



**HAL**  
open science

## Minisatellite Markers Reveals Frequent Genetic Exchanges among House Mouse Subspecies

Eric Rivals

► **To cite this version:**

Eric Rivals. Minisatellite Markers Reveals Frequent Genetic Exchanges among House Mouse Subspecies. Rencontres ALPHY - Génomique Evolutive, Bioinformatique, Alignement et Phylogénie, Feb 2007, Montpellier, France. pp.1. lirmm-00195524

**HAL Id: lirmm-00195524**

**<https://hal-lirmm.ccsd.cnrs.fr/lirmm-00195524v1>**

Submitted on 11 Dec 2007

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

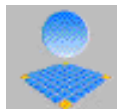
# Minisatellite Markers Reveals Frequent Genetic Exchanges among House Mouse Subspecies

Eric Rivals

rivals@lirmm.fr

LIRMM, CNRS, Université Montpellier 2

<http://www.lirmm.fr/~rivals>



# Outline

1. Minisatellite data
2. Methods
  - 2.1 Protocol
  - 2.2 Molecular Divergence Estimation - Alignment
  - 2.3 Robustness and Confidence
3. Results
  - 3.1 Coalescence
  - 3.2 Intruders
4. Conclusion

# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom

# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom
- ▶ > 5% in bacteria *E. ruminatum*

# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom
- ▶ > 5% in bacteria *E. ruminatum*
- ▶ pattern between 7 and 100 bps, up to 20 Kb long

# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom
- ▶ > 5% in bacteria *E. ruminatum*
- ▶ pattern between 7 and 100 bps, up to 20 Kb long
- ▶ **Polymorphism**: Hypervariable in *H.s.*, (> 0.5% per gamete)

# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom
- ▶ > 5% in bacteria *E. ruminatum*
- ▶ pattern between 7 and 100 bps, up to 20 Kb long
- ▶ **Polymorphism**: Hypervariable in *H.s.*, (> 0.5% per gamete)  
Simply variable in *M.m.*(add > 3 units: <  $5 \cdot 10^{-6}$  per gamete)



# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom
- ▶ > 5% in bacteria *E. ruminatum*
- ▶ pattern between 7 and 100 bps, up to 20 Kb long
- ▶ **Polymorphism**: Hypervariable in *H.s.*, (> 0.5% per gamete)  
Simply variable in *M.m.*(add > 3 units: <  $5 \cdot 10^{-6}$  per gamete)
- ▶ Mouse: simple intra-allelic tandem duplication and contraction  
[Bois et al., 2002]

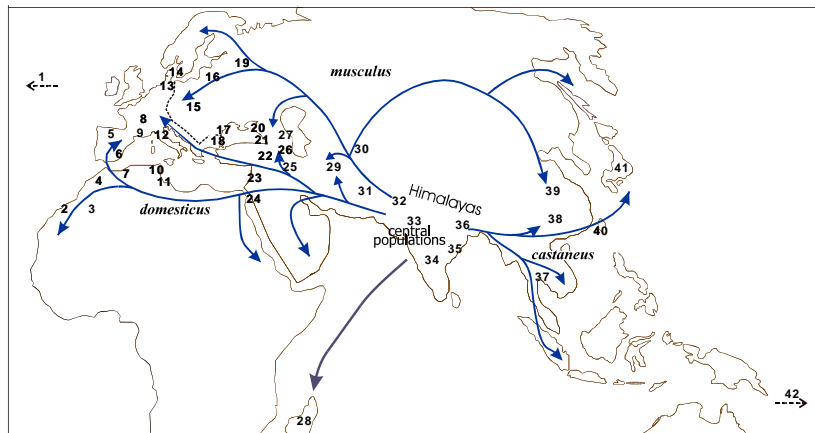
# Minisatellites (MS)

- ▶ **Tandem repeat** loci present in genome of all kingdom
- ▶ > 5% in bacteria *E. ruminatum*
- ▶ pattern between 7 and 100 bps, up to 20 Kb long
- ▶ **Polymorphism**: Hypervariable in *H.s.*, (> 0.5% per gamete)  
Simply variable in *M.m.*(add > 3 units: <  $5 \cdot 10^{-6}$  per gamete)
- ▶ Mouse: simple intra-allelic tandem duplication and contraction  
[Bois et al., 2002]
- ▶ MS informative for intra-species evolution

# Minisatellite data

- ▶ Four minisatellite loci: MMS 24, 26, 80, and 30 respectively on chromosomes 7 (22 cM), 9 (68 cM and 79 cM), and X (43 cM)
- ▶ Panel of 116 individuals of various geographical origins
- ▶ Maps obtained by MVR-PCR as in [\[Bois et al., 2002\]](#)
- ▶ High diversity in length and array structure  
haplotypic diversity ( $H_e$ ) in [0.90, 0.99]

# Geographical origin of wild mice



# Mouse minisatellite maps of MMS30 (X chr)

**Repeat unit:** 39 bps

Variant code    sequence

*K*    =    "aggagattcagttcaca**C**tatacagaagatggtgtcagc"

*L*    =    "aggagattcacttcaga**G**tatacagaagatggtgtcagc"

# Mouse minisatellite maps of MMS30 (X chr)

**Repeat unit:** 39 bps

Variant code    sequence

*K*    =    "aggagattcagttcaca**C**tatacagaagatggtgtcagc"

*L*    =    "aggagattcacttcaga**G**tatacagaagatggtgtcagc"

Example of **maps** in wild mice

ID (species, location) map

---

SPR\_FRAN\_Ardeche    KGKGLKHLKLLKYKG

CEN\_INDE\_Gauhati    GKKKKWGGKKYKWKGWGHoGoKWKKKo**L**YY

CEN\_INDE\_Varanasī    GKKKKWGGKKYKWKGWGHoGoKWKKKo**K**YY

# Mouse minisatellite maps of MMS30 (X chr)

**Repeat unit:** 39 bps

Variant code    sequence

*K*    =    "aggagattcagttcaca**C**tatacagaagatggtgtcagc"

*L*    =    "aggagattcacttcaga**G**tatacagaagatggtgtcagc"

Example of **maps** in wild mice

ID (species, location) map

---

SPR\_FRAN\_Ardeche    KGKGLKHLKLLKYKG

CEN\_INDE\_Gauhati    GKKKKWGGKKYKWKGWGHoGoKWKKKo**L**YY

CEN\_INDE\_Varanasī    GKKKKWGGKKYKWKGWGHoGoKWKKKo**K**YY

DOM\_GEOR\_Adjarie    GYKKKWGKLYoWKGWKGKoGGYWYKKoK**Y**YYKG

DOM\_OCEA\_Tahiti    GYKKKWGKLYoWKGWKGKoGGYWYKKoK**KK**YYYYKG

MUS\_GEOR\_Tbilissi    GYYKGYKYKGYKKKWGKoKYoWKYYKG

---

# Methods



# Protocol of the analysis

Input: set of sequences (maps)

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]
2. Inference of evolutionary tree from the distances

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]
2. Inference of evolutionary tree from the distances  
*FastME* [Desper, Gascuel, 2002]

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]
2. Inference of evolutionary tree from the distances  
*FastME* [Desper, Gascuel, 2002]
3. Test robustness of the trees w.r.t. alignment parameters

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]
2. Inference of evolutionary tree from the distances  
*FastME* [Desper, Gascuel, 2002]
3. Test robustness of the trees w.r.t. alignment parameters  
Criterion: Percentage of explained variance (VAF)

# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]
2. Inference of evolutionary tree from the distances  
*FastME* [Desper, Gascuel, 2002]
3. Test robustness of the trees w.r.t. alignment parameters  
Criterion: Percentage of explained variance (VAF)
4. Assess confidence of the tree internal nodes



# Protocol of the analysis

Input: set of sequences (maps)

1. Comparison all against all  $\Rightarrow$  pairwise distance matrix  
*MS\_Align* [Bérard, Rivals, 2003]
2. Inference of evolutionary tree from the distances  
*FastME* [Desper, Gascuel, 2002]
3. Test robustness of the trees w.r.t. alignment parameters  
Criterion: Percentage of explained variance (VAF)
4. Assess confidence of the tree internal nodes  
Criterion: Rate of elementary well designed quartets (Re)  
*Qualitree* [Garreta, Guénoche, 2000]

# Evolutionary model

- ▶ Substitution : WGY  $\rightarrow$  WKY

# Evolutionary model

- ▶ Substitution : WGY  $\rightarrow$  WKY
- ▶ Deletion: WGY  $\rightarrow$  WY

# Evolutionary model

- ▶ Substitution : WGY  $\rightarrow$  WKY
- ▶ Deletion: WGY  $\rightarrow$  WY
- ▶ Insertion (dual): WY  $\rightarrow$  WGY

# Evolutionary model

- ▶ Substitution : WGY  $\rightarrow$  WKY
- ▶ Deletion: WGY  $\rightarrow$  WY
- ▶ Insertion (dual): WY  $\rightarrow$  WGY
- ▶ Tandem duplication: WKY  $\rightarrow$  WKKY

# Evolutionary model

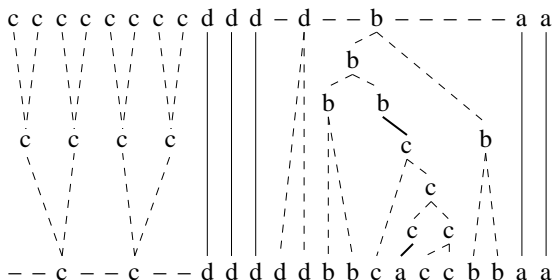
- ▶ Substitution : WGY  $\rightarrow$  WKY
- ▶ Deletion: WGY  $\rightarrow$  WY
- ▶ Insertion (dual): WY  $\rightarrow$  WGY
- ▶ Tandem duplication: WKY  $\rightarrow$  WKKY
- ▶ Tandem contraction (dual): WKKY  $\rightarrow$  WKY

# Evolutionary model

- ▶ Substitution : WGY  $\rightarrow$  WKY
- ▶ Deletion: WGY  $\rightarrow$  WY
- ▶ Insertion (dual): WY  $\rightarrow$  WGY
- ▶ Tandem duplication: WKY  $\rightarrow$  WKKY
- ▶ Tandem contraction (dual): WKKY  $\rightarrow$  WKY

$\Rightarrow$  variation in their number of units

## Example of an alignment of 2 maps



An alignment produced by *MS\_Align* between maps `ccccccccdddbbaa` and `ccccccccdddbbaa` with the costs  $A = C = 1$ ,  $I = D = 40$ ,  $\mathcal{M}(a, b) = \mathcal{M}(a, d) = \mathcal{M}(b, d) = 20$ ,  $\mathcal{M}(a, c) = \mathcal{M}(b, c) = \mathcal{M}(c, d) = 10$ . Its cost is  $14 \times A + \mathcal{M}(b, c) + \mathcal{M}(c, a) = 34$ . Plain lines: matches, dashed lines: amplifications and contractions, bold lines: mutations.



## Percentage of explained variance (VAF)

$$\text{VAF} = 1 - \frac{\sum_{(i,j):i<j}(D(i,j) - T(i,j))^2}{\sum_{(i,j):i<j}(D(i,j) - D_m)^2}$$

where

$D(i,j)$  : alignment distance between  $i$  and  $j$

$T(i,j)$  : tree distance between  $i$  and  $j$

$D_m$  : average alignment distance over all pairs  $(i,j)$

Value in  $[0, 1]$

## Rate of elementary well designed quartets (Re)

For an internal edge  $e$ , for all quartets  $(i, j, k, l)$   
s.t.  $e$  splits  $(i, j)$  and  $(k, l)$ :

$R(e)$  = percentage of these quartets satisfying

$$(D(i, j) + D(k, l)) < \min(D(i, l) - D(j, k), (D(i, k) - D(j, l)))$$

where

$D(i, j)$  : alignment distance between  $i$  and  $j$

Value in  $[0, 1]$

# Results

## Identical alleles

Locus	2	3	$\geq 4$	Total	$\neq$ origin	$\neq$ subspecies
MMS 24	7	4	1	27	8 (18)	0 (1)
MMS 26	6	2	3	36	10 (26)	5 (1)
MMS 30	9	2	1	38	8 (18)	2 (0)
MMS 80	10	8	0	44	10 (22)	0 (0)

## Identical alleles

Locus	2	3	$\geq 4$	Total	$\neq$ origin	$\neq$ subspecies
MMS 24	7	4	1	27	8 (18)	0 (1)
MMS 26	6	2	3	36	10 (26)	5 (1)
MMS 30	9	2	1	38	8 (18)	2 (0)
MMS 80	10	8	0	44	10 (22)	0 (0)

### Example

At **MMS 30**: DOM\_BULG\_Vlas\_DBV,  
DOM\_TUNI\_Monastir\_22MO, and SPR\_MARO\_Azzemour\_9852  
GYKKKGWKG<sub>o</sub>GGYWYKK<sub>o</sub>KKKYYYKG

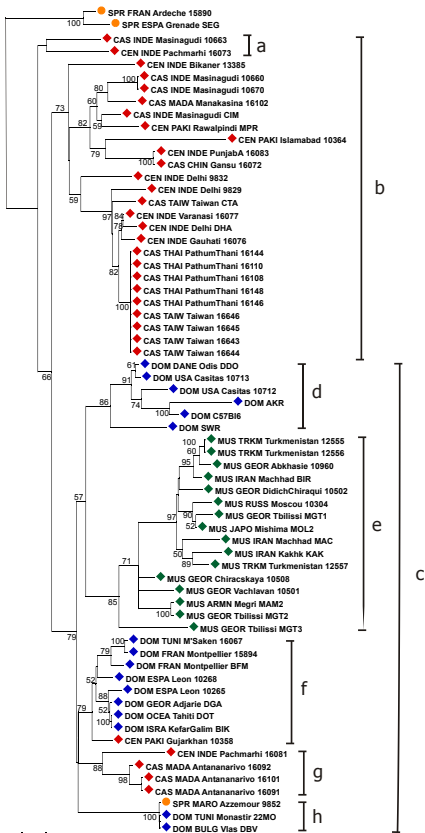
## Identical alleles

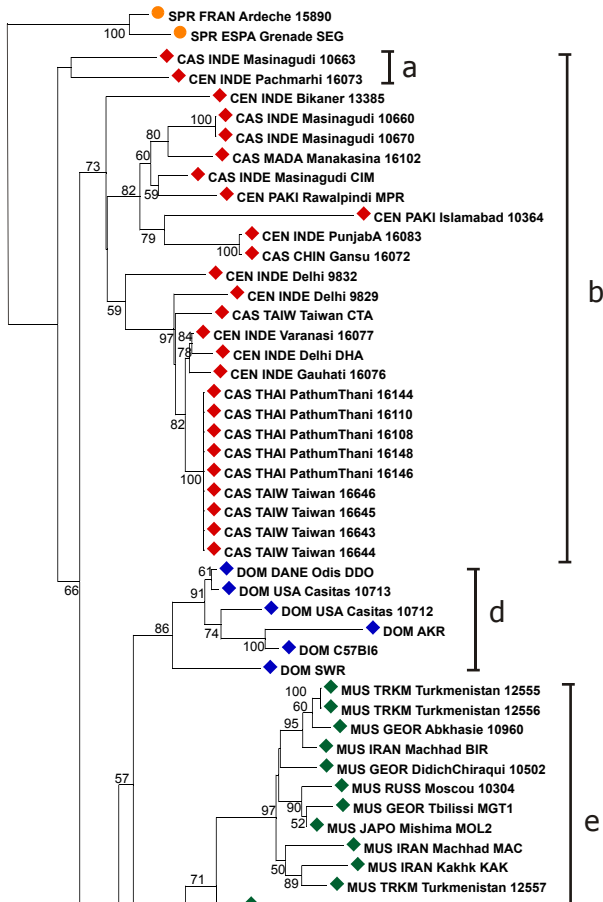
Locus	2	3	$\geq 4$	Total	$\neq$ origin	$\neq$ subspecies
MMS 24	7	4	1	27	8 (18)	0 (1)
MMS 26	6	2	3	36	10 (26)	5 (1)
MMS 30	9	2	1	38	8 (18)	2 (0)
MMS 80	10	8	0	44	10 (22)	0 (0)

### Example

**At MMS 30:** DOM\_BULG\_Vlas\_DBV,  
DOM\_TUNI\_Monastir\_22MO, and SPR\_MARO\_Azzemour\_9852  
GYKKKGWGK<sub>o</sub>GGYWYKK<sub>o</sub>KKKYYYKG

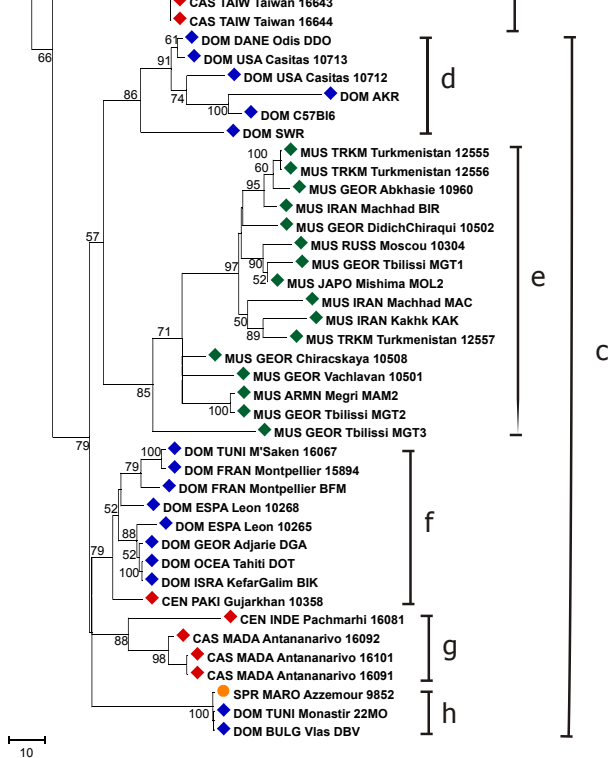
**At MMS 26:** CEN\_INDE\_Dehli\_DHA; DOM\_OCEA\_Tahiti\_DOT  
YGGGGGGGGAGGGGAGAAGGYAAGGGGAAAAGAGAAGAAGGGG

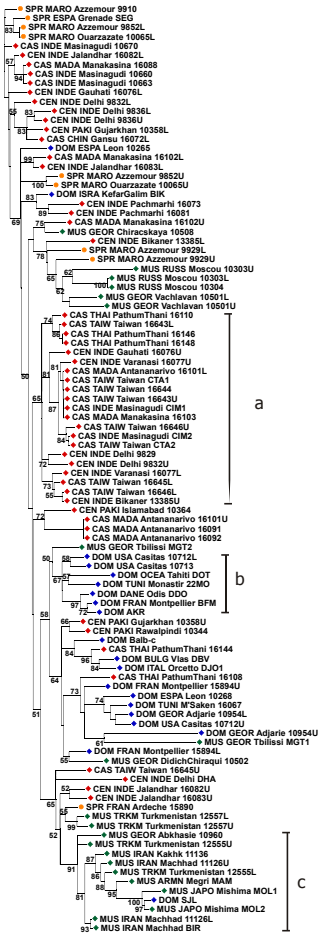


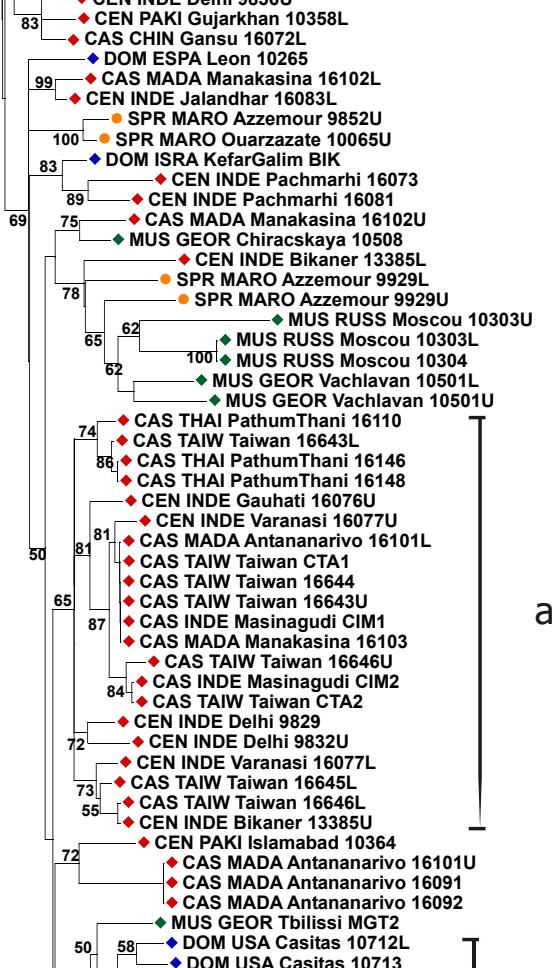


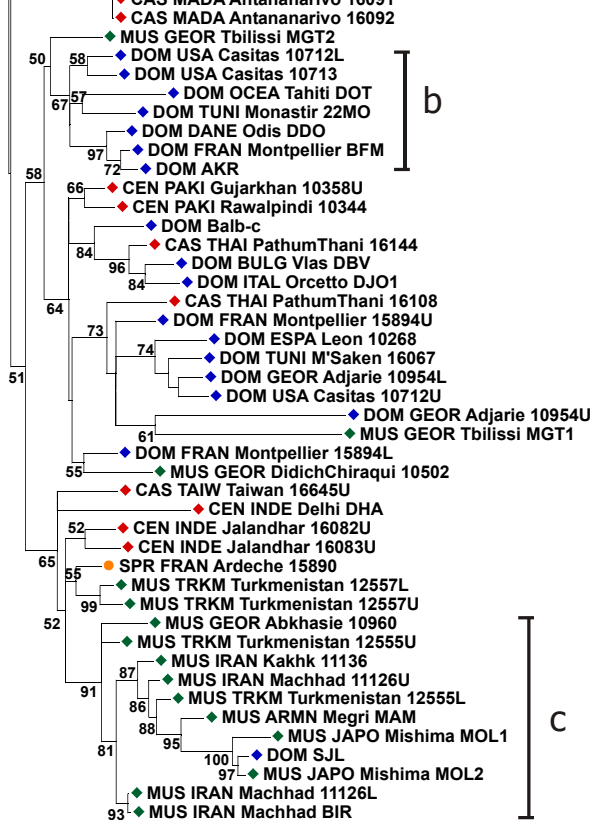


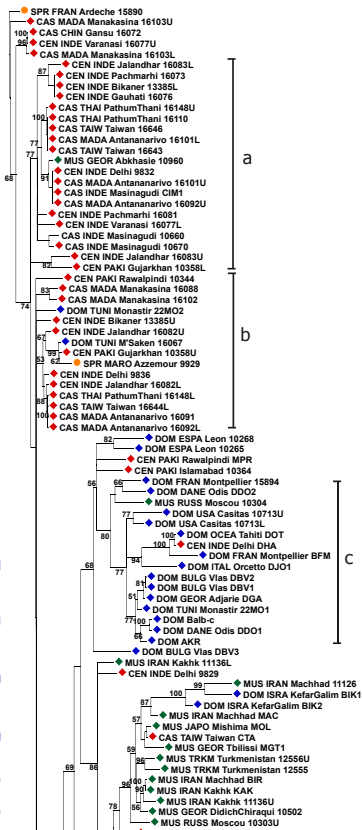
# MMS 30 coalescence

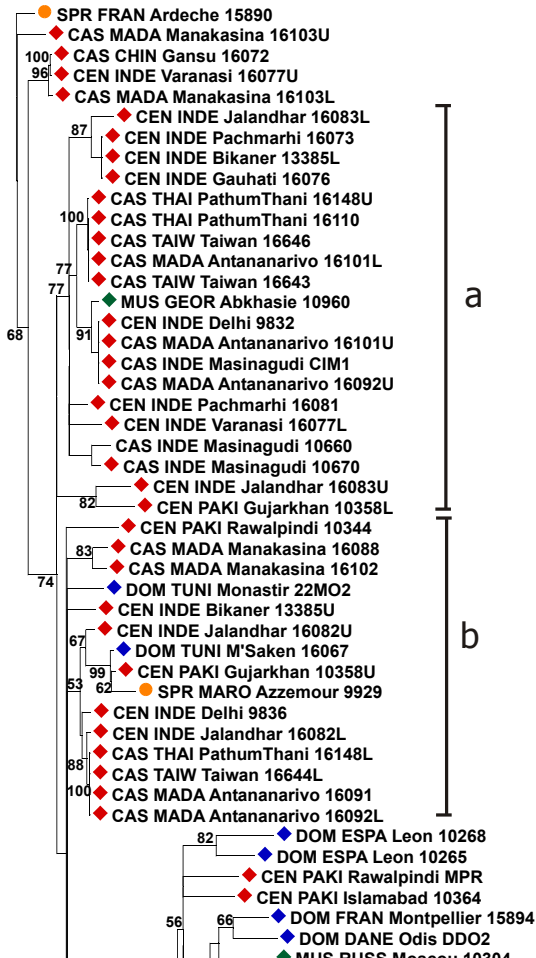




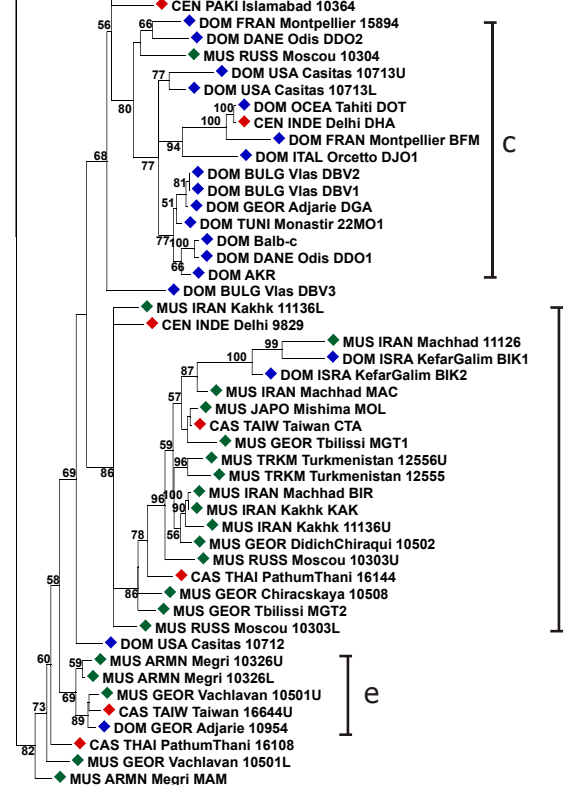


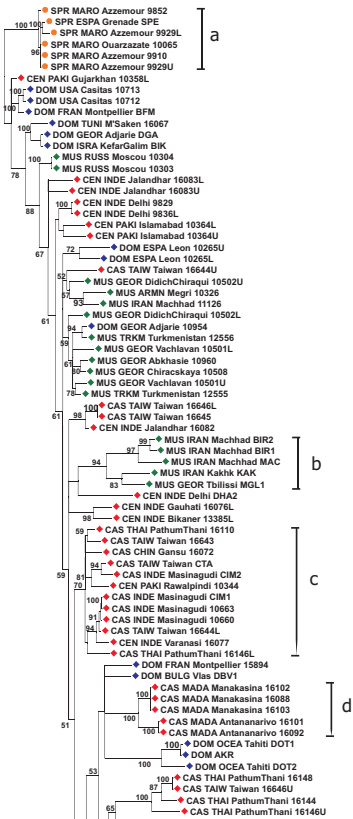




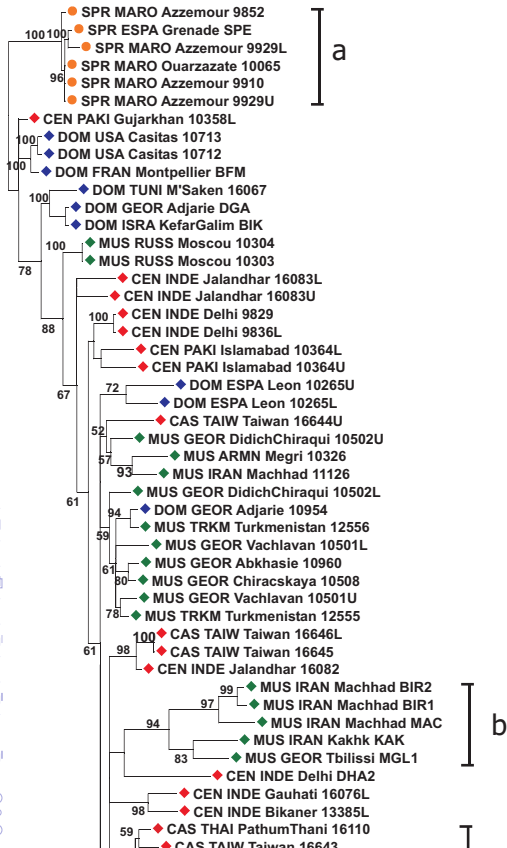


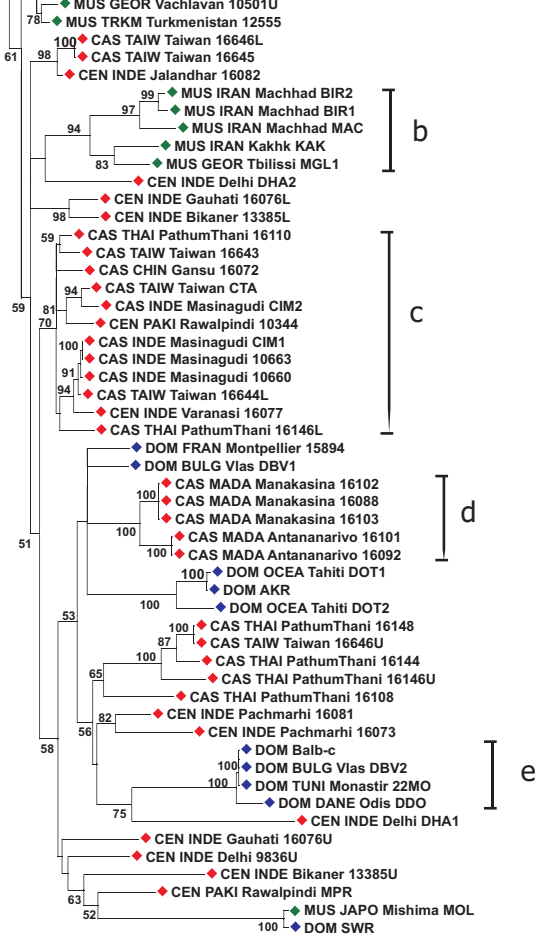
# MMS 26 coalescence











# Intruders

Locus ID		clade	Average distance to			
			CAS	CEN	DOM	MUS
24	CAS THAI Pathumtani 16108	DOM	52	53	40	61
24	CAS THAI Pathumtani 16144	DOM	45	47	37	60
24	DOM SJL	MUS	71	74	74	53
26	MUS GEOR Abkhasie 10960	CAS	23	34	84	72
26	CEN INDE Dehli DHA	DOM	99	96	58	91
26	MUS RUSS Moscou 10304	DOM	69	62	60	92
26	CAS TAIW Taiwan CTA	MUS	77	80	73	42
80	DOM GEOR Adjarie 10954	MUS	37	39	56	28
80	DOM BULG Vlas DBV1	CAS	40	50	50	51
80	DOM FRAN Montpellier 15894	CAS	42	49	51	50

# MMS24 intruders alignments

DOM_ESPA_Leon	CTCCC~CCT~~oTCTTCoTC~oTCToT~~oTTCCCC~~
DOM_USA_Casit	CTCCo~CCo~oo~CTTCoTC~oTCTo~~ooTTCCCC~~
DOM_GEOR_Adja	CTCCT~CCTT~o~CTTCoTCCoTCTo~~ooTTCCCC~~
DOM_TUNI_M'Sa	CTCCT~CCT~~oTCTTCoTC~oTCTo~~ooTTC~~~~
DOM_FRAN_Mont	CTCCT~CCT~~oTCTTC~~~~oTCTT~~~oTTCCCC~~
CAS_THAI_Path	CTCCT~CCT~~oTCTTC~~~~oTCoT~~~CT~~~~
CAS_THAI_Path	CTCCT~CCTT~~TCTTCTTC~TTCTTTT~~TTC~~~~
DOM_BULG_Vlas	CTCCTTC~TT~~TCTTCTTC~TTCTTTT~~TTCCCCTC
DOM_ITAL_Orce	CTCCT~CCTT~~TCTTCTTC~TTCTTT~~oTTCCCCT~
	**** *.. **** **.

## MMS30 intruders alignments

```
DOM ESPA  GYKKKWGK LKYLWKGWGK oGGYWYKK oKKK~YYY~KG
DOM TURQ  GYKKKWGK WKY oWKGWGK oGGYLYKK oKKK~YYY~KG
DOM TURQ  GYKKKWGK WKY oWKGWGK oGGYLYKK oK~~~YYY~KG
DOM GEOR  GYKKKWGK LKY oWKGWGK oGGYWYKK oK~~~YYY~KG
DOM ISRA  GYKKKWGK LKY oWKGWGK oGGYWYKK oKKK~YYY~KG
DOM ESPA  GYKKKWGK LKW oWKGWGK oGGYWYKK oKKK~YYY~KG
DOM FRAN  GYKKKWGK LKYLWKGWGK WGGYWYKK oKKK~YY~~~G
DOM FRAN  GYKKKWGK LKY oWKGWGK WGGY WYKK oKKK~YY~~~G
DOM ITAL  GYKKKWGK LKY oWKGWGK oGGYWYKK oKKK~YY~~~G
DOM TURQ  GYKKKWGK LKY oWKGWGL WGGYWYKK oKKK~YYY~KG
CEN PAKI  GYKKKWGK oKYKWKWGK oGGYWYKK oKKK~YYY~KG
CEN INDE  GYKKKWGL WKY o oK oWGL WGGYWYKK oKKKKYY~~KG
CAS MADA  GYKKK-GLLKYLoK GWGLoGGKWKKK oKKKKYY~~KG
CAS MADA  GYKKKWGL LKYL oK GWGLoGGKWKKK oKKKKYY~~KG
***** . . . . * . ** . ** .      **   **   .*
```

## MMS30 intruders alignments

```
DOM ESPA  GYKKKWGK LKYLWKGWGK oGGYWYKK oKKK~YYY~KG
DOM TURQ  GYKKKWGK WKY oWKGWGK oGGYLYKK oKKK~YYY~KG
DOM TURQ  GYKKKWGK WKY oWKGWGK oGGYLYKK oK~~~YYY~KG
DOM GEOR  GYKKKWGK LKY oWKGWGK oGGYWYKK oK~~~YYY~KG
DOM ISRA  GYKKKWGK LKY oWKGWGK oGGYWYKK oKKK~YYY~KG
DOM ESPA  GYKKKWGK LKW oWKGWGK oGGYWYKK oKKK~YYY~KG
DOM FRAN  GYKKKWGK LKYLWKGWGK WGGYWYKK oKKK~YY~~~G
DOM FRAN  GYKKKWGK LKY oWKGWGK WGGY Y Y Y K K oKKK~YY~~~G
DOM ITAL  GYKKKWGK LKY oWKGWGK oGGYWYKK oKKK~YY~~~G
DOM TURQ  GYKKKWGK LKY oWKGWGL WGGYWYKK oKKK~YYY~KG
CEN PAKI  GYKKKWGK oKYKWKWGK oGGYWYKK oKKK~YYY~KG
CEN INDE  GYKKKWGL WKY o o K o WGL WGGYWYKK oKKKKYY~~KG
CAS MADA  GYKKK-GL LKYL oKGWGL oGGKWKKK oKKKKYY~~KG
CAS MADA  GYKKKWGL LKYL oKGWGL oGGKWKKK oKKKKYY~~KG
***** . . . . * . ** . ** .      **   **   .*
```

## MMS30 intruders alignments

```
DOM ESPA  GYKKKWGK LKYLWKGWGK o GGYWYKK o KKK~YYY~KG
DOM TURQ  GYKKKWGK WKY o WKGWGK o GGYLYKK o KKK~YYY~KG
DOM TURQ  GYKKKWGK WKY o WKGWGK o GGYLYKK o K~YY~YY~KG
DOM GEOR  GYKKKWGK LKY o WKGWGK o GGYWYKK o K~YY~YY~KG
DOM ISRA  GYKKKWGK LKY o WKGWGK o GGYWYKK o KKK~YYY~KG
DOM ESPA  GYKKKWGK LKW o WKGWGK o GGYWYKK o KKK~YYY~KG
DOM FRAN  GYKKKWGK LKYLWKGWGK WGGYWYKK o KKK~YY~YY~G
DOM FRAN  GYKKKWGK LKY o WKGWGK WGGY WYKK o KKK~YY~YY~G
DOM ITAL  GYKKKWGK LKY o WKGWGK o GGYWYKK o KKK~YY~YY~G
DOM TURQ  GYKKKWGK LKY o WKGWGL WGGY WYKK o KKK~YYY~KG
CEN PAKI  GYKKKWGK o KYKWKWGK o GGYWYKK o KKK~YYY~KG
CEN INDE  GYKKKWGL WKY o o K o WGL WGGY WYKK o KKKKYY~KG
CAS MADA  GYKKK-GL LKYL o KGWGL o GGKWKKK o KKKKYY~KG
CAS MADA  GYKKKWGL LKYL o KGWGL o GGKWKKK o KKKKYY~KG
***** . . . . * . ** . ** .      **   **   . *
```

# Conclusion



# Conclusion

- ▶ MS analysis revealed:
  1. species-wide genetic flow
  2. past and present exchanges within the species range

# Conclusion

- ▶ MS analysis revealed:
  1. species-wide genetic flow
  2. past and present exchanges within the species range
- ▶ when handled with appropriate comparison algorithms  
[Bérard, Rivals, 2003]

# Conclusion

- ▶ MS analysis revealed:
  1. species-wide genetic flow
  2. past and present exchanges within the species range
- ▶ when handled with appropriate comparison algorithms  
[Bérard, Rivals, 2003]
- ▶ MS versus **SNPs**

# Conclusion

- ▶ MS analysis revealed:
  1. species-wide genetic flow
  2. past and present exchanges within the species range
- ▶ when handled with appropriate comparison algorithms [Bérard, Rivals, 2003]
- ▶ MS versus SNPs and micro-satellites

# Conclusion

- ▶ MS analysis revealed:
  1. species-wide genetic flow
  2. past and present exchanges within the species range
- ▶ when handled with appropriate comparison algorithms [Bérard, Rivals, 2003]
- ▶ MS versus SNPs and micro-satellites
- ▶ Mice genomes: set of interrelated gene pools, still able to exchange genes, even on chromosome X
- ▶ Difficult to find genes important for speciation

## Publications and algorithms

- ▶ S. Bérard, E. Rivals, *Comparison of Minisatellites*, *J. of Computational Biology*, p. 357-372, vol. 10(3-4), 2003.
- ▶ S. Bérard, F. Nicolas, J. Buard, O. Gascuel, E. Rivals, *A Fast and Specific Alignment Method for Minisatellite Maps*, *Evolutionary Bioinformatics Online*, 2:327–344, 2006.

*MS\_Align* <http://atgc.lirmm.fr/>

- ▶ F. Bonhomme, E. Rivals, A. Orth, G.R. Grant, A. J. Jeffreys, P.R.J. Bois  
*Species wide distribution of highly polymorphic minisatellite markers reveals long range gene flow and frequent genetic exchanges among House Mouse subspecies* submitted

# Credits and collaborators

- ▶ ISEM, Montpellier, France
  - F. Bonhomme
  - A. Orth
- ▶ Dpt Genetics, Univ. Leicester, GB
  - G. Grant
  - A.J. Jeffreys
- ▶ St Jude Childrens Research Hospital, Memphis, USA:
  - P. Bois
- ▶ Support: [ACI IMPBIO REPEVOL](#), BioSTIC LR, Génopole LR.

[ACI IMPBIO REPEVOL](#)

<http://www.lirmm.fr/~rivals/RESEARCH/REPEVOL/>