M	M	A	M	M
	2f	29	H	M	M	M	A	M	M
	1m	29	M	H	M	H	H	M	M
	1f	29	M	M	H	M	A	M	M
	1m	29	M	M	M	H	A	M	M
	3m	29	M	M	M	M	A	M	H
	1f	30	H	M	M	M	A	M	H
	1f	30	M	M	H	H	A	M	M
	1f, 1m	30	M	M	H	H	A	M	M
	1f	30	M	M	H	H	H	M	H
	1m	30	M	M	M	H	A	M	H
	1f	31	H	M	A	M	A	M	M
	1m	31	H	M	H	H	A	M	M
	1m	32	A	H	H	M	A	M	M
	1m	32	A	M	M	A	H	M	H
	1m	32	H	H	H	H	H	M	H
	1m	32	H	M	A	H	A	M	M
	1m	33	H	A	H	H	H	M	H
	1m	35	A	A	H	H	A	M	H
	1f	35	A	H	H	H	A	M	A
Vilanova i la Geltrú	1f	31	A	M	A	H	M	M	M
	1f	31	A	M	H	H	H	M	M
	1f	31	A	M	M	A	H	M	M
	1m	31	H	M	M	A	A	M	M
	1f	32	A	H	M	H	H	M	H
	2f	32	A	M	M	A	A	M	M
	1m	32	H	H	M	A	A	M	M
	1m	32	H	M	H	A	A	M	M
	1f	33	A	H	M	H	A	M	H
	1m	33	H	M	A	A	A	M	M
La Granada	1f, 1m	27	M	M	M	M	H	M	M
	1f	28	M	M	M	H	H	M	M
	2f	29	A	M	M	M	H	M	M
	1f	29	H	M	M	H	H	M	M
	1f	29	M	M	M	A	H	M	M
	1f, 2m	29	M	M	M	H	A	M	M
	1m	30	A	M	H	M	H	M	M
	1m	30	A	M	M	H	H	M	M
	2f	30	A	M	M	M	A	M	M
	2f, 3m	30	H	M	M	A	H	M	M
	3f, 1m	30	H	M	M	H	A	M	M
	1f	30	H	M	M	M	H	H	H
	1f	30	M	M	A	M	A	M	M
	1m	30	M	M	M	H	A	H	M
	1f, 2m	31	A	M	M	H	A	M	M
	1f, 1m	31	H	M	H	H	A	M	M
	7f, 2m	31	H	M	M	A	A	M	M
	1f, 1m	31	H	M	M	H	A	H	M
	1m	31	H	M	M	H	A	M	H
	1f	31	H	M	M	H	H	A	M
	1f	31	M	M	H	H	A	M	H

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Appendix (*cont.*)

			Robertsonian translocations						
Locality	Sex	2n	3.8	4.14	5.15	6.10	7.17	9.11	12.13
	1f	31	M	M	M	A	A	H	M
	1m	32	A	H	M	H	A	M	M
	1f	32	A	M	M	A	A	M	M
	2m	32	A	M	M	H	A	M	H
	1f	32	A	M	M	H	H	H	H
	2f	32	H	M	H	H	A	M	H
	2f, 1m	32	H	M	M	A	A	H	M
	2m	32	H	M	M	A	A	M	H
	1f	32	M	M	M	A	A	A	M
	1f	33	A	H	M	A	H	H	M
	1f	33	A	M	M	H	A	A	M
	1f	33	H	M	H	A	A	M	H
	1f	33	M	M	M	A	A	A	H
	1f	34	A	M	A	H	H	H	H
	1f	34	A	M	H	A	A	H	M
	1m	34	A	M	H	A	A	M	H
	1m	35	A	M	H	A	A	A	M
Calafell	2m	35	A	H	H	A	A	H	M
	2m	35	A	M	A	A	A	H	M
	1f	35	A	M	H	A	A	A	M
	1m	36	A	H	A	A	A	M	H
	1m	36	A	H	A	A	H	H	H
	1m	36	A	M	A	A	A	A	M
	1m	36	A	M	H	A	A	A	H
	4f, 2m	37	A	H	A	A	A	A	M

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