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High-Resolution Comparative Mapping of the Proximal Region of the Mouse X Chromosome

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The murine homologues of the loci for McLeod syndrome (XK), Dent's disease (ClCN5), and synaptophysin (SYP) have been mapped to the proximal region of the mouse X chromosome and positioned with respect to other conserved loci in this region using a total of 948 progeny from two separate *Mus musculus* × *Mus spretus* backcrosses. In the mouse, the order of loci and evolutionary breakpoints (EB) has been established as centromere–(*DXWas70*, *DXHXF34h*)–EB–*Clcn5*–(*Syp*, *DXMit55*, *DXMit26*)–*Tfe3*–*Gata1*–EB–*Xk*–*Cybb*–telomere. In the proximal region of the human X chromosome short arm, the position of evolutionary breakpoints with respect to key loci has been established as DMD–EB–XK–PFC–EB–GATA1–C1CN5–EB–DXS1272E–ALAS2–EB–DXF34–centromere. These data have enabled us to construct a high-resolution genetic map for the ~3-cM interval between *DXWas70* and *Cybb* on the mouse X chromosome, which encompasses 10 loci. This detailed map demonstrates the power of high-resolution genetic mapping in the mouse as a means of determining locus order in a small chromosomal region and of providing an accurate framework for the construction of physical maps.

INTRODUCTION

The positioning of approximately 70 loci on the X chromosomes of both mouse and human has confirmed the prediction made by Ohno (1973) that X-linkage of genes is largely preserved in mammals (Herman *et al.*, 1994; Willard *et al.*, 1994). However, comparison of the relative positions of these loci in human and mouse has revealed that subchromosomal blocks of homologous loci have been rearranged with respect to each other during the 100 million years of evolutionary time that separate the two species (Amar *et al.*, 1988; Searle *et al.*, 1989; Blair *et al.*, 1994a). A full understanding of the nature of these rearrangements is important for identifying mouse models for human genetic disease, as an identical comparative map position is one criterion for inferring genetic homology between similar phenotypes.

The human–mouse comparative map of the X chromosome is composed of a minimum of eight chromosomal segments (Blair *et al.*, 1994a). There are four blocks of homology in the ~20-Mb region of the proximal human X chromosome short arm; three lie in the proximal region of the mouse X chromosome, and the fourth lies in the distal region (Fig. 1). The largest block runs from Cybb to Pfc[2] and, on the human X chromosome, is flanked on the CYBB boundary by DMD and on the PFC boundary by GATA1. In the mouse, the *Cybb* boundary is flanked by *Gata1/Tfe3* and the *Pfc* boundary by *Lamp2*. The proximity of the small block of homology defined by Gata1/Tfe3 to the conserved segment that runs from Cybb to Pfc led to the suggestion that the current arrangement of loci has resulted from a partial inversion within a larger homologous block (Laval and Boyd, 1993a). GATA1 and TFE3 are known to lie approximately 150 kb apart in human (Derry *et al.*, 1994) and have not been separated by recombination events in the mouse (Blair and Boyd, 1994a; Blair *et al.*, 1994b; Merrell *et al.*, 1995). In human, proximal to GATA1/TFE3 lies a homologous block that runs from DXS1272E (also known as XE169 and SMCX) to ALAS2 (Willard *et al.*, 1994). The murine equivalent of this segment lies in the distal region of the mouse X chromosome (Chapman *et al.*, 1994; Agulnik *et al.*, 1994; Blair *et al.*, 1994a). Finally, close to the centromere in both species lies a complex locus defined by DXF34 (Laval and Boyd, 1993a,b).

While the construction of extensive YAC contigs has

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[2] When symbols refer to loci in conserved segments, and therefore to both species, they are given in nonitalicized lowercase, e.g., Gata1, compared with the human locus name GATA1 and the mouse locus name *Gata1*.

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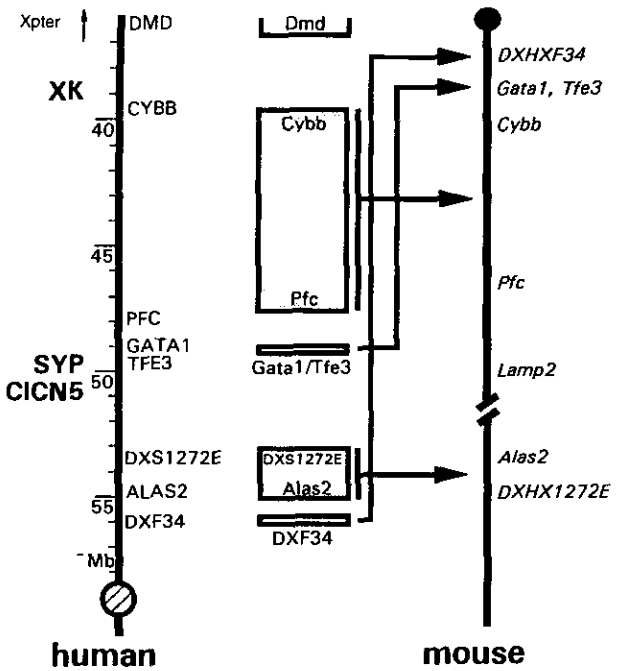

FIG. 1. Human–mouse comparative map of the proximal short arm (Xp21.1–centromere) of the human X chromosome. The approximate positions of loci that define the homologous blocks are indicated on the human physical map and on the mouse genetic map (Willard *et al.*, 1994; Herman *et al.*, 1994). In the center, the known extent of the human–mouse homologous blocks is shown. The block that runs from Cybb to Pfc contains five loci/groups of loci that have been positioned and ordered in both species (Cybb–Otc–DXHX676–Maoa, Maob, Ndp–Timp, Syn, Pfc). UBE1 also lies in this block of homology but has not been ordered with respect to the other loci on the mouse X chromosome. The block that runs from DXS1272E to ALAS2 in human contains five loci that have been positioned in the distal region of the mouse X chromosome but that have not all been ordered with respect to each other (ALAS2, DXHX674, DXHX679, DXS423E, DXS1272E). The orientation *DXHX674/DXHX679–DXS1272E*–telomere has been recently defined by Laval *et al.* (manuscript in preparation). See Table 1 for full details of loci used in this study.

enabled the definition of gene order and approximate distances between genes in the proximal human X chromosome short arm (Willard *et al.*, 1994), many of these loci have not been positioned, or not been positioned with sufficient detail, on the mouse X chromosome, and therefore the locations of evolutionary breakpoints in this region are poorly defined. This paper describes the mapping of the murine homologues of three such loci (XK, ClCN5, and SYP; see Fig. 1). The gene encoding XK is a novel membrane transport protein that has been recently cloned but has not yet been mapped in the mouse (Ho *et al.*, 1994). XK is mutated in patients suffering from McLeod syndrome, a complex disorder characterized by abnormalities in the neuromuscular and hemopoietic systems. XK lies ~200 kb distal to CYBB on the human X chromosome and therefore could lie either proximal to *Cybb* or close to *Dmd* in the central region of the mouse X chromosome. The isolation of ClCN5 (previously ClC-K2), a candidate gene for the X-linked nephrolithiasis Dent's disease, has also been reported recently (Fisher *et al.*, 1994). This gene, ClCN5, is a new member of the voltage-gated chloride channel family and lies close to DXS255, between GATA1 and DXS1272E on the human X chromosome, and therefore could lie in any one of several sites on the mouse X chromosome (Fig. 1). The murine homologue of synaptophysin (SYP) has been mapped previously to the proximal region of the mouse X chromosome by somatic cell hybrid analysis but has not been ordered with respect to other loci in the region (Özçelik *et al.*, 1990).

We report here the mapping of these three loci to the proximal region of the mouse X chromosome and their positioning with respect to other conserved loci in the region using a total of 948 progeny from two separate *Mus musculus* × *Mus spretus* backcrosses. These data and others obtained from mapping murine-specific probes and microsatellite-based loci on the same backcrosses have enabled us to construct a high-resolution genetic map for the ~3-cM interval between *DXWas70* and *Cybb*, which encompasses 10 loci and two evolutionary breakpoints. As a result, the human–mouse comparative map of the region has been significantly improved.

MATERIALS AND METHODS

Interspecific backcrosses. Loci were first positioned using an interspecific backcross bred at the MRC Radiobiology Unit and then, to achieve further separation of markers, on the European Collaborative Backcross. The backcross bred at the RBU (backcross A) comprises two sections: (3H1 or C3H ♀ × *Mus spretus* ♂) F1 females were mated to 3H1 or C3H ♂; 3H1 is an F1 hybrid produced by mating C3H/HeH ♀ to 101/H ♂. No significant difference has been found between any of the genetic distances calculated for X chromosomal loci, and therefore the results from both sections have been pooled (Blair *et al.*, 1993). A total of 225 animals have been typed for four loci in the proximal region of the mouse X chromosome, *DXWas70, DXHXF34, Tfe3,* and *Pfc* (Laval *et al.*, 1991; Blair *et al.*, 1994a and unpublished data). The second backcross (B), the European Collaborative Interspecific Backcross (EUCIB), was produced by mating (C57Bl/6 ♀ × *M. spretus* ♂) F1 females to either C57Bl/6 ♂ or *M. spretus* ♂ (Breen *et al.*, 1994). Approximately 900 backcross animals had been previously typed for *DXWas70* and four other markers on the mouse X chromosome (*DXMit8, Xist, Plp,* and *Grpr*).

Probes and filter hybridizations. Hybridization probes were used to detect most of the conserved loci, and the murine repeat sequence, *DXWas70,* used in this study (see Table 1 and Results). Partial human cDNAs were used to detect the murine homologues of the McLeod syndrome gene, XK (Ho *et al.*, 1994), the voltage-gated chloride channel gene, ClCN5, implicated in Dent's disease (Fisher *et al.*, 1994), and the GATA binding protein 1, GATA1 (Laval and Boyd, 1993a). The hybridization probe used to detect the murine homologue of the synaptophysin gene, SYP, was generated using primers designed from exon 4 of the human cDNA. The forward (GCACCAAGTGTACTTTGATGC) and reverse (GCCCTTTGTTATTCTCTC) primers represent positions 1570–1591 and 1735–1752, respectively, of the sequence given in Özçelik and co-workers (1990). Primers were used to amplify and label an approximately 180-bp product from mouse genomic DNA using standard polymerase chain reaction (PCR) conditions described previously (Blair *et al.*, 1993). Reactions were carried out in the presence of 1 m*M* $MgCl_2$ using an annealing temperature of 55°C. Probes were labeled with [^{32}P]dCTP by nick-translation or multipriming using commercially available kits (Amersham International plc). Southern blotting and filter hybridiza-

TABLE 1

X-Linked RFLVs or APVs Detected at Each Locus

Human locus symbol	Mouse locus symbol	Probe name	Gene name/details	Reference[a]	Restriction enzyme for RFLV	3H1 X-linked bands (kb) or product (bp)	*M. spretus* X-linked bands (kb) or product (bp)
—	*DXWas70*	70–68[b]	X-linked DNA segment	1	*Taq*I	3.5, 1.8	4.0, 3.0
DXF34	*DXF34*	pH3-7[c]	X-linked conserved sequence	2	*Eco*RI	4.0, 1.3	3.0
CLCN5	*Clcn5*	RL-6[d]	Voltage-gated chloride channel N5	3	*Pvu*II	9.4	3.5
SYP	*Syp*	mSYPE4[b]	Synaptophysin	4	*Taq*I	5.0	3.0
GATA1	*Gata*1	K14[d]	GATA binding protein 1	5	*Eco*RI	3.2	3.0
XK	*Xk*	XK[d]	McLeod syndrome gene	6	*Taq*I	0.8	2.2
CYBB	*Cybb*	CYBB[d]	Cytochrome b245 β chain	7	*Taq*I	4.0	2.3, 1.8
PFC	*Pfc*	mP-830[e]	Properdin factor complement	8	*Taq*I	3.1	5.0
TFE3	*Tfe3*	APV	Transcription factor enhancer 3	9, 10	*Hha*I[f]	455	267, 188
—	*DXMit26*	APV	X-linked microsatellite	11, 12		220	206
—	*DXMit55*	APV	X-linked microsatellite	11, 12		116	100
—	*DXMit54*	APV	X-linked microsatellite	11, 12		144	212

[a] References: (1) Disteche *et al.*, 1987; (2) Laval and Boyd, 1993b; (3) Fisher *et al.*, 1994; (4) Özçelik *et al.*, 1990; (5) Zon *et al.*, 1990; (6) Ho *et al.*, 1994; (7) Royer-Pokora *et al.*, 1986; (8) Goundis and Reid, 1988; (9) Roman *et al.*, 1992; (10) Blair and Boyd, 1994b; (11) Dietrich *et al.*, 1992; (12) Research Genetics, Huntsville, AL.

[b] Mouse genomic DNA.

[c] Human genomic DNA.

[d] Human cDNA.

[e] Mouse cDNA.

[f] Requires digestion with *Hha*I to observe the APV.

tions were carried out at 63°C as described previously (Blair *et al.*, 1994a).

PCR-based assays. Amplification product variants (APVs) between *M. musculus* and *Mus spretus* at *Tfe3* (transcription factor enhancer 3) and the microsatellite-based loci *DXMit55, DXMit26,* and *DXMit54* were detected by PCR (see Table 1 and Results). PCR was routinely carried out in a standard buffer containing 1.5 m*M* $MgCl_2$ using an annealing temperature of 55°C. Products were analyzed after fractionation on standard 3% agarose gels.

RESULTS

Amplification product variants (APVs) or restriction fragment length variants (RFLVs) between *M. musculus* strains and *M. spretus* were identified for all loci, and X-linkage confirmed using their F1 progeny (see Table 1; data not shown). Prior to the high-resolution mapping described below, loci were localized to the proximal region of the mouse X chromosome using a panel of backcross animals with single recombination events that divided the X chromosome into 10 intervals (Laval and Boyd, 1993b). In this way, we were able to position *Xk, Clcn5,* and *Syp* proximal to *Pfc* (data not shown). These three loci, and the others described in Table 1, were mapped against two *M. musculus* × *M. spretus* backcross panels (see Materials and Methods).

When 225 animals from the first interspecific backcross were typed for *DXWas70* and *Pfc,* 18 single recombination events were identified in this interval, and thus the estimated genetic distance between these two loci is 8.0 ± 1.8 cM. These 18 recombination events were typed for all of the loci given in Table 1, including *Xk, Clcn5,* and *Syp* (Figs. 1 and 2). Pedigree analysis established the order of loci as (*DXWas70, DXHXF34h*)–(2.2 ± 0.9)–(*Clcn5, Syp, DXMit26, DXMit55*)–(0.5 ± 0.5)–(*Gata1, Tfe3, Xk*)–(0.5 ± 0.5)–*Cybb*–(2.6 ± 1.1)–*DXMit54*–(2.2 ± 0.9)–*Pfc* (Fig. 3a). Cosegregating loci are shown in brackets, and the figures represent the calculated genetic distance (in centimorgans) between adjacent loci. These results demonstrate that the conserved segment known previously to contain *Gata1* and *Tfe3* can be extended to contain *Clcn5* and *Syp.* In addition, as *Xk* was found to lie proximal to *Cybb* and not close to *Dmd* in the central region of the mouse X chromosome, the conserved segment previously defined by *Cybb–Pfc* can be redefined as the region delineated by *Xk* and *Pfc.*

As we could not determine the order of several loci in the first backcross, we identified a further set of recombination events in this region from the high-resolution European Collaborative Interspecific Backcross (Breen *et al.*, 1994). We had previously scored this backcross for *DXWas70,* and, as the results described above indicated that the *DXWas70–DXMit54* interval would be relevant to our studies, we scored the entire backcross for *DXMit54* to identify all of the single recombination events between these two markers. Of 723 backcross animals scored for both loci, 38 were found to contain recombination events in this interval, and the genetic distance between the two loci was calculated to be 5.3 ± 0.8 cM, which was not significantly different from that measured in the first backcross (5.7 ± 1.5 cM; 13 recombination events were detected in

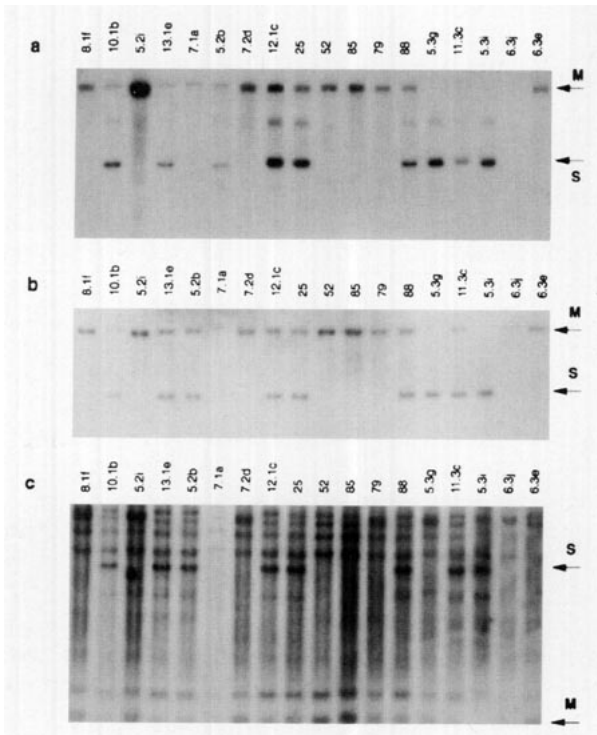

FIG. 2. Recombination events from backcross A typed for (**a**) *Clcn5,* (**b**) *Syp,* and (**c**) *Xk.* **M** and **S** indicate the *Mus musculus* and *Mus spretus* X-linked bands, respectively. Mouse reference numbers are given above each DNA track. For further details of these loci and the RFLVs detected in this work, see Table 1 and Materials and Methods.

225 backcross progeny scored for both *DXWas70* and *DXMit54*). Variants at the loci described in Table 1 were scored in 29 backcross animals that carried recombination events between *DXWas70* and *DXMit54.* Pedigree analysis enabled us to define the order of loci and estimate the genetic distances between loci to be (*DXWas70, DXHXF34*)–(0.7 ± 0.4)–*Clcn5*–(1.0 ± 0.5)–(*Syp, DXMit55, DXMit26*)–(0.5 ± 0.3)–*Tfe3*–(0.2 ± 0.2)–*Gata1*–(0.7 ± 0.4)–*Xk*–(2.2 ± 0.6)–*DXMit54* (Fig. 3b). As not all of the recombinants in any defined interval could be scored for variants at all loci, genetic distances were estimated by calculating the expected number of total recombinants from the proportion actually scored (values are in centimorgans). The results obtained from the EUCIB backcross established an order for the conserved loci in the region as *DXHXF34–Clcn5–Syp–Tfe3–Gata1–Xk–Cybb.* Furthermore, *Xk* has been placed distal to *Gata1,* and there appears to be no hidden rearrangements in the boundary between these blocks.

DISCUSSION

Previous mapping studies of *M. musculus* × *M. spretus* interspecific backcrosses established in our laboratory had established that the order of loci and evolutionary breakpoints (**EB**s) in the most proximal region of the mouse X chromosome was centromere–(*DXWas70, DXHXF34*)–**EB**–(*DXMit26, Gata1, Tfe3*)–**EB**–*Cybb*–telomere (Laval and Boyd, 1993b; Blair and Boyd, 1994a,b; see Fig. 1). In this paper we have positioned several additional markers into this interval and produced a high-resolution genetic map of the region based on 948 meioses with an order of loci and evolutionary breakpoints as centromere–(*DXWas70, DXHXF34*)–**EB**–*Clcn5*–(*Syp, DXMit55, DXMit26*)–*Tfe3–Gata1*–**EB**–*Xk–Cybb*–telomere (Fig. 4). This genetic map of ordered loci will provide an invaluable starting point for the construction of a YAC contig across the region and the subsequent production of a physical map. However, even at this resolution, we have been unable to separate the three loci *Syp, DXMit55,* and *DXMit26* by recombination, and therefore we suggest that they must lie within a few hundred kilobases of each other. We have also been unable to detect any recombination between *DXWas70* and *DXHXF34* in 225 mice in backcross A or in any of the 29 recombination events scored for these two loci in the *DXWas70* to *DXMit54* interval from backcross B. These observations indicate that the RFLVs detected at *DXWas70* and *DXHXF34* must lie extremely close on the mouse X chromosome and/or that it is possible that *DXHXF34* is the more proximal of the two loci.

The data reported here provide a greatly enhanced definition of the conserved segment previously represented by Gata1 and Tfe3, which lie approximately 150 kb apart on the human X chromosome (Derry *et al.,* 1994). This segment now extends from Clcn5 to Gata1

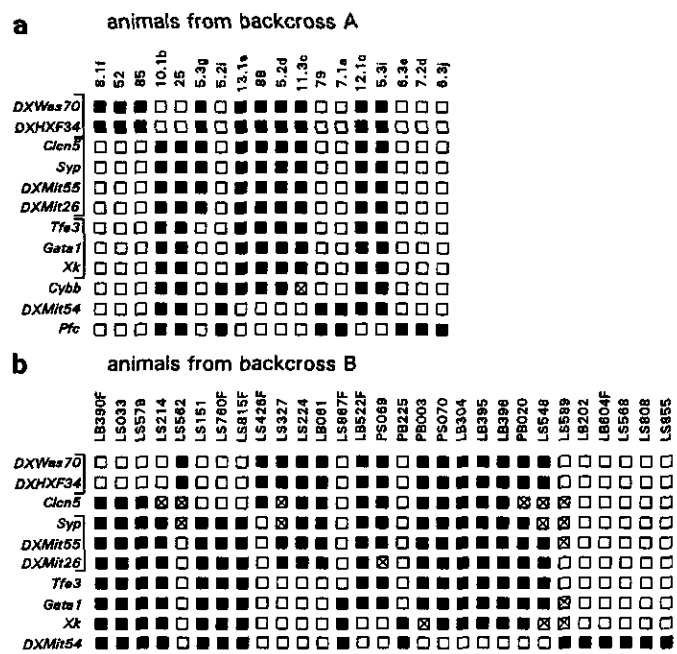

FIG. 3. Haplotype analysis of recombination events and loci in (**a**) backcross A (RBU) and (**b**) backcross B (EUCIB). In each case, loci are shown, in order from the centromere, on the left, and mouse reference numbers are given at the top. (■) *Mus spretus* allele inherited on recombinant maternal X chromosome; (□) *Mus musculus* allele inherited on recombinant maternal X chromosome; (⊠) this combination was not scored.

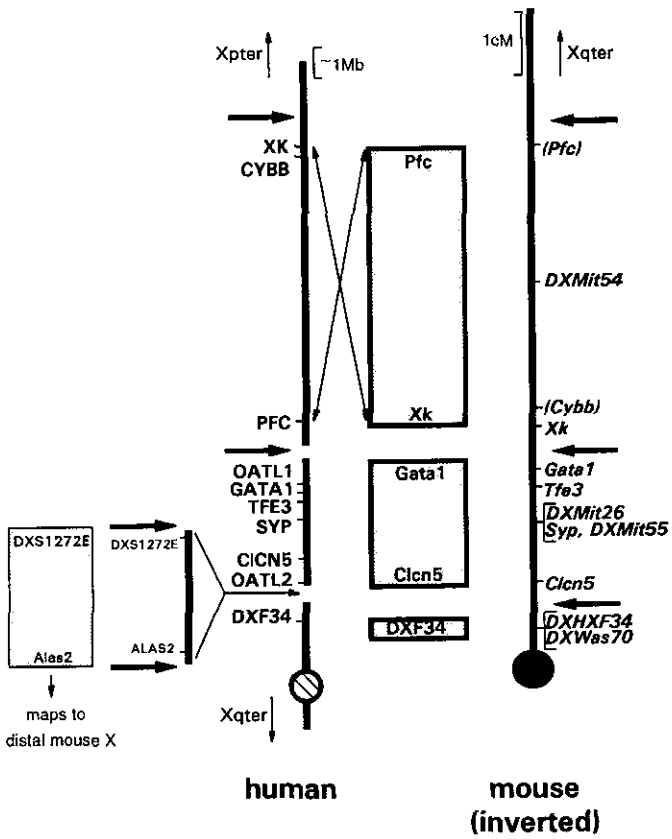

FIG. 4. The high-resolution comparative map of the proximal human X chromosome short arm. The human X chromosome short arm is drawn approximately to scale using the estimated physical distances given in Willard *et al.* (1994), with the section corresponding to the conserved segment that lies in the distal mouse X chromosome detached to allow alignment with the mouse X chromosome. The map of the mouse X chromosome is based on the genetic distances calculated from the data from backcross B (EUCIB) presented in this report, with the positions of two loci (*Cybb* and *Pfc*, given in parentheses) estimated from the data obtained from backcross A. Evolutionary breakpoints are indicated by boldface arrows. The extent of the blocks of human–mouse homology is shown in the center, with lightface arrows indicating that inversion of the XK to PFC block has occurred during the evolutionary time that separates the two species.

and contains four loci that have been mapped and ordered on both the human and the mouse X chromosomes (Fig. 4). The orientation of these loci reported here provides strong evidence that it arose through partial inversion within a larger homologous segment that originally extended from Xk to Clcn5 (Laval and Boyd, 1993a). The estimated size for this region on the human X chromosome is approximately 2 Mb (Willard *et al.*, 1994), and we have defined the genetic distance between *Clcn5* and *Gata1* to be approximately 1.5 cM in the mouse. The most proximal locus in human, ClCN5, lies 1–2 Mb away from DXS1272E, the nearest conserved locus that lies in a block of homology at the distal end of the mouse X chromosome (Fig. 1). In the mouse, *Clcn5* lies approximately 0.7 cM away from *DXHXF34/DXWas70,* and it can be estimated that these three loci lie less than 1 Mb apart if it is assumed that the relationship between the genetic and the physical distances is constant for the whole region. It is of interest to note that the evolutionary breakpoints that define this conserved segment on the human X chromosome lie in the vicinity of a cluster of repeated sequences associated with pseudogenes of the ornithine aminotransferase locus. The proximal boundary lies between ClCN5 and DXS1272E in the region of OATL2, and the distal boundary lies above GATA1 close to OATL1 (Willard *et al.*, 1994). There is as yet no evidence that any OAT pseudogenes or related sequences lie in this region of the mouse X chromosome, and it remains to be determined whether these sequences have played a role in the subchromosomal rearrangements that have led to the current order of loci on the human X chromosome.

Mapping of human disease loci in the mouse indicates the position of loci potentially associated with homologous mutant phenotypes. Thus, any existing mouse mutants that are homologues for McLeod syndrome or Dent's disease should map to the proximal region of the mouse X chromosome. Loci responsible for two murine mutations (tattered, *Td,* and scurfy, *sf*) have been positioned in the proximal region of the mouse X chromosome (Lyon and Searle, 1989; Lyon *et al.*, 1990). Both loci have been shown to cosegregate in separate backcrosses of ~200–300 progeny with *Gata1, Tfe3,* and *DXMit26* (Blair *et al.*, 1994b; Merrell *et al.*, 1995). However, neither of the phenotypes associated with these mutations shows any obvious similarities with the features of McLeod syndrome or Dent's disease. Scurfy, which is characterized by a tight, scaly skin and hematological abnormalities, has been proposed as a murine homologue for the human immunodeficiency disease, Wiskott–Aldrich syndrome (WAS) (Lyon *et al.*, 1990). Its cosegregation with *Gata1* and *Tfe3* supports this hypothesis, as the WAS gene has been recently cloned and shown to lie between GATA1 and TFE3 (Derry *et al.*, 1994). Tattered, which is characterized by patches or streaks of scarred skin first visible at 5–6 days, has been proposed to be homologous to incontinentia pigmenti type 1 (IP1), a skin disorder associated with a series of scattered X;autosome translocation breakpoints lying between DXS255 and the centromere (Gorski *et al.*, 1991; Hatchwell, 1994). The mapping data of Merrell *et al.* (1995) place *Td* between *DXWas70* and *Cybb* on the mouse X chromosome, which does not exclude it as a candidate for the murine homologue of IP1. The data presented here should enable the position of *Td* to be determined with respect to the evolutionary breakpoints in the region and thereby provide evidence for or against the proposed homology.

In conclusion, we have constructed an integrated comparative and high-resolution genetic map of the *DXHXF34–Cybb* region of the mouse X chromosome, which spans approximately 3 cM and contains 10 loci, including those that encode the human disease genes XK and ClCN5. This detailed map demonstrates the

power of high-resolution genetic mapping in the mouse as a means of determining locus order in a small chromosomal region and of providing an accurate framework for the construction of physical maps.

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