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Genome imprinting phenomena on mouse chromosome 7

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Summary

Heterozygotes for the reciprocal translocation T(7;15)9H were intercrossed, with albino (*c*) and underwhite (*uw*) as genetic markers, in order to study genetic complementation in mouse chromosome 7. Chromosome 15 is known to show normal complementation. Neither reciprocal cross in which one parent was *c/c* and the other wild type yielded albino progeny at birth although about 17% would be expected, but albino foetuses were recovered when the mother was *c/c* and father wild type. These products of maternal duplication/paternal deficiency for distal 7 were markedly retarded with small placentae. No albino foetuses were found when the father was *c/c* and mother wild type, which suggested earlier lethality. Equivalent crosses with *uw* (chromosome 15) as proximal marker gave normal underwhite progeny when the mother was *uw/uw* but small placentae, retardation and neonatal death of presumptive underwhites in the reciprocal cross. These abnormal newborn would have had a maternal duplication/paternal deficiency for proximal 7. These and other findings indicate that one region of defective complementation probably lies distal to the breakpoint of T(7;18)50H at 7E2-F2, while another is between the centromere and 7B3. Examination of man-mouse homologies suggests that the loci for three pathological human conditions (Beckwith–Weidemann syndrome, dystrophia myotonia and rhabdomyosarcoma) with differential parental transmission may be located in homologous regions to those affected by imprinting phenomena on mouse chromosome 7.

1. Introduction

The term 'imprinting' has been used for many years in connection with the elimination of certain chromosomes or chromosome sets in insects and, more recently, with X-inactivation phenomena in mammals (see Cattanach & Beechey, 1990). However, it was Lyon & Glenister (1977) who first suggested it might explain a mammalian autosomal phenomenon, namely the differences in parental transmission revealed by translocation intercrosses involving mouse chromosome 17 and by the hairpin-tail (T^{hp}) deletion on the same chromosome. Evidence from both genetic studies and nuclear transfer experiments and from the non-survival of andro- and gynogenones has shown that some genetic material must be inherited from both parents for normal development (for review see Solter, 1988). There appears to be a requirement for differential imprinting by maternal and paternal genomes of certain genes or chromosomal regions in the zygote, but the proportion of the zygotic genome which is affected and the actual nature of the imprint are still uncertain.

The search for examples of differential genomic imprinting in mouse autosomes has made use of the fact that translocation heterozygotes generate unbalanced gametes with losses and/or gains of genetic material. Snell (1946) was the first to intercross such heterozygotes and show that gametes with complementary duplications and deficiencies can fuse to form normal zygotes, which can be detected if one parent is homozygous for a visible genetic marker in the region concerned which is not carried by the other parent. If complementation does not occur when expected, or is defective, then it can be assumed that the genetically marked region contains some factors which require differential genetic imprinting. Heterozygotes for Robertsonian translocations and monobrachial compounds of these with high frequencies of non-disjunction have been used to identify which mouse chromosomes are affected (Cattanach, 1986). For further localization of such factors, genetically marked intercrosses of heterozygotes for reciprocal translocations have been used. If the genetic marker is

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distal to the translocation breakpoint then, with normal meiotic disjunction and gametic complementation, one-sixth of surviving offspring should be homozygous for it (Searle *et al.* 1971) but if proximal the frequency is usually less than 5%, as complementation then requires adjacent-II disjunction.

Searle & Beechey (1978) raised the possibility that chromosome (henceforth abbreviated to Chr) 7 showed defective complementation because (i) the results of specific locus experiments suggested that while uniparental disomy for Chr 9 led to viable dilute short-ear offspring (*d se/d se*), the same phenomenon was not seen in Chr 7, since no pink-eyed dilution chinchilla ($p\ c^{ch}/p\ c^{ch}$) offspring were reported (L. B. Russell, 1971), (ii) intercrosses of heterozygotes for a translocation, now extinct but known to involve Chr 7, with shaker-1 (*sh-1*) as genetic marker, failed to produce any *sh-1* offspring (Snell, 1946). Defective complementation was confirmed by intercrossing heterozygotes for two translocations involving Chr 7, namely T(7;15)9H and T(7;18)50H (Searle & Beechey, 1985). Directional caracul (Ca^d) was used as a distal Chr 15 marker with T9H but neither of the expected homozygotes (Ca^d/Ca^d or +/+) were recorded among the intercross progeny. Since genetically marked Robertsonian intercrosses have shown normal complementation for markers on Chr 15 (Cattanach, 1982; Lyon, 1983) any defective complementation with T9H must involve Chr 7. Underwhite (*uw*) was used as a proximal Chr 15 genetic marker for T9H, but *uw* offspring were only seen when mothers were *uw/uw*, though more data were needed. Pink-eyed dilution (*p*) was used as a proximal Chr 7 genetic marker for T50H but *p* offspring were only recovered from T50H/+ intercrosses when fathers were *p/p*.

Further crosses have now been carried out with T9H and the proximal marker *uw*, as well as with a distal Chr 7 marker, albino (*c*). The latter allows detection of the duplication/deficiency phenotype (*c/c*) much earlier than did Ca^d.

Two different regions on Chr 7 which contain factors involved in differential genomic imprinting are defined by these studies. The proximal region leads to retardation and neonatal death with maternal duplication/paternal deficiency while the distal one leads to foetal retardation and lethality with maternal duplication/paternal deficiency and earlier lethality with paternal duplication/maternal deficiency.

2. Materials and methods

The translocation T(7B3;15C)9H has a breakpoint about 14 cM proximal to the *c* locus on Chr 7 and 26 cM distal to *uw* on Chr 15 (Searle, 1989). Fig. 1 shows positions of genetic markers in relation to the T9H breakpoints on the G-banded map. Reciprocal crosses were made between T9H *c*/+*c* and T9H +/++ mice, also between T9H *uw*/+ *uw* and T9H +/++. Offspring were examined for visible products of complementation, namely albino or underwhite mice (Fig. 2). The latter have very light coats at weaning age; moreover, both albino and underwhite eyes are unpigmented at birth (Green, 1989) and can be distinguished from wild type pigmented eyes from about the 11th day of intrauterine development. Therefore, 11–18 day foetuses from further inter-

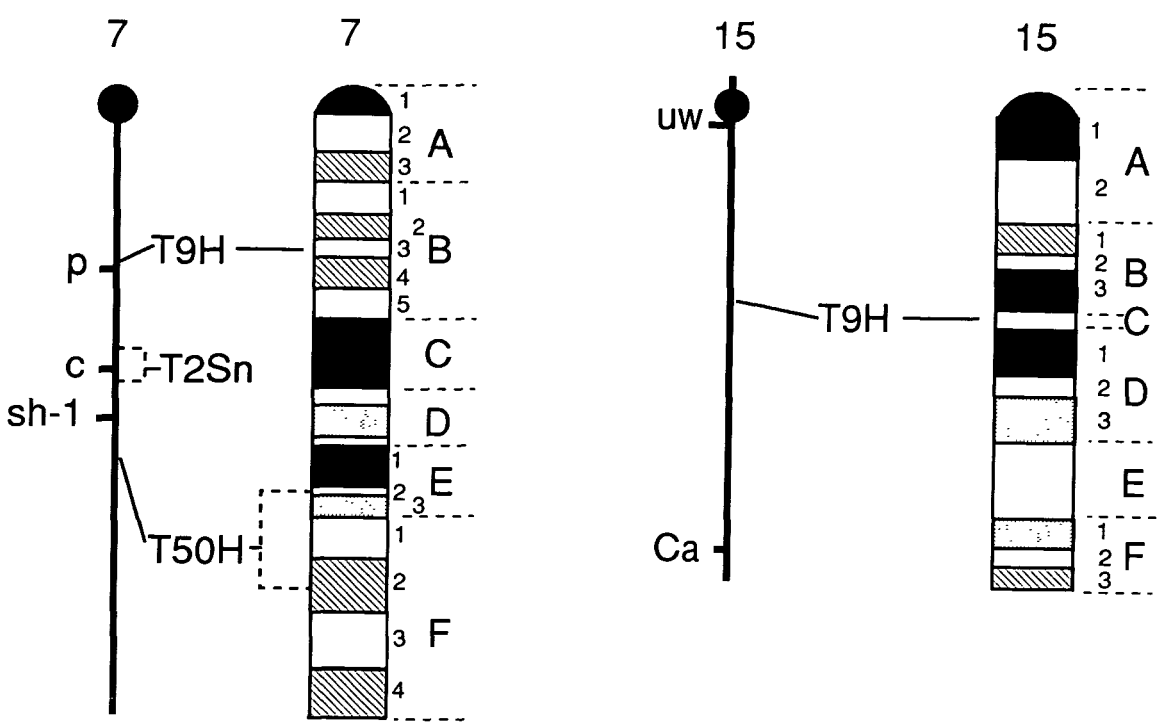

Fig. 1. G-banded and linkage maps of mouse chromosomes 7 and 15, to show locations of translocation breakpoints and of loci used in translocation intercrosses.

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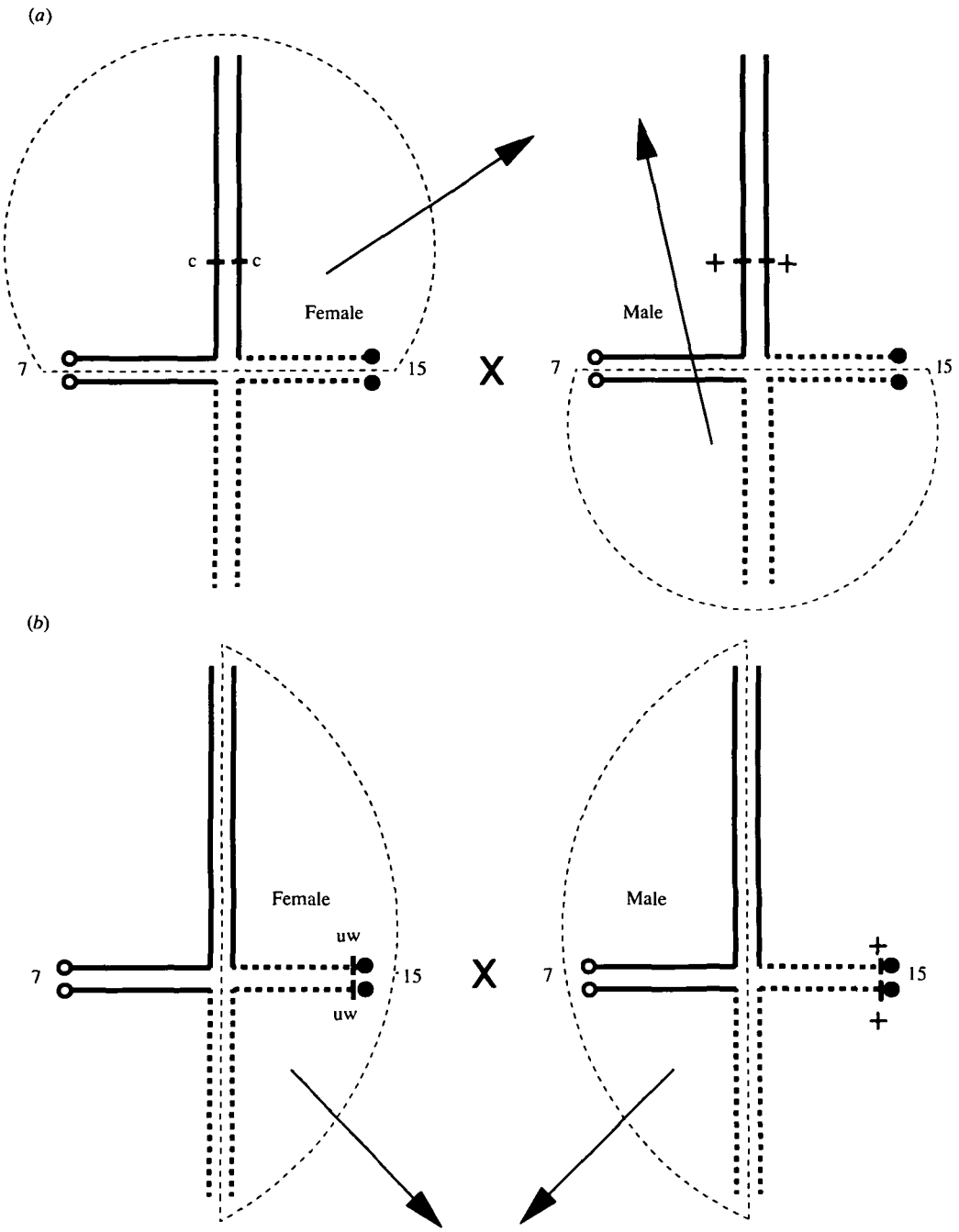

Fig. 2. Diagrams of types of translocation intercrosses used to detect defective complementation in Chr 7. Meiotic cross-shaped configurations of T9H/+ are shown, with interrupted lines enclosing gametic products which, when combined (arrows) will give chromosomally balanced T9H/+ offspring homozygous for the marker gene and thus visibly different from wild type. (*a*) Products of normal meiotic segregation, leading to maternal duplication/paternal deficiency for distal 7, accompanied by paternal duplication/maternal deficiency for distal 15. (*b*) Products of adjacent-II segregation (centromeric non-disjunction) leading to maternal duplication/paternal deficiency for proximal 15, accompanied by paternal duplication/maternal deficiency for proximal 7. This type of segregation is rarer than alternate or adjacent-I and leads to a 5% or lower frequency of complementation products with respect to a proximal marker rather than the 16–17% expected with a distal one and normal segregation.

crosses were examined when it became clear that they could provide additional information.

3. Results

As Table 1 shows, the reciprocal T9H/+ intercrosses with *c* as distal genetic marker failed to produce any albinos at birth, when a frequency of about one-sixth would be expected. This is in line with previous results using Ca^a (Searle & Beechey, 1985). When underwhite (Chr 15) was used as a proximal genetic marker in T9H/+, intercross results depended on which parent was marked (Table 1). If it was the female then underwhite offspring were detected at weaning age

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Table 1. *Results of intercrossing T(7;15)9H heterozygotes with one parent homozygous for distal or proximal genetic marker and the other wild type*

Cross No.	Parental genotype ♀	♂	Marked region	Stage examined	Number classified: With marker	Without	Percent with marker: Expected	Observed
1	*c/c*	+/+	7 dist.	Newborn	0	244	16·7	0
				Foetus	23	211	16·7	10
2	+/+	*c/c*	7 dist.	Newborn	0	71	16·7	0
				Foetus	0	48	16·7	0
3	*uw/uw*	+/+	15 prox.	Weaning	2	35	< 5*	5·7
4	+/+	*uw/uw*	15 prox.	Weaning	0	55	< 5*	0
5	*c/c*	*uw/uw*	7 dist. 15 prox.	Newborn	8 *uw*†	172	< 5* (*uw*)	4·7

* Lower frequency because the result of adjacent II segregation (see text).
† Presumed *uw* because albinos die *in utero* (see cross 1).
N.B. The data from cross 3 and some of those from cross 4 have been published in Searle & Beechey (1985).

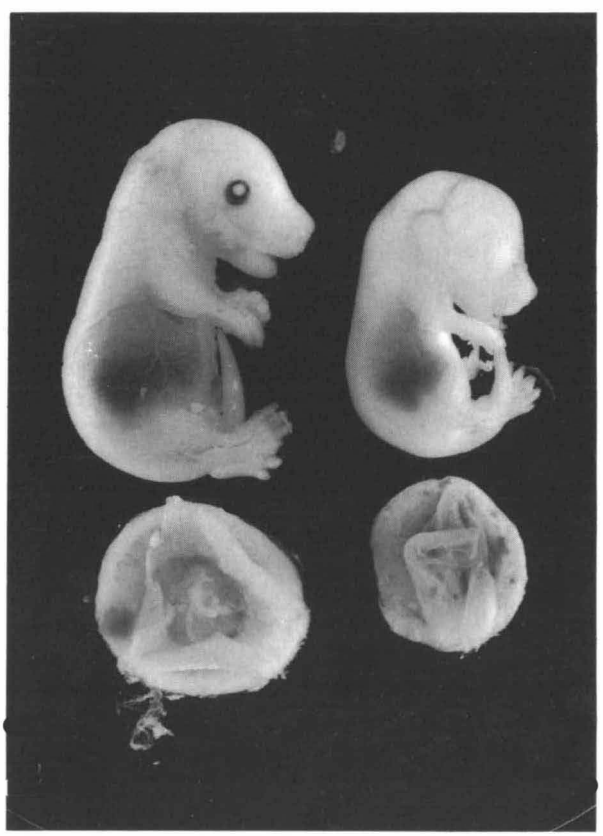

Fig. 3. Comparison of 15·5-day wild type (left) and presumptive albino foetuses and placentae from the same uterus in a T9H *c*/+ *c* ♀ × T9H +/+ + ♂ intercross to show extent of retardation in the albino product of complementation.

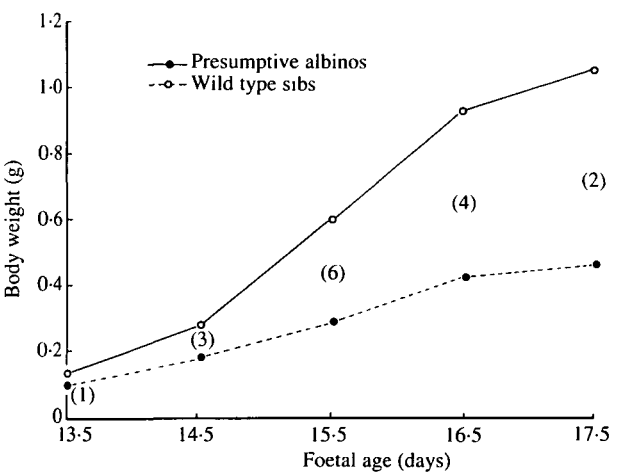

Fig. 4. Mean body-weights of albino foetuses and wild type sibs from T9H *c*/+ *c* ♀ × T9H +/+ + ♂ intercrosses at different ages of gestation, to show increasing divergence. Numbers of comparisons at each foetal age shown in parentheses.

(Searle & Beechey, 1985) but none were seen in reciprocal crosses. Subsequent T9H/+ intercrosses in which the female parent was albino and the male underwhite (Table 1, cross no. 5), with classification at birth, gave 8 presumptive *uw/uw*, all of which were small, while none survived the neonatal period. Like albinos, newborn underwhites have unpigmented eyes, and these newborn young were presumed to be underwhite rather than albino because (i) no albinos survived to be born in intercrosses of the same translocation when the *c* marker alone was used (Table 1, cross no. 1) and (ii) the frequency of these abnormal newborn agreed with expectation for a proximal marker (*uw*) but not for a distal one (*c*).

Foetuses from the T9H/+ intercrosses with *c* as genetic marker were examined between days 11–18 of gestation to search for the missing complementation types. When the female parent was albino some foetuses lacked eye pigment and were therefore presumptive albinos (Table 1). They and their placentae showed marked growth retardation (Fig. 3), with increasing divergence between wild type and *c/c* foetal weights as pregnancy proceeded (Fig. 4). Albino placental weights remained fairly constant over the period of study, apart from one outlier (Fig. 5) and averaged about 50% of wild type placental weights. However, in the reciprocal cross (with males being albino) no foetuses lacked eye pigmentation (Table 1), when 8 would have been expected, a significant

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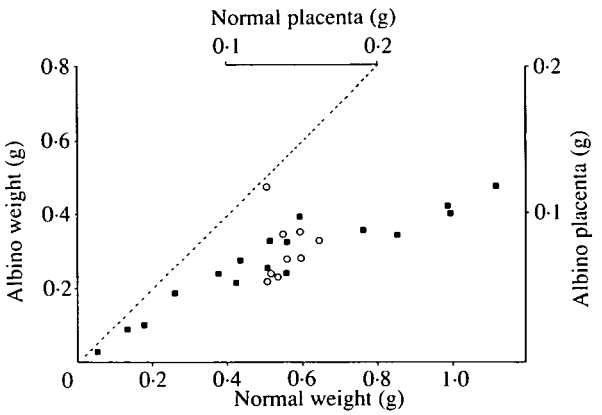

Fig. 5. A plot of foetal (■) and placental (○) weights of albino *vs.* wild type litter-mates from T9H *c*/+ *c* ♀ × T9H +/+ + ♂ intercrosses. The interrupted line (45°) shows the expected linear regression if albino and wild type weights were equal.

deviation ($P = 0{\cdot}006$). This suggested that embryos with paternal duplication/maternal deficiency for distal 7 die before the onset of eye pigmentation on the 11th day of gestation.

Information on possible intrauterine effects from maternal duplication/paternal deficiency of the proximal region of Chr 7 was obtained from the following intercrosses:

1. T9H *c*/+ + ♀ × T9H *uw*/+ *uw* ♂. 174 12·5–17·5 day foetuses were examined, 8 (4·6%) lacked eye pigmentation. In all of these, placentae weighed less than in dark-eyed litter-mates, while in 7 the foetuses weighed less also. It was noted that two of these foetuses were markedly smaller than normal litter-mates, with body and placental weights which averaged 60% and 47% of normal respectively. Thus they resembled the albino foetuses found in T9H *c*/+ *c* × T9H +/+ + crosses. For the other 6 foetuses, corresponding figures were 93% and 77%. It was known from previous work (Searle *et al.* 1971) that translocation intercrosses could produce homozygotes for a genetic marker even when one parent was only heterozygous for it and the other wild type, as with *c* in this cross. Calculations based on the above paper and the known distance between the T9H breakpoint and the *c* locus gave an estimate of 0·6% as the expected frequency of *c* in progeny of the above cross, in good agreement with the observed frequency of 1·15% for the two small foetuses. It seems very probable, therefore, that these were indeed *c*/*c* and the other less affected foetuses without eye pigmentation were *uw*/*uw*.

2. T9H *c*/+ *c* ♀ × *uw* T9H/*uw* + ♂. 74 13·5–17·5 day foetuses were examined, 11 (14·9%) lacked eye pigmentation. Ten of those were weighed; in all of them both foetuses and placentae were smaller than wild type sibs. Most of these were expected to be albino (*c*) because of the higher frequency of complementation found with distal markers (*c*) than with proximal (*uw*) and five clearly fell into the same category as the presumptive albinos in the T9H *c*/+ *c* ♀ × T9H +/+ + ♂ crosses, with placental weights 39%–60% of normal litter-mates. The others had higher placental weight ratios (64%–95% of normal); some were probably *uw*/*uw*.

Taken as a whole, these crosses suggest that paternal duplication/maternal deficiency for proximal 15, i.e. maternal duplication/paternal deficiency for proximal 7, leads to some foetal retardation and reduction in placental size but this is less pronounced than with maternal duplication/paternal deficiency for distal 7.

4. Discussion

The results with T9H and T50H show that there are at least two regions of defective complementation on Chr 7, one being proximal to the T9H breakpoint at 7B3 and the other distal. Two other lines of evidence suggest that the second region is more distal on Chr 7 than the B3 G-band:

1. The extinct translocation (now known as T(7;?)2Sn used by Snell (1946) for his intercrosses with *sh-1* as marker had a breakpoint very close to *c* on Chr 7. No *sh-1* were obtained in 31 offspring from *sh-1* females or 80 offspring from *sh-1* males although this locus is now known to be distal to the translocation breakpoint, so that a frequency of one-sixth *sh-1* would be expected. If this absence of *sh-1* stems from Chr 7 complementation lethality rather than from the unknown chromosome (which seems very likely when all the linkage test and complementation data are considered) then this region of defective complementation is distal to the *c* locus at 7E1–7E2.

2. Eicher (1988) intercrossed T(7;18)50H heterozygotes in which males were homozygous for fused phalanges (sy^{fp}), a Chr 18 marker distal to the T50H breakpoint (Lane *et al.*, 1981). Out of 53 offspring, one (in a litter of one) was classified as sy^{fp} but died soon after birth. This is a significant difference ($P < 0{\cdot}01$) from the 9 expected after normal complementation. This suggests defective complementation either with paternal duplication/maternal deficiency for distal 18 or maternal duplication/paternal deficiency for Chr 7 distal to the T50H breakpoint between 7E2 and 7F2. T(10;18)18H, with a Chr 18 breakpoint slightly distal to that of T50H, shows normal complementation for distal regions (Searle & Beechey, 1978), so it seems likely that the defective complementation affecting sy^{fp} is a Chr 7 phenomenon beyond the T50H breakpoint at 7E2-7F2.

Three insertions, Is(In7;X)1Ct, Is(7;InX)1Neu and Is(7;1)40H, all involve Chr 7 and might provide some evidence on complementation phenomena in central regions of this chromosome. Is40H/+ males are sterile but outcrosses of balanced female heterozygotes have shown that duplications of the inserted region (7B1-7F1) are lethal *in utero* and cause exencephaly (Searle *et al.* 1983). This severe effect may be connected with maternal duplication and some imprinting factor in the region concerned, which partially overlaps the

proximal region of non-complementation on Chr 7 (and possibly also the distal region). In contrast, the Is1Ct (7C-7F1) and Is1Neu (7C-7D) duplications are both viable and fertile in females (Cattanach, 1961; Adler & Neuhäuser-Klaus, 1987; see also Searle, 1989), although Is1Ct males with the duplication (type II) are runted and have a low viability. The male data are more comparable to those of Is40H, since in females the adjacent X-chromosome results in inactivation of inserted autosomal material in approximately 50% of cells (Cattanach, 1974). Balanced (type I) Is1Ct heterozygotes have not been successfully intercrossed, nor have crosses of type II females and type I males thrown any light on whether there is successful complementation for maternal duplication/paternal deficiency of the C-F1 region of Chr 7. Intercrosses of Is1Neu carriers may prove more rewarding.

While results for T9H/+ intercrosses with *uw* and T50H/+ intercrosses with *p* agree in suggesting that maternal duplication/paternal deficiency for the proximal part of Chr 7 leads to defective complementation, there seems to be some difference between the two in the time of action of the lethal effect, namely antenatal in T50H but neonatal in T9H. This may be connected with the different genetic backgrounds but it is also possible that there is some factor between the T9H and T50H breakpoints (at 7B3 and 7E2-F2) which increases the severity of the effect with the latter.

The earlier death with paternal duplication/maternal deficiency of the distal region of Chr 7 parallels the results of nuclear transplantation experiments (Surani, 1986; Solter, 1988) in which androgenones, with two male pronuclei, generally fail to implant but form extra-embryonic components, while gynogenones, with two female pronuclei, do implant but die a few days later. These effects in distal Chr 7, as well as those of maternal duplication/paternal deficiency on Chr 6 in the centromere-B3 region (Beechey & Cattanach, 1989), and of proximal Chr 2 (Cattanach, 1986 and unpublished) are clear-cut examples of non-complementation intrauterine lethality and thus the most drastic imprinting effects yet found on mouse chromosomes.

In the distal region of Chr 7, defective complementation was seen to be associated with a marked reduction in placental as well as foetal size. Defective complementation of maternal duplications and paternal deficiencies in a proximal region of mouse 11 is also associated with small body size, while large body size occurs in the reciprocal cross (Cattanach & Kirk, 1985). The authors suggested that these anomalies were connected with hormonal control of foetal growth mediated through the placenta; differences in placental size from 14 days gestation onwards have in fact been found (Cattanach & Beechey, 1990). The Chr 7 effects on size might also be connected with disturbances in placental gene action but no connection between mouse 7 and placental gene action is known (Jackson-Grusby *et al.* 1988).

Some regions of the human genome which have homologues on mouse 7 may also be subject to imprinting. Homologous genes to those on mouse 7 have been reported on human chromosome arms 6p, 10q, 11p and 11q, 15q, 16p and 19q (Searle *et al.* 1989). The proximal (centromere-B1) region of mouse 7 has at least six homologues in the human 19q12-q13 region (Fig. 6). The human gene for dystrophia myotonia (DM) is in the same region, at 19q13. Its severe congenital form (Steinert's disease) is associated with maternal transmission only (Harper, 1975, 1986), while in the homologous region of mouse 7 maternal duplication/paternal deficiency leads to neonatal death. Several regions with homologues to human 11p and 11q loci have been identified on mouse 7 distal to the 19q homologies (Lyon, 1989). The most distal group includes the locus for haemoglobin beta chain (*Hbb*), with human homologue (HBB) at 11p15·5, and for tyrosine hydroxylase (*Th*) with human homologue (TH) in the same sub-band. Both of these are in or near the distal 7 region of lethal complementation (Fig. 6). Two human pathological conditions, also located in this region, show evidence of imprinting effects. One is embryonal rhabdomyosarcoma (RMS), the locus of which is thought to map to 11pter–11p15·5 (Scrable *et al.* 1989). These malignant tumours arise from cells that are paternally isodisomic for loci on 11p.

Preferential retention of paternal human Chr 11 alleles is also observed (Schroeder *et al.* 1987) in Wilms tumour (WAGR), mapped more proximally to 11p13 and thought more likely to have a homologue on mouse Chr 2 (which has at least three 11p13 homologies) than Chr 7. However, imprinting phenomena also occur in different regions of mouse Chr 2 (Cattanach & Kirk, 1985), so the combination of two imprinting regions might well have occurred in human evolution. Beckwith–Wiedemann syndrome (BWS), located close to RMS at 11pter–p15·4, is also thought to be implicated in the imprinting process (Hall, 1990) since Lubinsky *et al.* (1974) reported that some of the male but all of the female carriers had affected children (see also Niikawa *et al.* 1986). Thus maternal transmission has severe effects in this syndrome, which contrasts with effects of paternal isodisomy in embryonal rhabdomyosarcoma and with the lethal effects of both maternal-only and paternal-only transmission in the distal part of mouse chromosome 7. However, this region of mouse Chr 7 appears to include homologous loci on other human chromosomes, such as 11q and 16, which might also be involved in imprinting phenomena. It should be noted also that detection of a human chromosome region in which transmission both through the mother only and through the father only is lethal *in utero* would probably be very difficult, since any small deletion in that region with a phenotypic effect would behave as if non-heritable.

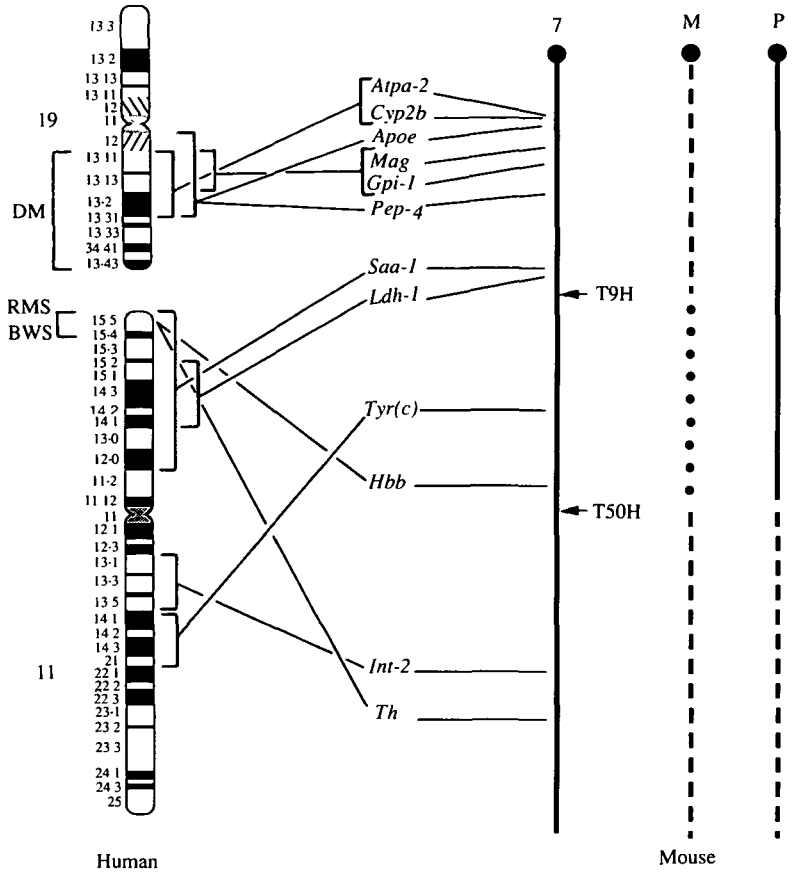

Fig. 6. The relationship between regions of defective complementation on mouse 7 (right) and loci (DM, RMS and BWS) on human chromosomes 11 and 19 (left) which show differential parental transmission. Positions of mouse loci with human homologues are shown on the mouse linkage map (Davisson *et al.* 1989) in relation to the T9H and T50H breakpoints, which delineate the regions of defective complementation, and on the human chromosomes (see McAlpine *et al.* 1989). It can be seen that the loci for dystrophia myotonia (DM), rhabdomyosarcoma (RMS) and Beckwith–Weidemann syndrome (BWS) all lie in regions which have homology with the imprinting regions on mouse 7. These regions are shown with interrupted lines where there is defective complementation with maternal duplication/paternal deficiency (M) or with paternal duplication/maternal deficiency (P). The continuous line shows a region of normal complementation, while the situation is unknown in the region with dotted line.

Tests for imprinting effects have now been carried out on all mouse autosomes except Chr 12, although in a few chromosome regions the situation is unknown. The latest data (Berger & Epstein, 1989; Cattanach & Beechey, 1990) suggest clear-cut imprinting effects in five of the 18 autosomes studied, namely Chrs 2, 6, 7, 11 and 17, i.e. 28% of the autosomes. Solter (1988) & Hall (1990) have named 16 different human hereditary conditions in which there is some evidence for differential parental transmission, which would suggest the intervention of imprinting phenomena. In eleven of these, i.e. 69%, their chromosomal location is such that a mouse homologue would be expected to lie on one of the mouse imprinting chromosomes (McAlpine *et al.* 1989; Searle *et al.* 1989). Thus loci for Wilms tumour (WAGR), Angelman (ANCR) and Prader-Willi (PWCR) syndromes would be expected on mouse Chr 2, although Nicholls *et al.* (1990) have mapped a conserved cDNA clone from the same region as the last two (human 15q11–q13) to mouse Chr 7. The locus for cystic fibrosis (CF) would be expected on Chr 6; for dystrophia myotonia (DM), embryonal rhabdomyosarcoma (RMS) and Beckwith–Wiedemann syndrome (BWS) on Chr 7; for Miller–Dieker syndrome (MDCR) and neurofibromatosis I (NFI) on Chr 11 and for insulin-dependent diabetes mellitus (IDDM) and spinocerebellar ataxia (SCA1) on Chr 17. The probability that homologues of such a high proportion of these suspect conditions should be located purely by chance on the imprinting mouse chromosomes is less than 0·02 ($\chi_1^2 = 5{\cdot}7$), so there are good reasons for believing that the imprinting regions of man and mouse have been conserved (Reik, 1989). What is needed now is more precise location of the regions involved and better understanding of the developmental defects which lead to the very severe examples of non-complementation that are found on mouse chromosome 7.

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References

Adler, I. D. & Neuhäuser-Klaus, A. (1987). Seventeen stocks of mice with reciprocal or Robertsonian translocations. *Mouse News Letter* **77**, 139–142.

Beechey, C. V. & Cattanach, B. M. (1989). Chromosome 6 and genetic imprinting. *Mouse News Letter* **84**, 82–83.

Berger, C. N. & Epstein, C. J. (1989). Genomic imprinting: normal complementation of murine chromosome 16. *Genetical Research* **54**, 227–230.

Cattanach, B. M. (1961). A chemically-induced variegated-type position effect in the mouse. *Zeitschrift für Vererbungslehre* **92**, 165–182.

Cattanach, B. M. (1974). Position effect variegation in the mouse. *Genetical Research* **23**, 291–306.

Cattanach, B. M. (1982). Non-disjunction tests with Robertsonian translocations. *Mouse News Letter* **66**, 62–63.

Cattanach, B. M. (1986). Parental origin effects in mice. *Journal of Embryology and Experimental Morphology* Suppl. **97**, 137–150.

Cattanach, B. M. & Beechey, C. V. (1990). Chromosome imprinting phenomena in mice and indications in man. *Chromosomes Today*. (in the press).

Cattanach, B. M. & Kirk, M. (1985). Differential activity of maternally and paternally derived chromosome regions in mice. *Nature* **315**, 496–498.

Davisson, M. T., Roderick, T. H., Hillyard, A. L. and Doolittle, D, P. (1989). The locus map of the mouse. *Mouse News Letter* **84**, 15–23.

Eicher, E. M. (1988). Personal communication.

Green, M. C. (1989). Catalog of mutant genes and polymorphic loci. In *Genetic Variants and Strains of the Laboratory Mouse*, 2nd ed. (ed. M. F. Lyon and A. G. Searle), pp. 12–403. Oxford University Press.

Hall, J. G. (1990). Genomic imprinting – review and relevance to human diseases. *American Journal of Human Genetics* (in press).

Harper, P. S. (1975). Congenital myotonic dystrophy in Britain. II. Genetic basis. *Archives of Diseases in Childhood* **50**, 514–521.

Harper, P. S. (1986). Myotonic disorders. In *Myology* (ed. A. G. Engel and B. Q. Banker), pp. 1267–1293. New York: McGraw-Hill.

Jackson-Grusby, L. L., Pravtcheva, D., Ruddle, F. H. & Linzer, D. I. H. (1988). Chromosomal mapping of the prolactin/growth hormone gene family in the mouse. *Endocrinology* **122**, 2462–2466.

Lane, P. W., Searle, A. G., Beechey, C. V. & Eicher, E. M. (1981). Chromosome 18 of the house mouse. *Journal of Heredity* **72**, 409–412.

Lubinsky, M., Herrmann, J., Kosseff, A. L. & Opitz, J. M. (1974). Autosomal-dominant sex-dependent transmission of the Wiedemann–Beckwith syndrome. *Lancet* i, 932.

Lyon, M. F. (1983). The use of Robertsonian translocations for studies on nondisjunction. In *Radiation-induced Chromosome Damage in Man*. (ed. T. Ishihara and M. S. Sasaki), pp. 327–346. New York: Alan R. Liss.

Lyon, M. F. (1989). Mouse chromosome atlas. *Mouse News Letter* **84**, 24–45.

Lyon, M. F. & Glenister, P. H. (1977). Factors affecting the observed number of young resulting from adjacent-2 disjunction in mice carrying a translocation. *Genetical Research* **29**, 83–92.

McAlpine, P. J., Shows, T. B., Boucheix, C., Stranc, L. C., Berent, T. G., Pakstis, A. J. & Doute, R. C. (1989). Report of the nomenclature committee and the 1989 catalog of mapped genes. *Cytogenetics and Cell Genetics* **51**, 13–66.

Nicholls, R. D., Williams, C. A. & Butler, M. G. (1990). Chromosome imprinting of 15q11q13 suggested by study of Prader–Willi and Angelman syndromes. Abstracts, Joint Meeting of B.S.C.B., B.S.D.B. and A.S.G.B.I., Manchester, April 1990.

Niikawa, N., Ishikiriyama, S., Takahashi, S., Inagawa, A., Tonoki, H., Ohta, Y., Hase, N., Kamei, T. & Kajii, I. (1986). The Wiedemann–Beckwith Syndrome: pedigree studies in five families with evidence for autosomal dominant inheritance with variable expressivity. *American Journal of Medical Genetics* **24**, 41–55.

Reik, W. (1989). Genomic imprinting and genetic disorders in man. *Trends in Genetics* **5**, 331–336.

Russell, L. B. (1971). Definition of functional units in a small chromosomal segment of the mouse and its use in interpreting the nature of radiation-induced mutations. *Mutation Research* **11**, 107–123.

Schroeder, W. T., Chao, L. T., Dao, D. D., Strong, L. C., Patrick, S., Riccardi, V., Lewis, W. H. & Saunders, G. F. (1987). Nonrandom loss of maternal chromosome 11 alleles in Wilms tumour. *American Journal of Human Genetics* **40**, 413–420.

Scrable, H., Cavenee, W., Ghavimi, F., Lovell, M., Morgan, K. & Sapienza, C. (1989). A model for embryonal rhabdomyosarcoma tumorigenesis that involves genomic imprinting. *Proceedings of the National Academy of Sciences, USA* **86**, 7480–7484.

Searle, A. G. (1989). Numerical variants and structural rearrangements. In *Genetic Variants and Strains of the Laboratory Mouse*. (ed. M. F. Lyon and A. G. Searle), pp. 582–619. Oxford University Press.

Searle, A. G. & Beechey, C. V. (1978). Complementation studies with mouse translocations. *Cytogenetics and Cell Genetics* **20**, 282–303.

Searle, A. G. & Beechey, C. V. (1985). Noncomplementation phenomena and their bearing on nondisjunctional effects. In *Aneuploidy* (ed. V. L. Dellarco, P. E. Voytek and A. Hollaender), pp. 363–376. New York: Plenum.

Searle, A. G., Ford, C. E. & Beechey, C. V. (1971). Meiotic disjunction in mouse translocations and the determination of centromere position. *Genetical Research* **18**, 215–235.

Searle, A. G., Peters, J., Lyon, M. F., Hall, J. G., Evans, E. P., Edwards, J. H. & Buckle, V. J. (1989). Chromosome maps of man and mouse IV. *Annals of Human Genetics* **53**, 89–140.

Searle, A. G., Beechey, C. V., de Boer, P., de Rooij, D. G., Evans, E. P. & Kirk, K. M. (1983). A male-sterile insertion in the mouse. *Cytogenetics and Cell Genetics* **36**, 617–626.

Snell, G. D. (1946). An analysis of translocations in the mouse. *Genetics* **31**, 157–180.

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

Surani, M. A. H. (1986). Evidences and consequences of differences between maternal and paternal genomes during embryogenesis in the mouse. In *Experimental Approaches to Mammalian Embryonic Development* (ed. J. Rossant and R. A. Pedersen), pp. 401–435. Cambridge University Press.