Genet. Res., Camb. (1998), **71**, *pp.* 119–125. *With* 1 *figure*. Printed in the United Kingdom © 1998 Cambridge University Press

Restoration of the Mendelian transmission ratio by a deletion in the mouse chromosome 1 HSR

DIETER WEICHENHAN*, BÄRBEL KUNZE, WALTHER TRAUT AND HEINZ WINKING

Institut für Biologie, Medizinische Universität zu Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany

(*Received 21 November 1997 and in revised form 6 January 1998*)

Summary

The house mouse, *Mus musculus*, harbours a variable cluster of long-range repeats in chromosome 1. As shown in previous studies, some high-copy clusters such as the *MUT* cluster are cytogenetically apparent as a homogeneously staining region (HSR) and are associated with a distortion of the Mendelian recovery ratio when transmitted by heterozygous females. The effect is caused by a decreased viability of +/+ embryos. It is compensated by maternal or paternal *MUT*. In this study, a deletion derivative of *MUT*, MUT^{del}, shows normal transmission ratios and no compensating capability. In this respect, MUT^{del} behaves like a wild-type cluster. Hence, both properties – transmission ratio distortion and compensating capability – map to the deleted region. The deletion comprises three-quarters of the *MUT* HSR and does not extend to the nearest markers adjacent to the HSR.

1. Introduction

Chromosome 1 of the house mouse (*Mus musculus*) contains a cluster of long-range repeats (LRR; ~ 100 kb repeat length) with variable copy numbers (locus *D1Lub1*, 53·1 cM; for review see Traut *et al.*, 1994). High-copy cluster variants of more than 200 LRRs are C-band positive (Kunze *et al.*, 1996) and appear as homogeneously staining regions (HSRs; Traut *et al.*, 1984). Most clusters, however, such as that in laboratory strain C57BL/6, are low-copy clusters of about 60 repeats and cytogenetically inconspicuous. Such clusters are considered 'wild-type' (+) clusters. LRRs harbour the *Sp100-rs* gene the function of which is unknown (Weichenhan *et al.*, 1995, 1997).

Individuals with chromosome 1 HSRs occur in many feral mouse populations (Winking *et al.*, 1991; Agulnik *et al.*, 1993*a*). Two of the high-copy clusters studied in more detail – one from a population in Mutten, Switzerland (*MUT*) and one from a population in Siberia – displayed non-Mendelian inheritance: they were preferentially transmitted from heterozygous females to viable offspring (Agulnik *et al.*, 1990; Weichenhan *et al.*, 1996). Preferential recovery of maternal *MUT*, i.e. *MUT*/+ embryos, was shown to be caused by preferential post-implantation lethality of the +/+ embryos (Weichenhan *et al.*, 1996). Normal Mendelian ratios were restored with the introduction of paternal *MUT*. Distortion of the Mendelian transmission ratio (a maternal effect) and restoration of the Mendelian transmission ratio (a zygotic effect) are therefore properties of the high-copy cluster or of loci linked to the high-copy *MUT* cluster.

Here we investigate transmission of a cluster variant, MUT^{del}, which arose by spontaneous deletion of a considerable number of repeats from *MUT* (Kunze *et al.*, 1996). We show that MUT^{del} is transmitted at a normal Mendelian ratio; it has lost both properties of *MUT*: maternal distortion and zygotic restoration of the Mendelian ratio. Molecular characterization of the deletion shows that these properties map to a chromosome region that includes the cluster but does not extend to the closest adjacent markers proximal or distal to the cluster.

2. Materials and methods

A cytogenetically inconspicuous LRR cluster in chromosome 1 is the prevailing type in feral mice and thus termed the + cluster. As representative with a

* Corresponding author. Telephone: +49 451 5004103. Fax: +49 451 5004815. e-mail: weichenh@molbio.mu-leubeck.de.

+ cluster, outbred NMRI-animals were used. The cytogenetically conspicuous cluster *MUT* (Weichenhan *et al.*, 1996) was introduced by six backcross generations into an NMRI background. Subsequently a homozygous *MUT* stock was established. In that stock, a deleted version of *MUT*, termed MUT^{del}, was detected cytogenetically. Since homozygous MUT^{del} females were subfertile, a homozygous MUT^{del} stock could not be established. MUT^{del} was maintained by backcrossing and intercrossing in an NMRI background.

Pre-implantation loss was determined by comparing the number of implantation sites with the respective number of corpora lutea. Post-implantation loss was determined by comparing the number of live embryos (day 10 to day 13 *p.c.*) with that of implantation sites.

Genotypes of live embryos (day 10 to day 13 *p.c.*) were determined by C-banding of metaphase chromosomes (Sumner, 1972), exploiting the C-band positive staining of *MUT* and MUT^{del} and the C-band negative staining of the + cluster (Traut *et al.*, 1984; Kunze *et al.*, 1996).

Genomic DNA was isolated from mouse liver either as described by Blin & Stafford (1976) or with the Genomic DNA Extraction Kit (Talent, Trieste, Italy) as recommended by the manufacturer. Plasmid DNA for probes was prepared by the CTAB method (del Sal *et al.*, 1988). Southern blotting, hybridization and autoradiography were performed as described previously (Kunze *et al.*, 1996). Total and poly(A)$^+$ RNAs were prepared from mouse liver and hybridized as described by Weichenhan *et al.* (1995).

MmHSRc10E-c3 is a cDNA probe from the *Sp100-rs* gene that is amplified in the *D1Lub1* cluster (Eckert *et al.*, 1991; Weichenhan *et al.*, 1997). The probe consists of six exons scattered over a genomic region of 23 kb or up to 40 kb, depending on the LRR copy (Eckert *et al.*, 1991; Plass *et al.*, 1995). Further cDNA probes were from the *M. musculus* genes *Acrg* (1·8 kb cDNA; Schurr *et al.*, 1990), *Sag* (1·5 kb cDNA; Tsuda *et al.*, 1988) and from the *M. caroli Sp100* gene (1·0 kb cDNA; probe comprises exons 6 to 17 which are not present in the partially homologous *Sp100-rs* gene; Weichenhan *et al.*, 1997).

MapPair primers for the anonymous chromosome 1 markers *D1MIT8, −10, −11, −44, −48, −50, −51* and *−53* were purchased from Research Genetics (Huntsville, USA). PCR was performed with *Taq* polymerase (Life Technologies, Eggenstein, Germany) on a Perkin Elmer GeneAmp 9600 apparatus using the standard protocol recommended by the distributor of the MapPairs. In brief, 10 μl reaction mixes contained 40 ng mouse DNA and 0·4 pmol of each primer. Denaturation was at 94 °C for 45 s, annealing at 50 °C for 45 s and extension at 72 °C for 60 s in 30 cycles. PCR products were analysed on 2% agarose gels using *Hpa*II-digested Bluescript SK+ (Stratagene, Heidelberg, Germany) as a length standard. Map positions of anonymous and gene markers were retrieved from the Mouse Genome Database (8, 1997).

3. Results

(i) *Transmission ratios of maternal* MUT^{del}

We have previously shown that +/+ offspring were underrepresented amongst the progeny of *MUT*/+ females and +/+ males (see Table 1, line 1; Weichenhan *et al.*, 1996). Here we examine a deletion derivative of *MUT*, MUT^{del}, which is a viable condition in both heterozygous and homozygous form.

In crosses of MUT^{del}/+ females with +/+ males, the ratio of MUT^{del}/+ to +/+ offspring was close to the 1:1 expectation (Table 1, line 2). Post-implantation losses were considerably lower in ♀ MUT^{del}/+ × ♂ +/+ crosses than in crosses of *MUT*/+ females with +/+ males (χ^2 test, $P < 0{\cdot}001$). Accordingly, in crosses of MUT^{del}/+ females with +/+ males, MUT^{del} shows the property of the wild-type cluster and not that of *MUT*.

Progeny of MUT^{del}/*MUT* females mated with +/+ males deviated from the Mendelian 1:1 ratio, MUT^{del}/+ embryos being underrepresented ($P < 0{\cdot}001$; Table 1, line 3). Post-implantation mortality exceeded 50% and could be mainly ascribed to the death of embryos with maternal MUT^{del}. When MUT^{del}/*MUT* females were mated with MUT^{del}/MUT^{del} males, the results were similar (Table 1, line 4): postimplantation mortality was high and not significantly different from that in the aforementioned cross ($0{\cdot}1 < P < 0{\cdot}5$), and embryos with maternal MUT^{del} were underrepresented. Thus, with respect to the Mendelian recovery ratio and post-implantation loss, these crosses resembled the ♀ *MUT*/+ × ♂ +/+ cross.

(ii) *Impaired fertility of homozygous* MUT^{del} *females*

In crosses of MUT^{del}/MUT^{del} females and +/+ males, 5 of 12 females did not become pregnant. In the pregnant females, post-implantation mortality was much higher than in heterozygous females (Table 2, line 2; compare with Table 1, line 2; $P < 0{\cdot}001$) and in homozygous *MUT* females (Table 2, line 1; $P < 0{\cdot}001$). Accordingly, fertility of homozygous MUT^{del} females in crosses with wild-type males is significantly reduced. Fertility of MUT^{del}/MUT^{del} males, in contrast, appeared to be normal as deduced from high litter sizes in matings with +/+ and MUT^{del}/+ females. Those males were used to generate the homozygous MUT^{del} females.

https://doi.org/10.1017/S0016672398003206 Published online by Cambridge University Press

Table 1. *Embryos from heterozygous females*

No.	Crosses: *n*	Female	Male	Corpora lutea	Implantation sites	Pre-implantation loss (%)	Live embryos: *n*	MUT^{del}/MUT^{del}	MUT/MUT	$MUT^{del}/+$	$MUT/+$	MUT^{del}/MUT	+/+	Post-implantation loss (%)	$MUT^{del}/+$ (%)	$MUT/+$ (%)	MUT^{del}/MUT (%)	Deviation from 1:1 (χ^2)
1[a]	12	$MUT/+$	+/+	152	134	11·8	84	—	—	—	65	—	19	37·3	—	77·4	—	25·6*
2	11	$MUT^{del}/+$	+/+	144	137	4·9	119	—	—	61	—	—	58	13·1	51·3	—	—	0·1
3	11	MUT^{del}/MUT	+/+	145	116	20·0	49[b]	—	—	7	40	—	—	57·8	14·9	85·1	—	23·2*
4	4	MUT^{del}/MUT	MUT^{del}/MUT^{del}	41	31	24·4	18	4	—	—	—	14	—	41·9	—	—	77·8	5·5**
5[a]	6	$MUT/+$	MUT/MUT	88	58	34·1	53[c]	—	23	—	29	—	—	8·6	—	55·7	—	0·7

[a] Data in lines 1 and 5 taken from Weichenhan *et al.* (1996).
[b] Two recognized triploids were excluded from genotyping.
[c] One recognized triploid was excluded from genotyping.
* $P < 0{\cdot}001$; ** $0{\cdot}01 < P < 0{\cdot}05$.

Table 2. *Embryos from homozygous* MUT *and* MUT^{del} *females*

No.	Crosses: *n*	Female	Male	Corpora lutea	Implantation sites	Pre-implantation loss (%)	Live embryos: *n*	$MUT/+$	MUT/MUT	$MUT^{del}/+$	MUT^{del}/MUT	Post-implantation loss (%)	$MUT^{del}/+$ (%)	MUT^{del}/MUT (%)	Deviation from 1:1 (χ^2)
1	4	MUT/MUT	+/+	43	42	2·3	26	26	—	—	—	38·1	—	—	—
2	12[a]	MUT^{del}/MUT^{del}	+/+	76	65	14·5	11	—	—	11	—	83·1	100	—	—
3	12[b]	MUT^{del}/MUT^{del}	MUT/MUT	108	79	26·9	58	—	—	—	58	26·6	—	100	—
4	11	MUT^{del}/MUT^{del}	$MUT/+$	135	97	28·1	36	—	—	7	29	62·9	19·4	80·6	13·4*

[a] Five of the 12 females did not become pregnant.
[b] Four of the 12 females did not become pregnant.
* $P < 0{\cdot}001$.

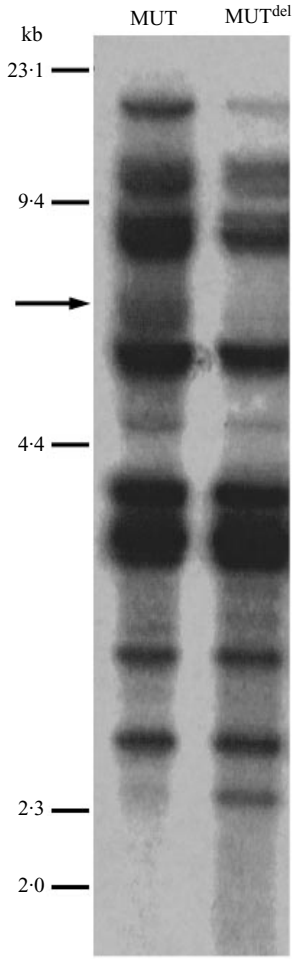

Fig. 1. Southern hybridization of MmHSRc10E-c3 to 5 μg each of *Eco*RI-digested genomic DNAs from homozygous *MUT* and MUT^{del} animals. Exposure times were 1 day (*MUT*) and 8 days (MUT^{del}). The arrow indicates a band in *MUT* that is not visible in MUT^{del}.

In crosses of MUT^{del}/MUT^{del} females with *MUT*/*MUT* males, four of 12 females did not become pregnant. Compared with crosses with +/+ males, post-implantation losses were reduced (Table 2, line 3; $P < 0{\cdot}001$). This indicates a compensating effect of the paternal genotype. To distinguish compensating *MUT* effects from genetic background effects, MUT^{del}/MUT^{del} females were mated with *MUT*/+ males. The proportion of live $MUT^{del}/+$ embryos was only 19·4% (Table 2, line 4). Thus, indeed paternal *MUT* and not the genetic background compensated post-implantation mortality. However, post-implantation mortality was not reduced by paternal MUT^{del}: pregnant MUT^{del}/MUT^{del} females mated with MUT^{del}/MUT^{del} males did not give rise to viable offspring. The inspection of two pregnant females revealed a resorption rate of 88% at day 12 of pregnancy.

MUT^{del}/MUT^{del} females and $MUT^{del}/+$ females for all aforementioned crosses had been derived from the same pool of ♀ $MUT^{del}/+ \times$ ♂ MUT^{del}/MUT^{del} progeny to minimize differences due to the genetic background. The ratio of MUT^{del}/MUT^{del} daughters to $MUT^{del}/+$ daughters in these progeny was not significantly different from 1:1 ($26:35$; $0{\cdot}1 < P < 0{\cdot}5$). Apparently, viability of homozygous MUT^{del} females is not impaired.

(iii) *Mapping the* MUT^{del} *deletion*

MUT^{del} was discovered by its reduced C-band size as a deletion derivative of *MUT*. From the ~ 920 LRR copies of the *MUT* cluster, ~ 280 remain in the MUT^{del} cluster (Kunze *et al.*, 1996). Thus, about 640 LRRs have been deleted.

*Eco*RI-digested genomic DNA of homozygous *MUT* and MUT^{del} animals was probed with the LRR-specific cDNA clone MmHSRc10E-c3. The hybridization patterns were similarly complex and nearly identical in *MUT* and MUT^{del} (Fig. 1), but one of the *MUT* bands was missing in MUT^{del} (Fig. 1, arrow), indicating the loss or underrepresentation of at least one LRR variant.

The LRR-specific *Sp100-rs* gene family in *MUT* encodes five transcripts of different sizes that are visible in Northern blots and probably derived from different gene copies (Weichenhan *et al.*, 1995). The same pattern of five transcripts was detected when poly(A)$^+$ RNA of a homozygous MUT^{del} animal was hybridized with a *Sp100-rs* cDNA probe (not shown). Thus, no transcript variant was lost by the deletion.

To determine the boundaries of the deletion, we performed MapPair PCR for several D1MIT markers from the vicinity of the cluster. The cluster maps to

Table 3. *Sizes of PCR products* (*in bp*) *of strains* MUT^{del} *and* MUT *with D1MIT MapPairs*

	Marker[a]							
Strain	*D1MIT44* 50·3	*D1MIT8* 52·0	*D1MIT53* 52·0	*D1MIT50* 53·0	*D1MIT51* 53·0	*D1MIT48* 54·0	*D1MIT10* 56·6	*D1MIT11* 58·7
MUT^{del}	190	200	150	130	250	140	140	100
MUT	190	200	150	130	250	140	140	100

[a] The figure below each marker indicates the map position in centimorgans.

https://doi.org/10.1017/S0016672398003206 Published online by Cambridge University Press

53·1 cM; markers from 50·3 cM to 58·7 cM were selected. None of them was deleted in homozygous MUT^{del} animals (Table 3). The closest markers were *D1MIT50* and *D1MIT51*, which map 0·1 cM proximally to the cluster, and *D1MIT48*, which maps 0·9 cM distally.

The presence of the genes *Acrg* (52·3 cM), *Sag* (53·6 cM) and *Sp100* (distally adjacent to the cluster; see Section 4) was tested by hybridization of cDNA probes to *Eco*RI-digested DNA. All probes recognized genomic fragments in homozygous MUT^{del} animals, some of the same size as in homozygous *MUT* animals, some with restriction fragment length polymorphisms (not shown). Thus, the deletion does not encompass the genes *Acrg*, *Sag* or *Sp100*; the respective genes map outside the borders of the MUT^{del} deletion.

4. Discussion

(i) *Phenotypic consequences of the* MUT^{del} *deletion*

MUT^{del} was derived from the *MUT* LRR cluster by a deletion (Kunze *et al.*, 1996). The deleted segment comprised roughly 640 of the 920 LRRs from the *MUT* cluster and little, if anything at all, from the adjacent proximal or distal chromosome regions. As we report in this paper, homozygous male carriers of the deletion are viable and fertile, whereas homozygous females carriers are viable but show impaired fertility.

MUT is associated with transmission ratio distortion in $MUT/+$ females mated to $+/+$ males. The distortion is due to preferential death of $+/+$ post-implantation embryos while no such disadvantage of $+/+$ embryos is evident in the reciprocal cross (Weichenhan *et al.*, 1996). The *MUT* genotype confers an adverse maternal effect (AME) on $+/+$ embryos (sensitive) but not on $MUT/+$ embryos (tolerant). Thus, like AME, AME tolerance is linked to *MUT*. AME tolerance can be contributed by paternal *MUT* and, therefore, is a zygotic effect (Weichenhan *et al.*, 1996). MUT^{del} has lost the AME property and acts like the + genotype (Table 1, line 2). In MUT^{del}/MUT females, the Mendelian transmission ratio is distorted, with underrepresentation of $MUT^{del}/+$ embryos (Table 1, line 3). Paternal MUT^{del} is unable to restore the Mendelian 1:1 ratio (Table 1, line 4). Like +, MUT^{del} does not confer AME tolerance on the embryos. In summary, both AME and AME tolerance of *MUT* are absent in MUT^{del} and, hence, map to the chromosome region that is deleted in the MUT^{del} genome.

Homozygous MUT^{del} females show reduced fertility in combination with paternal + (Table 2, line 2) while no such impairment is evident in the reciprocal cross. Partial restoration of fertility by paternal *MUT* but not by paternal MUT^{del} indicates similarity to AME tolerance. We consider it possible but have no further evidence that partial restoration of fertility and AME tolerance are the same phenomenon.

AME and AME tolerance are properties associated with *MUT*. They map to the MUT^{del} deletion region, which comprizes a part of the LRR cluster and little if anything at all of the immediate proximal or distal vicinity. Although we cannot exclude that genes in the immediate vicinity of the cluster or genes entrapped within the cluster are responsible for these properties, the cause may be the cluster itself.

In a similar system, chromosome 1 high-copy LRR clusters from Siberia showed transmission distortion like *MUT* (Agulnik *et al.*, 1990). The authors considered the effect to be caused by meiotic drive. Mapping of the responsible locus with *fz* (4·4 cM), *ln* (59·0 cM) and *Pep3* (71·0 cM) (Agulnik *et al.*, 1993*b*) is consistent with its location in or near the LRR cluster at 53·1 cM (updated map positions from Mouse Genome Database; 8, 1997). The similarity extends to the restoration of the Mendelian transmission ratio by a paternal high-copy cluster which was originally thought to have an effect on segregation during the second meiotic division of the oocyte (Agulnik *et al.*, 1993*c*).

It is tempting to assign the high LRR copy numbers a causative role in AME and/or AME tolerance, similar to the dosage-dependent action of *Enhancer of Segregation Distorten*, *E*(*SD*), in *Drosophila* (Brittnacher & Ganetzky, 1984; Temin, 1991). However, one of the low-copy LRR cluster genotypes tested, that of BALB/c, did not show transmission distortion when heterozygous with a high-copy cluster genotype (Agulnik *et al.*, 1993*b*; H. Winking, unpublished), i.e. BALB/c exhibits AME tolerance according to our terminology.

(iii) *Nature of the maternal effect*

The nature of AME is not clear. We envisage three possible forms of the inhibiting influence on the development of post-implantation embryos: (1) a maternal effect in the strict sense, (2) an interaction between the meiotic partners, and (3) an interaction between embryo and mother.

(1) A maternal effect in the strict sense, i.e. an RNA or protein with an inhibiting influence produced by the unreduced $MUT/+$ genome, and delivered to both types of eggs, *MUT* and +, may be the cause of AME. Zygotic AME tolerance provided by the *MUT* genome would then make the $MUT/+$ embryo resistant to that influence. A genetic system with similar components, the mouse DDK syndrome, has been proposed (Renard *et al.*, 1994; de Villena *et al.*, 1996). The inhibited stage in the DDK syndrome, however, is the pre-implantation stage. The post-

https://doi.org/10.1017/S0016672398003206 Published online by Cambridge University Press

implantation stage, at which AME becomes apparent, appears to be rather late for a typical maternal effect, which becomes effective in the early stages of development (Wilkins, 1993).

(2) An interaction between meiotic partners in the *t*-complex of the mouse was considered the cause for preferential impairment of + sperm in *t*/+ males (Seitz & Bennett, 1985; review by Silver, 1993). The system resembles that of *MUT*/+ females. To cause AME, the *MUT* genotype may either confer some toxic agent on the gamete or imprint the + genotype in some deleterious way. Known cases of imprinting regard differences of the female versus the male germline (reviews by Solter, 1988; and Jaenisch 1997). There are no reports yet, however, on particular genotypes producing imprints in the meiotic partner genome.

(3) The obvious site for an interaction between mother and post-implantation embryo is the uterus. The maternal and zygotic effects reported here bear some resemblance to a mouse model used to study spontaneous abortion. ♀ CBA/J × ♂ CBA/2J crosses – but not the reciprocal crosses – show a high rate of spontaneous resorption (Clark *et al*., 1980; Kiger *et al*., 1985). The maternal effect has been attributed to damage caused by tumour necrosis factor-alpha and natural killer cells (Gendron & Baines, 1988; Clark *et al*., 1991). The effect is abrogated by introduction of a paternal BALB/c genome; ♀ CBA/J × ♂ BALB/c crosses show normal rates of abortion (Kiger *et al*., 1985). One can envisage a scenario in which the *MUT*/+ uterus, unlike the +/+ or MUT^{del}/+ uterus, offers a hostile environment for the sensitive +/+ and MUT^{del}/+ embryos but not for the tolerant *MUT*/+ embryos. Transplantation experiments of *MUT*/+ and +/+ embryos are under way to decide upon this interpretation.

We thank Drs D. Malo (Montreal) and T. Shinohara (Bethesda) for providing the probes for *Acrg* and *Sag*, respectively. The technical assistance of Katja Andruleit and Elzbieta Manthey is gratefully acknowledged. This work was supported by the Deutsche Forschungsgemeinschaft.

References

Agulnik, S. I., Agulnik, A. I. & Ruvinsky, A. O. (1990). Meiotic drive in female mice heterozygous for the HSR inserts on chromosome 1. *Genetical Research* **55**, 97–100.

Agulnik, S., Adolph, S., Winking, H. & Traut, W. (1993*a*). Zoogeography of the chromosome 1 HSR in natural populations of the house mouse (*Mus musculus*). *Hereditas* **119**, 39–46.

Agulnik, S. I., Sabantsev, I. D., Orlova, G. V. & Ruvinsky, A. O. (1993*b*). Meiotic drive on aberrant chromosome 1 in the mouse is determined by a linked distorter. *Genetical Research* **61**, 91–96.

Agulnik, S. I., Sabantsev, I. D. & Ruvinsky, A. O. (1993*c*). Effect of sperm genotype on chromatid segregation in female mice heterozygous for aberrant chromosome 1. *Genetical Research* **61**, 97–100.

Blin, N. & Stafford, D. W. (1976). A general method for isolation of high molecular weight DNA from eukaryotes. *Nucleic Acids Research* **3**, 2303–2308.

Brittnacher, J. G. & Ganetzky, B. (1984). On the components of segregation distortion in *Drosophila melanogaster*. III. Nature of *Enhancer of SD*. *Genetics* **107**, 423–434.

Clark, D. A., McDermott, M. R. & Szewczuk, M. R. (1980). Impairment of host-versus-graft reaction in pregnant mice. II. Selective suppression of cytotoxic T-cell generation correlates with soluble suppressor activity and with successful allogeneic pregnancy. *Cellular Immunology* **52**, 106–118.

Clark, D. A., Lea, R. G., Podor, T., Daya, S., Banwatt, D. & Harley, C. (1991). Cytokines determining the success or failure of pregnancy. *Annals of the New York Academy of Sciences* **626**, 524–536.

del Sal, G., Manfioletti, G. & Schneider, C. (1988). A one-tube plasmid DNA mini-preparation suitable for sequencing. *Nucleic Acids Research* **16**, 9878.

de Villena, F. P.-M., Slamka, C., Fonseca, M., Naumova, A. K., Paquette, J., Pannunzio, P., Smith, M., Verner, A., Morgan, K. & Sapienza, C. (1996). Transmission-ratio distortion through F_1 females at chromosome 11 loci linked to *Om* in the mouse DDK syndrome. *Genetics* **142**, 1299–1304.

Eckert, W. A., Plass, C., Weith, A., Traut, W. & Winking, H. (1991). Transcripts from amplified sequences of an inherited homogeneously staining region in chromosome 1 of the house mouse (*Mus musculus*). *Molecular and Cellular Biology* **11**, 2229–2235.

Gendron, R. L. & Baines, M. G. (1988). Infiltrating decidual natural killer cells are associated wit spontaneous abortion in mice. *Cellular Immunology* **113**, 261–267.

Jaenisch, J. (1997). DNA methylation and imprinting: why bother? *Trends in Genetics* **13**, 323–329.

Kiger, N., Chaouat, G., Kolb, J.-P., Wegmann, T. G. & Guenet, J.-L. (1985). Immunogenic studies of spontaneous abortion in mice. Preimmunization of females with allogeneic cells. *Journal of Immunology* **134**, 2966–2970.

Kunze, B., Weichenhan, D., Virks, P., Traut, W. & Winking, H. (1996). Copy number of a clustered long-range repeat determines C-band staining. *Cytogenetics and Cell Genetics* **73**, 86–91.

Mouse Genome Database (MGD), Mouse Genome Informatics, The Jackson Laboratory, Bar Harbor, Main. World Wide Web (URL: http://www.informatics.jax.org/). (8, 1997).

Plass, C., Weichenhan, D., Kunze, B., Hellwig, T., Schneider, C., Bautz, F. A., Grzeschik, K.-H., Traut, W. & Winking, H. (1995). A member of the mouse LRR transcript family with homology to the human *Sp100* gene. *Hereditas* **122**, 245–256.

Renard, J.-P., Baldacci, P., Richoux-Duranthon, V., Pournin, S. & Babinet, C. (1994). A maternal factor affecting mouse blastocyst formation. *Development* **120**, 797–802.

Schurr, E., Skamene, E., Morgan, K., Chu, M. L. & Gros, P. (1990). Mapping of *Col3a1* and *Col6a3* to proximal murine chromosome 1 identifies conserved linkage of structural protein genes between murine chromosome 1 and human chromosome 2q. *Genomics* **8**, 477–486.

Seitz, A. W. & Bennett, D. (1985). Transmission distortion of *t*-haplotypes is due to interactions between meiotic partners. *Nature* **313**, 143–144.

Silver, L. M. (1993). The peculiar journey of a selfish chromosome, mouse *t* haplotypes and meiotic drive. *Trends in Genetics* **9**, 250–254.

Solter, D. (1988). Differential imprinting and expression of maternal and paternal genomes. *Annual Reviews of Genetics* **22**, 127–146.

Sumner, A. T. (1972). A simple technique for demonstrating centromeric heterochromatin. *Experimental Cell Research* **75**, 304–306.

Temin, R. G. (1991). The independent distorting ability of the *Enhancer of Segregation Distortion*, *E* (*SD*), in *Drosophila melanogaster*. *Genetics* **128**, 339–356.

Traut, W., Winking, H. & Adolph, S. (1984). An extra segment in chromosome 1 of wild *Mus musculus*: a C-band positive homogeneously staining region. *Cytogenetics and Cell Genetics* **38**, 290–297.

Traut, W., Winking, H., Plass, C., Weichenhan, D., Kunze, B., Hellwig, T. & Agulnik, S. (1994). An inherited homogeneously staining region derived from a long-range repeat family in the house mouse. In *Chromosomal Alterations: Origin and Significance* (ed. G. Obe & A. T. Natarajan), pp. 31–41. Berlin: Springer-Verlag.

Tsuda, M., Syed, M., Bugra, K., Whelan, J. P., McGinnis, J. F. & Shinohara, T. (1988). Structural analysis of mouse S-antigen. *Gene* **73**, 11–20.

Weichenhan, D., Kunze, B., Plass, C., Hellwig, T., Winking, H. & Traut, W. (1995). A transcript family from a long-range repeat cluster of the house mouse. *Genome* **38**, 239–245.

Weichenhan, D., Traut, W., Kunze, B. & Winking, H. (1996). Distortion of Mendelian recovery ratio for a mouse HSR is caused by maternal and zygotic effects. *Genetical Research* **68**, 125–129.

Weichenhan, D., Kunze, B., Zacker, S., Traut, W. & Winking, H. (1997). Structure and expression of the murine *Sp100* nuclear dot gene. *Genomics* **43**, 298–306.

Wilkins, A. S. (1993). *Genetic Analysis of Animal Development*, 2nd edn, pp. 19–24. New York: Wiley-Liss.

Winking, H., Weith, A., Boldyreff, B., Moriwaki, K., Fredga, K. & Traut, W. (1991). Polymorphic HSRs in chromosome 1 of the two semispecies *Mus musculus musculus* and *M. m. domesticus* have a common origin in an ancestral population. *Chromosoma* **100**, 147–151.