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Faint lined (*Fnl*): a novel X-linked coat mutant in the mouse

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Summary

We report here a novel X-linked mutant, named faint lined (*Fnl*), which was discovered in the litter of an irradiated 3H1 male (Dr Bruce Cattanach, personal communication). The mutation is associated with fine dorsal striping in affected heterozygous females and prenatal lethality in males. Approximately 50% of *Fnl*/+ females die *in utero* and surviving animals have a reduced weight at birth and weaning. Histological studies failed to reveal the underlying basis of the phenotype or any gross structural abnormalities in internal organs (*Fnl*/+ × *Mus spretus*) F1 affected females were backcrossed to 3H1 males and haplotype analysis positioned *Fnl* in the proximal region of the mouse X chromosome distal to *Ant2* and proximal to *Hprt*. Therefore, *Fnl* lies within a defined conserved segment and its human homologue can be predicted to lie in the ANT2–HPRT region in Xq25. Further genetic resolution of co-segregating markers flanking *Fnl* established that *Fnl* lies in a 7·6 ± 2·6 cM interval between *DXMit50* and *DXMit82*.

1. Introduction

In the late 1960s, Ohno hypothesized that if a gene mapped to the X chromosome of one mammal it would map to the X chromosome of all other mammals (Ohno, 1969). To date, only *Clcn4* and genes that map to the pseudoautosomal regions in the mouse have been found not to follow this rule (Blaschke & Rappold, 1997). Construction of comparative maps between the X chromosomes of various mammals has greatly helped in positioning genes across species and postulating animal models for human genetic disease. The X chromosome comparative map between mouse and human includes at least 10 conserved blocks inside which gene content and order has been preserved throughout evolution (Boyd *et al.*, 1998). Therefore, when a gene is assigned to a conserved block on the mouse X chromosome its position on the human X chromosome can easily be deduced. Thus, by combining mapping data from interspecific backcrosses with well-defined X chromosome comparative maps, mouse models for human disorders can readily be assessed. For example, by relating the predicted map position of the human homologue of the X-linked coat mutant tattered (*Td*), the suggestion that *Td* is a mouse model for the incontinenta pigmenti type 1 has been refuted (Yang-Feng *et al.*, 1986; Uwechue *et al.*, 1996).

Several X-linked mouse mutants are known to be associated with either dorsal striping or patchiness of the coat in heterozygous females and prenatal lethality of males: for example, bare patches (Phillips *et al.*, 1973; Angel *et al.*, 1993), lined (Cattanach *et al.*, 1984; Blair *et al.*, 1998), striated (Phillips, 1963; Angel *et al.*, 1993), stripey (Blair *et al.*, 1998) and tattered (Rasberry *et al.*, 1995; Uwechue *et al.*, 1996; Seo *et al.*, 1997). The stripes and patches seen in the mutant heterozygous females are a result of the X-inactivation process (Lyon, 1961), with the size and shape of the affected areas being dependent on the cell lineages involved and the degree of local cell mingling (Lyon, 1963, 1972).

This paper describes a novel X-linked mouse coat mutant, faint lined (*Fnl*), which is associated with faint dorsal lines in *Fnl*/+ females and prenatal lethality of males. The faint dark lines are most prominent at 8–10 days after birth (Fig. 1) and are similar to those seen in the lined mutant, which maps to the distal region of the mouse X chromosome (Cattanach *et al.*, 1984; Blair *et al.*, 1998). We report that *Fnl*/+ females are smaller than their +/+ littermates but have no gross structural abnormalities

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Fig. 1. *Fnl*/+ females (left and right) and +/+ littermate (centre) at 10 days old.

in any internal organs. We have mapped *Fnl* distal to *Ant2* and proximal to *Hprt*, which precludes it as an allele of lined, and places it in the AGTR2–CF8 segment conserved between the mouse and human X chromosomes.

2. Materials and methods

(i) *Animals*

The animal studies described in this paper were carried out under the guidance issued by the Medical Research Council in 'Responsibility in the Use of Animals for Medical Research' (July 1993). All animals were bred in the animal facility at the Mammalian Genetics Unit, Harwell. The mutant stock, which was difficult to keep because of the difficulty in recognizing *Fnl*/+ females and their low intrauterine viability, was maintained by mating *Fnl*/+ females to 3H1 males. 3H1 is an F1 hybrid produced by mating C3H/HeH females to 101/H males. *Mus spretus* animals were maintained by random mating within the stock.

For mapping of *Fnl*, (*Fnl*/+ × *Mus spretus*) F1 females were produced by *in vitro* fertilization (Glenister, 1987) as *Mus spretus* males failed to mate naturally with *Fnl*/+ females. Seven interspecific hybrid females were generated and all were back-crossed to 3H1 males as *Fnl*/+ animals could not be distinguished from their wild-type sibs. Three F1 hybrids produced some female offspring which could be unambiguously scored as *Fnl*/+ and hence these three could be assumed to carry the mutation. The sex ratio of progeny produced by these *Fnl*/+ females was 2:1 in favour of females (94:46), which indicated that *Fnl* was associated with prenatal lethality of males on a *Mus spretus* as well as a 3H1 background. Reliable identification of *Fnl*/+ females among the backcross progeny was not possible; therefore, DNA for genotype analysis was prepared from male backcross progeny that could be predicted to carry the wild-type allele at *Fnl*.

(ii) *Statistical analyses*

Two litters, which included 3 *Fnl*/+ and 7 +/+ females, were weighed and marked at birth, classified at 8–10 days old and weighed again at weaning (~ 21 days after birth). These data were examined using a two-factor analysis of variance after logarithmic transformation. Breeding data were compiled from litters that were complete at classification and analysed using maximum likelihood methods.

(iii) *Histological examinations*

Skins and organs of mutant and control females were fixed in 10% phosphate-buffered formalin, embedded in paraffin wax and serial sagittal sections were stained with haematoxylin and eosin. All organs were examined with a light microscope at ×40–400 magnification. For electron microscopy studies, tissues were fixed in 2·5% glutaraldehyde buffer, post-fixed in 1% osmium tetroxide and dehydrated prior to embedding in epon 812 resin for sectioning. Sections were stained with lead citrate and uranyl acetate.

(iv) *Molecular markers*

Primer pairs for microsatellites were synthesized by the UK MRC Resource Centre (http://www.hgmp.mrc.ac.uk) from sequences published by Research Genetics (http://www.resgen.com). Primer sequences and PCR conditions for the amplification of *Ant2* and *Agtr2* have been published previously (Ellison *et al*., 1996; Sutton & Wilkinson, 1997). All other PCR reactions were carried out in standard buffer containing 1·5 mM $MgCl_2$ at an annealing temperature of 55 °C.

3. Results

(i) *Reduced intrauterine survival and birth weight of Fnl*/+ *animals*

In the course of keeping the stock, it was noted that few *Fnl*/+ females were generated and that the sex ratio of missing animals suggested no preferential postnatal loss of *Fnl*/+ animals (see below). A more careful analysis of the breeding data was undertaken to investigate whether the paucity of *Fnl*/+ animals was caused by prenatal death or by a failure to recognize all animals that carried *Fnl*. As *Fnl*/Y males die before 15·5 days *post coitum* (L. Vizor, personal communication), a 1:1:1 ratio of *Fnl*/+ : +/+ : +/Y would be expected. Of the 453 animals bred during this investigation, 174 were +/+, 86 were classified as *Fnl*/+ and 193 were +/Y animals. Statistical

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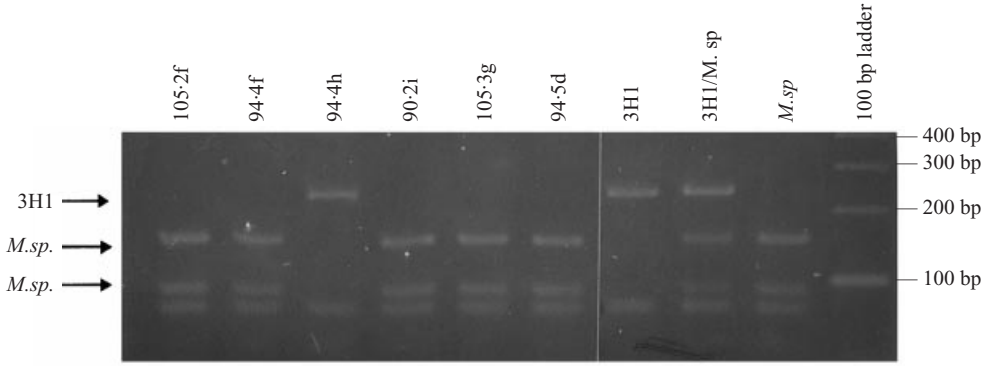

Fig. 2. PCR amplification products at *Ant2* produced from (*Fnl*/+ × *Mus spretus*) × 3H1 backcross males (+/Y) and controls (*M*. sp.–*Mus spretus*). Amplification products were digested with *Dde*I to reveal the variation between *Mus spretus* (150 bp, 90 bp) and 3H1 (240 bp) and an additional smaller invariant amplification product.

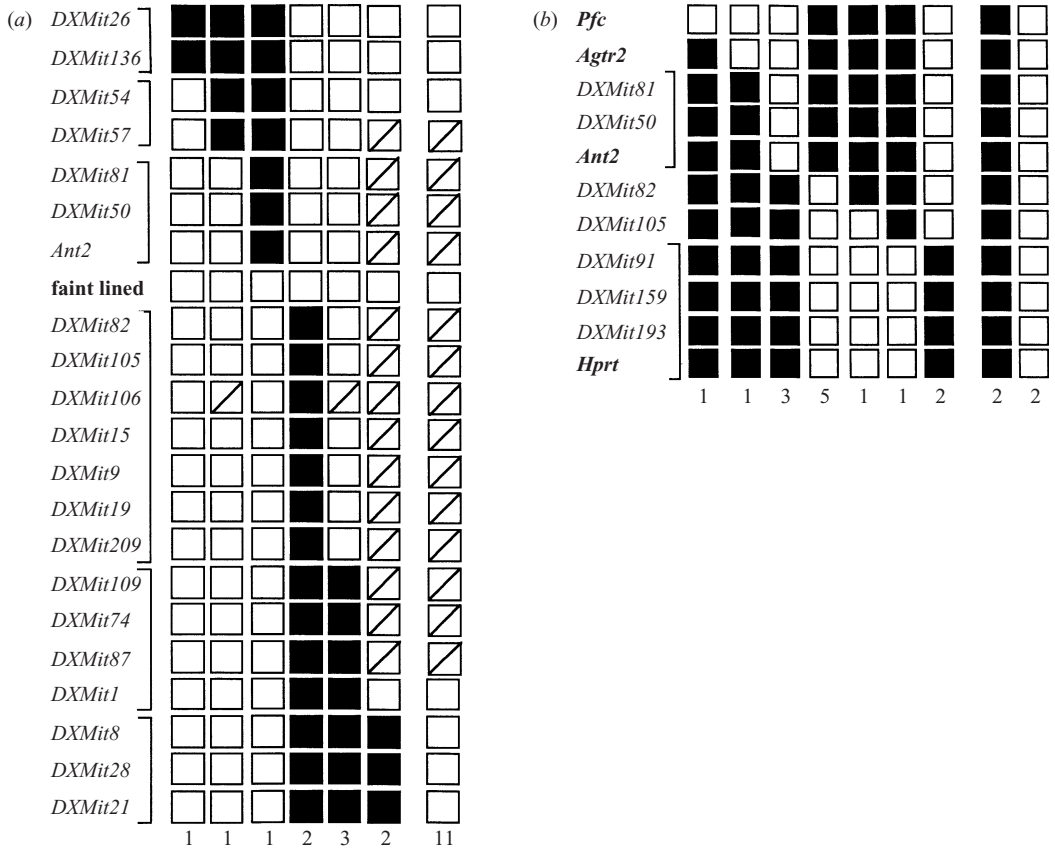

Fig. 3. Mapping of *Fnl*. (*a*) Haplotype analysis of 21 male backcross progeny from *Fnl*/*Mus spretus* interspecific hybrids. The order of loci, and genetic distances established in this cross, were (*DXMit26*, *DXMit136*) – (4·8 ± 4·7 cM) – (*DXMit54*, *DXMit57*) – (4·8 ± 4·7 cM) – (*DXMit81*, *DXMit50*, *Ant2*) – (4·8 ± 4·7 cM) – faint lined – (9·5 ± 6·4 cM) – (*DXMit82*, *DXMit105*, *DXMit106*, *DXMit15*, *DXMit9*, *DXMit19*, *DXMit209*) – (14·2 ± 7·6 cM) – (*DXMit109*, *DXMit74*, *DXMit87*, *DXMit1*) – (9·5 ± 6·4 cM) – (*DXMit8*, *DXMit28*, *DXMit21*). (*b*) Ordering of markers flanking *Fnl* by haplotype analysis of recombinants in the *Pfc*–*Hprt* interval from a well-characterized interspecific backcross (Laval & Boyd, 1993). Filled squares, 3H1 allele; open squares, *Mus spretus* allelle inherited from F1 female; striped squares, combination not tested. Co-segregating loci are bracketed.

analysis demonstrated that these numbers differed significantly from a 1:1:1 ratio ($\chi^2 = 43{\cdot}17$; d.f. = 2; $P = 3{\cdot}1 \times 10^{-6}$). When a maximum likelihood test was applied to the data, the best fit indicated that approximately 53% were dying prenatally and none appeared to be misclassified as wild-type ($\chi^2 = 0{\cdot}0508$; $P = 0{\cdot}82$). Examination of the sex of animals missing between birth and classification indicated that these were in the 3:2 ratio (69:43, female:male) expected if approximately 50% of *Fnl*/+ animals die *in utero*. Therefore we suggest that there is no preferential loss of *Fnl*/+ animals between birth and classification.

It was noticed that *Fnl*/+ females were generally smaller than their +/+ littermates. This was verified

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by weighing individual animals at birth and wearning. *Fnl*/+ females were found to weight only 77·2% and 69·3% as much as their littermates at birth and weaning respectively ($F(1,5) = 8{\cdot}8$, $P = 0{\cdot}012$ at birth; and $F(1,5) = 14{\cdot}95$, $P = 0{\cdot}012$ at weaning). There was no significant difference between the growth rate of the *Fnl*+ and +/+ sibs between birth and weaning.

(ii) *Histological studies*

Fnl/+ females are characterized by faint dorsal stripes that can be scored readily between 8 and 10 days after birth (Fig. 1) but which cannot be seen after weaning. Skins from 10- and 14-day-old *Fnl*/+ and control littermates were sectioned and stained with haematoxylin and eosin. However, all epidermal and dermal structures, including hair follicles and melanocytes, appeared normal and no explanation could be found for the fine stripes observed. Hair from normal and striped regions of the coat was plucked and compared. The four major hair types (monotrichs, awls, auchenes, zizags) could be seen in both sets of hair samples. However, because of the subtlety of the striping, it was difficult to be sure that no hair from the normal region of the coat was present in the sample plucked from the striped region. No gross abnormalities were observed in any of the internal organs examined (heart, liver, kidney and lung), though they were generally smaller and less mature (data not shown). Furthermore, no gross abnormalities were seen in intracellular structures, including lysosomes, in a range of tissues (skin, heart, liver, kidney, lung, brain, spleen) examined by electron microscopy.

(iii) *Mapping studies*

Localization of the mutation on the X chromosome was carried out by interspecific backcross analysis. Mutant (*Fnl*/+ × *Mus spretus*) F1 females were mated to 3H1 males and DNA was prepared from 21 male backcross progeny. *Fnl* was first positioned in the *DXMit26–DXMit8* interval by scoring *DXMit26*, *DXMit8* and *DXMit21*, which lie in the proximal, central and distal regions of the mouse X chromosome respectively (Blair & Boyd, 1994). Microsatellites known to lie between *DXMit26* and *DXMit8* were then selected and tested against the recombinants (Dietrich *et al*., 1996). *Fnl* was found to lie distal to *DXMit81* and *DXMit50* and proximal to *DXMit82*, *DXMit105*, *DXMit106*, *DXMit159*, *DXMit91*, *DXMit193* and *DXMit209*. To place *Fnl* on the comparative map, critical recombinants were genotyped for the amplification product variant at *Ant2* (Fig. 2), the gene encoding adenine nucleotide translocase-2 that had been reported to lie in the vicinity of *DXMit50* (Ellison *et al*., 1996; Sutton & Wilkinson, 1997). *Fnl* was found to lie distal to *Ant2* and the genetic order and distances were established

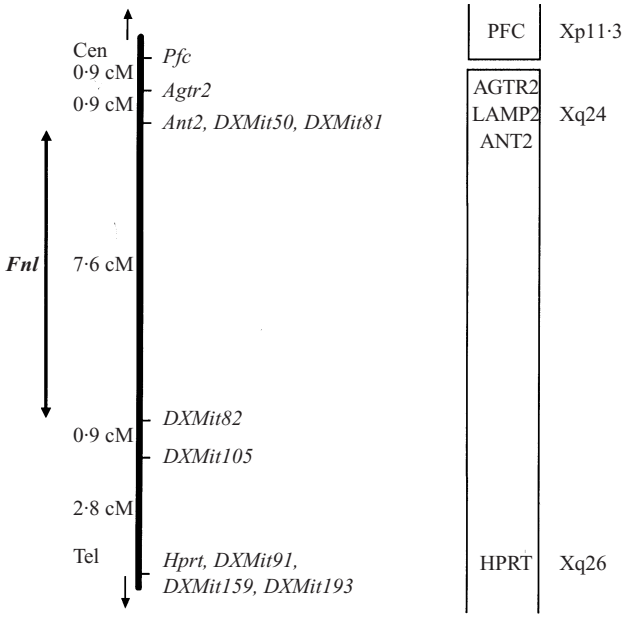

Fig. 4. Genetic map depicting the position of *Fnl* with the corresponding regions of the human X chromosome shown on the right. Note that *DXMit50* is the nearest proximal flanking marker to *Fnl* as it has been shown to lie distal to *Ant2* and *DXMit81* (Sutton & Wilkinson, 1997).

as: *Ant2*, *DXMit81*, *DXMit50* – (4·8 ± 4·7 cM) – *Fnl* – (9·5 ± 6·4 cM) – *DXMit82*, *DXMit105*, *DXMit106*, *DXMit159*, *DXMit91*, *DXMit193*, *DXMit209* (Fig. 3*a*). These data place *Fnl* in the AGTR2–CF8 segment conserved between the human and mouse X chromosomes.

To narrow the critical interval and to confirm the position of *Fnl* on the comparative map, a well-characterized (3H1 × *Mus spretus*) F1 × 3H1 backcross (Laval & Boyd, 1993) was used to order the markers that co-segregated distally to *Fnl*. All recombinants between *Pfc* and *Hprt* were analysed from this backcross (18 recombinants from a total of 104 backcross progeny scored for both *Pfc* and *Hprt*). The 18 recombinants were genotyped for *DXMit81*, *DXMit50*, *DXMit82*, *DXMit105*, *DXMit159*, *DXMit91*, *DXMit193* and *Ant2*. These recombinants were also typed at the locus encoding the angiotensin AT_2 receptor, *Agtr2*, which is the most proximal locus of the conserved segment that stretches from *Agtr2* to *Cf8* and contains *Hprt* (Hein *et al*., 1995; Sutton & Wilkinson, 1997). The following genetic order and distances were calculated: *Pfc* – (0·9 ± 0·9 cM) – *Agtr2* – (0·9 ± 0·9 cM) – *Ant2*, *DXMit50*, *DXMit81* – (7·6 ± 2·6 cM) – *DXMit82* – (0·9 ± 0·9 cM) – *DXMit105* – (2·8 ± 1·6 cM) – *DXMit91*, *DXMit193*, *DXMit159*, *Hprt* (Fig. 3*b*). Thus, we can conclude that *Fnl* lies in the 7·6 ± 2·6 cM interval between the co-segregating markers *DXMit50*, *DXMit81* and *Ant2* and *DXMit82* (Fig. 4). The distance between the flanking markers measured in these studies is not significantly different

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from the $14{\cdot}2 \pm 7{\cdot}6$ cM calculated from the data obtained from the backcross segregating faint lined. It also agrees well with that presented by Sutton & Wilkinson (1997), who calculated the genetic distance between *Ant*, *DXMit50* and *DXMit105* to be $7{\cdot}5 \pm 2{\cdot}5$ cM. In the same report, these authors also determined the order of markers as cen – *Ant2* – *DXMit81* – *DXMit50* – *tel* using a different backcross, and therefore the nearest flanking markers to *Fnl* are *DXMit50* and *DXMit82* on the proximal and distal sides respectively.

4. Discussion

Faint lined is a novel X-linked mutant associated with prenatal lethality in males and fine dorsal striping in heterozygous females. On a 3H1 genetic background, 53% of affected females die *in utero* and surviving heterozygotes are significantly smaller than their littermates at birth and weaning. However, the aetiology of the phenotype observed in *Fnl*/+ females was not revealed by histological studies. The observations of low birth weight, death before birth and difficulties in scoring the phenotype in *Fnl*/+ females indicate that surviving animals are more likely to have an X-inactivation pattern skewed in favour of cells with an active X chromosome carrying the wild-type locus at *Fnl*. This hypothesis is supported by finding female offspring with an extreme tabby (*Ta*) phenotype, presumed to be *Ta* +/+ *Fnl*, when *Fnl*/+ females were mated to *Ta* males (H. J. Blair, personal communication). Whether this skewing of X-inactivation pattern in the coat also occurs in other organs remains to be established.

The characteristics of *Fnl*/+ females are very similar to those described for two other X-linked coat mutants: lined and stripey. These two mutants are known to carry nested chromosomal deletions that remove up to 2 cM of genetic material (Blair *et al*., 1998) and it is possible, since the first *Fnl*/+ female was found in the litter of an irradiated male, that *Fnl* is also associated with a genomic deletion. Although no chromosome rearrangement could be seen on G-banded metaphases prepared from *Fnl*/+ animals (E. P. Evans, personal communication), the presence of a deletion in the *Fnl* critical interval cannot be ruled out as none of the X chromosome deletions described to date in the mouse has been detectable on metaphase chromosomes (Blair *et al*., 1998; Cattanach *et al*., 1991).

Although *Fnl* is phenotypically similar to lined and stripey, the mapping studies described here reveal that *Fnl* cannot be allelic to lined or to any of the other X-linked coat mutants associated with prenatal lethality in males, i.e. bare patches (Angel *et al*., 1993), striated (Angel *et al*., 1993) and tattered (Uwechue *et al*., 1996). However, harlequin (*Hq*), an X-linked coat mutant in which males and homozygous females are smaller than normal but fully viable and fertile (Barber, 1971), has been reportd to lie in the vicinity of *Hprt* (Brockdorff *et al*., 1987). *Hq*/Y and *Hq*/*Hq* animals are almost completely bald and *Hq*/+ females have bald patches that can be difficult to see (Falconer & Isaacson, 1972). Brockdorff *et al*. (1987) positioned *Hq* $14{\cdot}4 \pm 4$ cM proximal to *G6pd*, which lies 1 cM distal to *DXMit1* (Boyd *et al*., 1998). *Fnl* lies $23{\cdot}8 \pm 9{\cdot}2$ cM proximal to *DXMit1* (see legend to Fig. 3) and therefore is likely to lie proximal to *Hq*. However, because small numbers of animals were analysed in both crosses, we cannot exclude *Hq* from the *Fnl* critical interval. We have not seen bald patches on the coats of *Fnl*/+ animals but it is possible that *Fnl* is a more severe allele of *Hq* or may carry a deletion that removes *Hq* and another locus which is essential for embryonic survival of males.

Fnl maps distal to *Ant2* and proximal to *Hprt*. Three genes – *Ant2*, *Agtr2* and *Pem* – were excluded as possible candidate genes for the *Fnl* mutation by virtue of their genetic location. Originally, *Lamp2*, a glycoprotein associated with the membrane of lysosomes, was thought to co-segregate with *DXMit50* and therefore close to *Fnl* (Hein *et al*., 1995). *Lamp1*, a protein closely related to *Lamp2*, has been implicated in early melanocyte formation (Zhou *et al*., 1993). It was possible therefore that mutations in *Lamp2* could have an effect on coat pigmentation and result in the phenotype observed in *Fnl*. However, the failure to observe structural lysosomal abnormalities with electron microscopy suggested that this was not the case, a finding which is supported by recent mapping evidence that places *Lamp2* just proximal to *DXMit50* and outside the *Fnl* critical interval (http://www.hgmp.mrc.ac.uk/Mbx; Mbx database).

In conclusion, *Fnl* is a novel X-linked mutant that lies in the AGTR2–CF8 chromosomal segment conserved between the mouse and human X chromosomes, and its human homologue can be predicted to lie in Xq25. It is of interest to note that two disorders that affect the hair, congenital generalized hypertrichosis (MIM 307150; Figuera *et al*., 1995) and Bazex–Dupré–Christol syndrome, which is associated with hypotrichosis (MIM 301845; Vabres *et al*., 1995; Kidd *et al*., 1996), have been mapped to Xq24–Xq27.

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