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The HSR on chromosome 1 of the house mouse, *Mus domesticus*: distribution and frequency in Switzerland

ROLAND HÜBNER[1,2,*], TIZIANO MADDALENA[1], JEREMY B. SEARLE[2]† AND PETER VOGEL[1]

[1] *Institut de zoologie et d'écologie animale (IZEA), Université de Lausanne, Lausanne, Switzerland*
[2] *Department of Zoology, University of Oxford, Oxford, UK*

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Summary

A total of 357 house mice (*Mus domesticus*) from 83 localities uniformly distributed throughout Switzerland were screened for the presence of a homogenously staining region (HSR) on chromosome 1. Altogether 47 mice from 11 localities were HSR/+ or HSR/HSR. One sample of 11 individuals all had an HSR/HSR karyotype. Almost all mice with the variant were collected from the Rhone valley (HSR frequency: 61%) and Val Bregaglia (HSR frequency: 81%). For samples from most of the area of Switzerland, the HSR was absent. There was no strong association between the geographic distribution of the HSR and the areas of occurrence of metacentrics. However, at Chiggiogna the HSR was found on Rb (1·3). Possible explanations for the HSR polymorphism are discussed.

1. Introduction

The chromosomes of drug-resistant cell lines and tumour cells sometimes contain segments with uniform G-band staining of medium intensity and variable size, known as homogeneously staining regions (HSRs). In 1982, Adolph discovered an HSR that can be part of an individual's regular karyotype and can be transmitted in the germ line (Traut *et al.* 1984). This HSR is located between bands C5 and D on chromosome 1 in the house mouse from western Europe (*Mus domesticus*; also known as *M. musculus domesticus*). There is a polymorphism for presence or absence of this HSR within wild populations of *M. domesticus*, so that individuals can be classified as HSR/HSR, +/HSR or +/+. The HSR is widespread in western Europe and is particularly associated with populations characterized by metacentric chromosomes (Table 1). In Asia and eastern Europe, populations of the house mouse *M. musculus* (also known as *M. musculus musculus*) may also be characterized by an HSR polymorphism. In this case an HSR-bearing chromosome 1 has two homogeneously staining blocks (Volobouev, 1983), a condition generated from the ancestral single-banded HSR-bearing chromosome by a paracentric inversion (Agulnik *et al.* 1990*b*; Winking *et al.* 1991*a*). Molecular studies have revealed that a 'long-range repeat' family of *ca.* 50 copies on a normal chromosome 1 are present in *ca.* 800 copies on an HSR-bearing chromosome 1 (Purmann *et al.* 1992; Plass *et al.* 1992). These repeats contain two coding regions of 1·3 and 4·5 kb length (Eckert *et al.* 1991), one of which has similarities to the human nuclear autoantigen Sp100 (Hübner, 1992). The amplified genes of the HSR are actively transcribed (Eckert *et al.* 1991).

The HSR in house mice is relatively easily scored, and therefore amenable to population genetic and biogeographical analysis. The presence of an HSR can generally be detected in G-banded or conventionally stained chromosomes, as the chromosome 1 tends to be about a third longer than normal. However, in common with other HSRs, there is length variability and individuals are best karyotyped using G-banding, to avoid missing individuals with a small HSR. The high-copy cluster of repeated sequences in the house mouse stains positively after C-banding, though less darkly than the pericentromeric heterochromatin (Adolph, 1982; Traut *et al.* 1984).

There have been two published studies that specifically address between-site variation in frequency of the HSR in *M. musculus*. Winking *et al.* (1991*a*) studied 157 mice over a small geographic area (the

* Corresponding author. Present address: Lab. Biochimie (B6), Institut de Chimie, Université de Liège, Sart-Tilman, B-4000 Liège, Belgium.
† Present address: Department of Biology, University of York, York, U.K.

Table 1. *Chromosomal characteristics of the 28 populations of* Mus domesticus *where the chromosome 1 HSRs have been found*

Locality	Min. 2n	Metacentrics	Reference
Swabia (Southern Germany)			
Altdorf	38	4·12	c
Hohenentringen	38	4·12	c, e
Holzelfingen	38	4·12	k
Rottenburg	38	4·12	c
Schwalldorf	38	4·12	c
Trasenberg	38	4·12	c, e
Wendelsheim	38	4·12	c
Bichishausen	36	4·12/13·14	c
Blönried	36	4·12/11·13	c
Hard bei Haigerloch	36	4·12/??	k
Indelhausen	36	4·12/8·10/13·14	c, e
Kreßbach	36	4·12/5·15	c
Ödenwaldstetten	36	4·12/5·15/8·10	c, e
Trochtelfingen	36	4·12/5·15	c
near Barcelona (Spain)			
San Martino Sarroca	31	4·14/5·15/6·10/9.11/12·13	b, c, e
near Pavia (Northern Italy)			
Cascina Chiarello	38	16·17	d, e
Grisons (Switzerland)			
Mutten	38	4·12	a, e
Vicosoprano	39	10·11	h, k
Tunisia			
Monastir	21 (XO)	1·11/2·16/3·12/4·6/5·14/7·18/8·9/10·17/13·15	f
Sidi-Bouzid	40	—	f
Belgium			
Jesus-Eick	40	—	g
Caithness and Sutherland (Scotland)			
Ribigill	40	—	j
Achiemore	36	4·10/9·12	i
Bunahoun	36	4·10/9·12	j
Thrumster	36	4·10/9·12	j
Mains of Olrig	33	4·10/6·13/9·12/11·14	i
Seater	32	4·10/6·13/9·12/11·14	i, j
Argentina			
Posadas	40	—	l

Key to references: (a) Gropp *et al.* 1972; (b) Adolph & Klein, 1981; (c) Adolph, 1982; (d) Gropp *et al.* 1982; (e) Traut *et al.* 1984; (f) Saïd *et al.* 1986; (g) Bauchau *et al.* 1989; (h) Winking *et al.* 1991*b*; (i) Searle, 1991; (j) Searle *et al.* 1993; (k) Agulnik *et al.* 1993*c*; (l) Giménez & Bidau, 1993.

Baltic island of Öland) and Sabantsev *et al.* (1993) studied 284 mice over a huge continental expanse (Siberia and middle Asia). From these studies and others on *M. domesticus* (see references in Table 1) it is clear that there is considerable variation in HSR frequency between particular well-studied sites. Thus, at Tomsk (Western Siberia, n =.37), Ottenby (Öland, n = 76), site OK in Novosibirsk (Western Siberia, n = 44) and Hohenentringen (Southern Germany, n = 44), HSR frequencies were 0%, 4%, 51% and 76%, respectively. However, it is not clear whether this merely reflects site-by-site variation or whether there are clear regional differences in the frequency of the HSR. In this paper we report a study that addresses this issue in *M. domesticus*. By collecting house mice uniformly throughout Switzerland we have been able to examine the regional pattern in HSR frequency within an area of *ca.* 40000 km^2.

The study also examines the degree to which the HSR is associated with metacentrics in *M. domesticus*. It is possible that the HSR has tended to be found in areas with metacentrics (Table 1) because cytogeneticists tend to concentrate their activity in such places. Switzerland is divided into substantial areas with or without metacentrics (Hübner, 1992) so, given our uniform coverage, we can produce the first unbiased appraisal of the degree of association between these two types of chromosome markers.

2. Materials and methods

Both adult and immature *M. domesticus* were collected from farms and other buildings throughout Switzerland at various times of the year during the period 1988–91.

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Chromosome preparations were made from bone marrow cells according to the method of Ford (1966). The mice were injected with 0·04% Colcemid (0·01 ml per gram body weight), 1 h before they were killed. For each individual, one slide was stained by the C-banding method of Sumner (1972) and 2–3 slides were exposed to the G-banding treatment of Seabright (1971) or Evans (1986). For the C-banding preparations, at least 10 well-spread metaphase cells were inspected to make chromosome counts and to determine presence/absence of the HSR. For the G-banded preparations, 20 metaphases were analysed to confirm presence of the HSR and identity of any metacentric.

3. Results

Altogether 357 mice from 83 localities in Switzerland and adjacent regions were karyotyped (Table 2, Fig. 1). Fifty-five localities were characterized by 1–9 metacentrics (Table 2). Forty-seven mice from 11 localities were either HSR/+ or HSR/HSR (Table 3) (and the overall frequency of the HSR variant was 10% among the mice examined).

In all HSR/HSR and HSR/+ individuals, the chromosomal position of the HSR was confined to the region between bands C5 and D on chromosome 1, as expected for *M. domesticus* (Traut *et al.* 1984). No major size variation was detected; the length of the HSR was about 20–25% of the length of chromosome 1 (estimated from photographs). The individual from Chiggiogna (Table 3) had a rather larger HSR than normal (about 30% of chromosome 1). In this case, chromosome 1 was part of a huge metacentric chromosome, Rb (1·3), that was very conspicuous in chromosome spreads.

There is a striking pattern of geographic distribution of the HSR within Switzerland. Almost all individuals with this variant were collected from the Rhone valley (Valais) and Val Bregaglia (Table 3, Fig. 1). The Rhone valley is within the western part of Switzerland, which is characterized by mice with the standard $2n = 40$, all-telocentric karyotype. Among the 32 mice (5 sites) sampled from the Rhone valley the frequency of the HSR variant was 61%. Val Bregaglia is within the eastern part of Switzerland, dominated by populations with metacentric chromosomes. In Val Bregaglia itself chromosome number varied between $2n = 34$–40 with individuals homozygous or heterozygous metacentric for arm combinations Rb (4·12), Rb (10·11) and Rb (16·17), or homozygous telocentric (Table 3). This valley is at the contact between two major karyotypic groups: the Rb (4·12) cluster to the north of the Alps and the Rb (16·17) cluster to the south (Hübner 1992). Among the 18 mice (5 sites) sampled from Val Bregaglia the frequency of the HSR variant was 81%.

There was no clear environmental peculiarity associated with populations characterized by the HSR and the mice in these populations were as healthy as those without the HSR. HSR mice were not found preferentially on farms where rodenticides were used.

4. Discussion

In Swiss house mice there is no particular tendency for the HSR and metacentrics to occur together. One of the two geographic regions where the HSR is common is an area where no metacentrics have been found (the Rhone valley) and in most of the places within Switzerland where metacentrics occur no HSRs have been found (Fig. 1).

Therefore, it must be suspected that the apparent geographic association between the HSR and metacentrics, as revealed in Table 1, does not have a biological basis but rather reflects biased sampling. In addition to the Rhone valley, there appear to be at least two other places within the range of *M. domesticus* where the HSR is found well outside the distribution of metacentrics: Sidi-Bouzid in Tunisia (Saïd *et al.* 1986) and Posadas in Argentina (Giménez & Bidau, 1993). Also, although the HSR is found throughout the range of *M. musculus* (Winking *et al.* 1991*a*, Sabantsev *et al.* 1993), metacentrics are only known from one locality in that semispecies (Zima *et al.* 1990).

How do we explain the presence of the HSR in wild populations of the house mouse? The fact that the HSR represents an amplification of a sequence with similarity to an immunological gene (Hübner, 1992) brings to mind the possibility that the HSR has a role in resistance to pathogens. Clearly, pathogens are sometimes distributed patchily over the range of the species; so the high frequency of the HSR in some regions and not others in Switzerland could be compatible with such a role.

Unfortunately, there have been no studies on pathogen resistance of HSR individuals. However, other aspects of fitness have been studied. The viability and fertility of HSR mice have been examined under laboratory and field conditions. The work of Agulnik *et al* (1993*b*) suggests that HSR/HSR *M. musculus* may have low viability and fertility. However, they were working with animals of mixed laboratory mouse-wild mouse background, and Winking *et al.* (1991*a*) found no such effects with equivalent wild-strain animals. Also, Winking *et al.* (1991*b*), working with both *M. domesticus* and *M. musculus*, have found HSR/+ individuals no less fertile than +/+ animals.

Also worth noting are the recent segregation data collected by Ruvinsky and colleagues on *M. musculus*. They found HSR/+ females to show meiotic drive for the HSR, with this meiotic drive conditional on the karyotype of the fertilizing sperm (Agulnik *et al.* 1990*a*, 1993*a*, *b*; see also Pomiankowski & Hurst 1993). If such meiotic drive currently occurs in nature, or has occurred in the past, it would be an important factor in understanding the geographic distribution

Table 2. *Chromosome number (2n) and number of different metacentrics in samples of house mice from Switzerland and adjacent areas. The female from Ecublens had an XO karyotype*

Code	Locality	2n	Number of individuals		Number of different metacentrics
			Females	Males	
AB	Abtwil	24	1	0	—
AG	Agno	24	1	0	8
AL	Altdorf I	32	0	2	4
AT	Altdorf II	31	0	1	5
AR	Araschgen	28	0	1	—
BA	Bassins	40	1	2	—
BW	Basel – W	40	6	1	—
		39	1	0	1
BM	Bauma	24	2	1	8
BE	Bellinzona	24	2	5	8
BO	Bois de Chênes	40	1	0	—
BR	Brederis (Austria)	22	2	7	9
BG	Brig	40	1	0	—
BU	Buchs	22	5	0	9
CA	Chamoson	40	1	3	—
CE	Cheiry	40	3	4	—
CG	Chiggiogna	31	1	0	5
CI	Chiasso	24	9	1	8
CL	Claro	26	1	2	7
CO	Colombier	40	3	2	—
CM	La Combaz d'Aarau	40	0	1	—
CV	Couvet	40	4	4	—
DN	Donath	37	0	1	2
		36	6	0	2
		35	1	0	3
DE	Domat/Ems I	31	1	0	5
DM	Domat/Ems II	30	0	1	5
		29	8	5	6
		28	2	0	6
DO	Dornbirn (Austria)	27	3	0	7
EC	Ecublens	40	0	3	—
		39	1	0	—
EL	Elm	24	0	2	8
ER	Erstfeld I	32	1	1	4
		31	2	0	5
ES	Erstfeld II	34	0	1	3
FI	Fiez	40	2	4	—
FL	Filisur	32	0	1	4
FO	La Fontaine	40	9	2	—
GW	Gähwil	24	1	2	8
GA	Grandson	40	3	0	—
GR	Grüsch	28	1	0	6
		27	3	3	7
		26	2	2	7
GS	Gstaad	40	5	2	—
GU	Guntmadingen	24	0	1	8
HE	Heimenschwand	40	0	1	—
HU	Hünikon	24	5	1	8
HG	Hugstetten I	38	1	1	1
	(Germany)	37	2	0	2
HT	Hugstetten II	36	0	1	2
KA	Kau	22	1	0	9
KU	Küssnacht	24	3	2	8
LA	Lausanne	40	1	0	—
LI	Liestal	39	1	2	1
		38	0	1	2
LU	Lumino	26	5	2	7
		28	1	1	6
MN	Männedorf	24	1	0	8
MD	Malans-Dorf	26	0	1	7
MA	Malans	26	3	2	7

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Table 2 (*cont.*)

Code	Locality	2n	Number of individuals		Number of different metacentrics
			Females	Males	
MI	Milchbuck	24	2	1	8
MO	Montbovon	40	2	1	—
MR	Morzine (France)	40	3	2	—
MU	Müstair	40	3	2	—
NY	Nyon	40	1	2	—
OL	Olivone	24	1	2	8
PR	Preonzo	28	3	2	6
PV	Préverenges	40	2	1	—
PO	Promontogno	38	4	1	1
QU	Quartino	24	5	4	8
RI	Riehen	39	1	0	1
RO	Romoos	26	2	2	7
RU	Rüttenen	40	1	0	—
		39	0	1	1
		38	3	5	2
SW	Schnottwil	40	0	2	—
SM	Schmiedtrued	26	1	1	7
SE	Sementina	24	0	2	8
SP	Spreitenbach	24	3	1	8
SA	St Aubin	40	8	3	—
ST	Steinegg	22	2	0	9
SS	St Sulpice	40	8	8	—
SN	Susten	40	5	3	—
SU	Surava	32	4	6	4
TH	Thayngen	22	1	3	9
TR	Trin	38	1	1	1
TI	Tiengen (Germany)	35	0	1	3
		34	1	1	3
		33	1	0	4
VC	Villa di Chiavenna I (Italy)	35	1	1	3
		34	1	1	3
VT	Villa di Chiavenna II (Italy)	35	1	1	3
		34	1	1	3
VE	Verbier	40	1	4	—
VI	Vicosoprano	39	1	0	1
		38	2	1	1
VS	Visperterminen	40	1	3	—
VP	Vicosoprano II	40	1	0	—
WO	Worb	40	3	0	—
YV	Yverdon	40	0	1	—
ZO	Zofingen	26	1	1	7

and frequency of the HSR in the house mouse. However, once again, this work has involved individuals with mixed laboratory mouse-wild mouse genetic background and it remains to be seen whether it has relevance to wild house mice. Even if meiotic drive for the HSR can be demonstrated in wild *M. musculus*, it may relate to the chromosome 1 paracentric inversion (Agulnik *et al.* 1993*a*) which does not occur in *M. domesticus*.

How do our studies of *M. domesticus* in Switzerland add to this understanding of the HSR polymorphism in the house mouse? First, we found a high proportion of homozygotes among those individuals carrying the HSR, in support of the contention of Winking *et al.* (1991*a*) that HSR/HSR mice do not suffer great inviability. Several of our samples (including one of 11 individuals) consisted solely of HSR/HSR mice (Table 3). Secondly, our data confirm the existence of extreme between-site variation in HSR frequency, with some samples (of up to 16 individuals) with 0% and others, as described above, with 100% (Tables 2 and 3). Thirdly, our data suggest that the HSR is absent or at very low frequency over much of Switzerland (Fig. 1). This situation may be the norm throughout the distribution of the house mouse; published reports have been biased towards information on where the HSR has been found rather than where it has been looked for and not found. Fourthly, we have shown that there are clear regional differences in the frequency of the HSR over the geographic area of Switzerland. The HSR is at high frequency in some regions and absent (or at very low frequency) in others. If the occurrence of the HSR relates to pathogen resistance, it would be important to explain

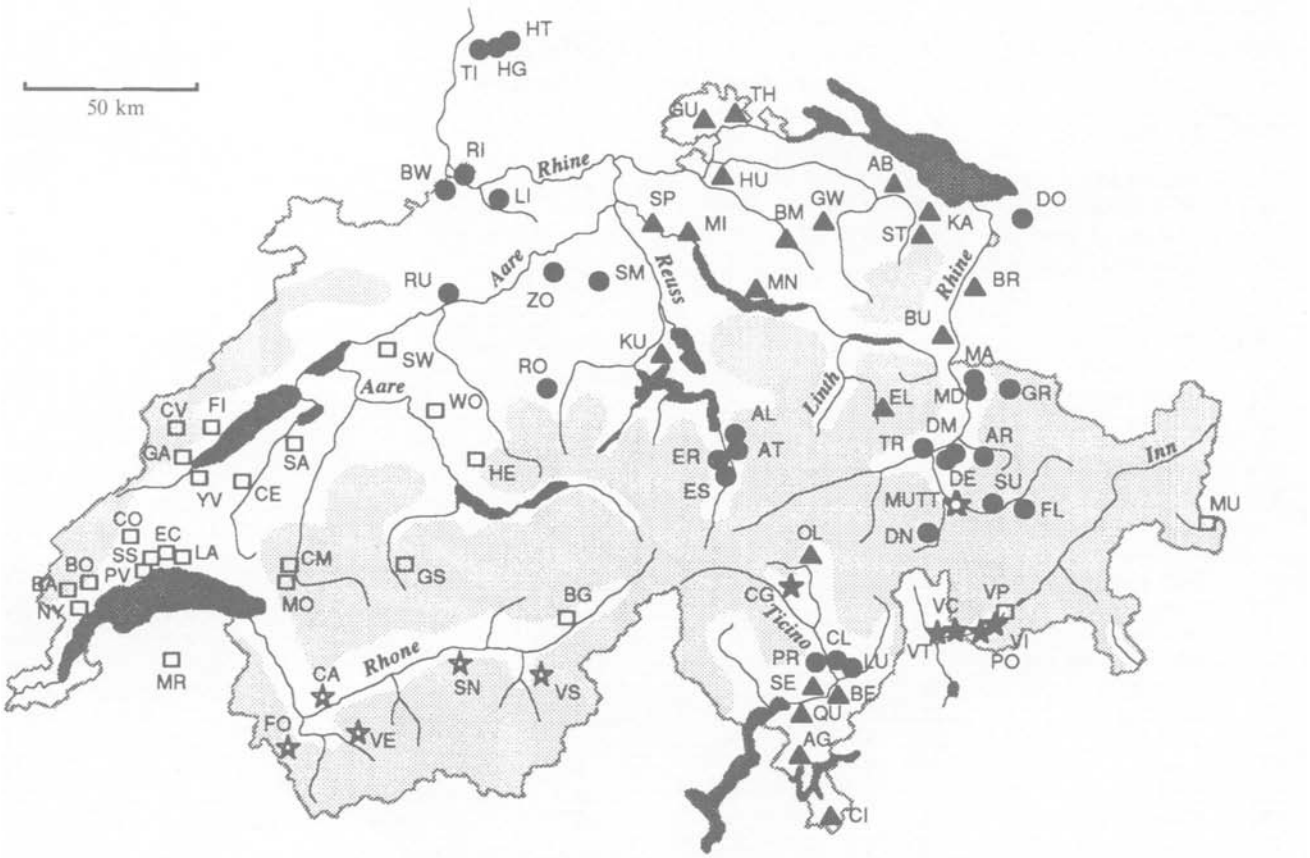

Fig. 1. Collection localities of house mice from Switzerland and adjacent areas (*i.e.* Italian entrance of Val Bregaglia, Vorarlbeg in Austria, Freiburg area in southern Germany, Haute Savoie in France). Symbols for populations: open squares = all-telocentric ($2n = 40$) populations, closed circles = metacentric ($2n \geqslant 26$) populations, closed triangles = metacentric ($2n = 22$ or 24) populations, open stars = all-telocentric populations with chromosome 1 HSR, closed stars = metacentric populations with chromosome 1 HSR, closed star with white centre (MUTT) = Mutten population from Table 1. Two-letter codes correspond to localities given in Table 2. Shading represents a mean January temperature of below −2 °C. Major rivers are indicated.

Table 3. *Characteristics of the samples where the chromosome 1 HSR was encountered in Switzerland*

				Karyotype			
Code	Locality	2n	N	HSR/HSR	HSR/+	+/+	Different metacentrics
	Valais						
CA	Chamoson	40	4	—	4	—	—
FO	La Fontaine	40	11	11	—	—	—
SN	Susten	40	8	—	3	5	—
VE	Verbier	40	5	—	5	—	—
VS	Visperterminen	40	4	3	—	1	—
	Upper Ticino						
CG	Chiggiogna	31	1	1	—	—	1·3/2·14/4·12/10·11/13·16
	Val Bregaglia						
VP	Vicosoprano II	40	1	—	1	—	—
VI	Vicosoprano I	39	1	—	1	—	10·11
		38	3	—	1	2	10·11
PO	Promontogno	38	5	5	—	—	10·11
VC	Villa di Chiavenna I	35	2	2	—	—	4·12/10·11/16·17
		34	2	2	—	—	4·12/10·11/16·17
VT	Villa di Chiavenna II	35	2	2	—	—	4·12/10·11/16·17
		34	2	2	—	—	4·12/10·11/16·17

this geographic pattern in terms of the epidemiology of the disease(s).

So far, we have discussed selective factors that may be important in explaining the HSR polymorphism. But is it possible to discount the null hypothesis that the HSR variant is selectively neutral?

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Neutral polymorphisms are transient; given sufficient time either the ancestral type or derived variant will go extinct (Kimura, 1983). The HSR polymorphism appears to predate the separation of *M. musculus* and *M. domesticus*, which may have occurred 500000 years ago (Winking *et al.* 1991*b*; Boursot *et al.* 1993). At first sight, this long survival of the polymorphism appears to argue against neutrality, but if the effective population size of the house mouse has been large since the HSR variant arose (as is probable), then survival of the polymorphism is not surprising (Kimura, 1983).

On the basis of present information, founder effects and genetic drift can explain the distribution of the HSR variant in Swiss house mice as readily as selection. House mice apparently invaded Switzerland within the last 10000 years (Auffray *et al.* 1990; Hübner, 1992). If the invaders were largely +/+ but with some individuals carrying the HSR variant, then as a neutral marker, the HSR would have remained at low frequency or become extinct over most of Switzerland. However, by chance, HSR mice could have come to dominate small founding populations of certain alpine valleys. The high frequency of the HSR variant in the Rhone valley and Val Bregaglia could have arisen in this fashion.

So, for *M. domesticus* at least, it cannot be disproved that the HSR variant is selectively neutral, even though HSR individuals have a substantial amplification of a transcribed gene. Clearly, a combination of further studies on (*a*) fitness and segregation, (*b*) molecular genetics and physiology, and (*c*) population genetics, are all necessary to understand this strange polymorphism.

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