A Short Pseudoautosomal Region in Laboratory Mice

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The pseudoautosomal region (PAR) of mammalian sex chromosomes is a small region of sequence identity that is the site of an obligatory pairing and recombination event between the X and Y chromosomes during male meiosis. During female meiosis, X chromosomes can pair and recombine along their entire length; recombination in the PAR is therefore $\sim 10\times$ greater in male meiosis compared with female meiosis. A consequence of the presence of the PAR in two copies in males and females is that genes in the region escape the process of X-inactivation. Although the structure and gene content of the human PAR at Xq/Yq is well understood, the mouse PAR, which appears to be of independent evolutionary origin, is poorly characterized. Here we describe a yeast artificial chromosome (YAC) contig covering the distal part of the mouse X chromosome, which we have used to define the pseudoautosomal boundary, that is, the point of divergence of X-specific and X-Y-identical sequences. In addition, we have investigated the size of the mouse PAR by integrating a unique restriction endonuclease recognition site just proximal to the pseudoautosomal boundary by homologous recombination. Restriction digestion of this modified DNA and pulsed field gel electrophoresis reveal that the PAR in these cells is ~ 700 kb. Thus, the mouse PAR, although small in size, has retained essential sex chromosome pairing functions despite its rapid rate of evolution.

The mammalian sex chromosomes are thought to have evolved from a pair of homologous chromosomes. Since the acquisition of a sex-determining function, the similarity of the Y chromosome with the X has been almost completely eroded by a series of rearrangements and deletions (Ohno 1969; Graves 1995). Additions of autosomal segments have occurred during the evolution of the mammalian X and Y chromosomes, which have resulted in an enlarged region of homology between the two chromosomes (Graves 1995). These additions have been followed by further erosion of the Y chromosome. Only a small region of identity between the X and Y chromosomes of eutherian mammals has been retained and is required for sex chromosome pairing and chromosome segregation during male meiosis (Burgoyne 1982; Ellis and Goodfellow 1989; Rappold 1993). Genetic analysis has shown that loci within this region are capable of exchange between the X and Y, unlike the nonhomologous portions of these chromosomes, and they therefore behave like small autosomes. However, these loci show varying degrees of sex linkage and are thus pseudoautosomal (Burgoyne 1982; Ellis and Goodfellow 1989; Rappold 1993).

In mammals, gene dosage between XX females and XY males is compensated by the transcriptional silencing of a single X chromosome in every female cell, a process known as X-inactivation. Because both males and females have two copies of all pseudoautosomal genes, there is no requirement for dosage compensation, and all of the human pseudoautosomal region (PAR) genes and the single mouse PAR gene that have been examined so far have been proven to escape X-inactivation (Goodfellow et al. 1984; Ellison et al. 1992; Slim et al. 1993; Salido et al. 1996).

Two human PARs have been identified at the tips of Xp/

Yp and Xq/Yq. Both PARs have been extensively characterized and are spanned by genomic contigs. The larger of the two PARs (PAR1), at the tip of Xp and Yp, is 2.6 Mb in size and contains at least 11 genes and one pseudogene (Graves et al. 1998; Ried et al. 1998). The smaller PAR (PAR2), situated at the tips of Xq/Yq, is 0.4 Mb and contains a minimum of four genes (Freije et al. 1992; Ciccodicola et al. 2000). Although some of the genes located in the two human PARs have been cloned and mapped in the mouse, none of these genes are found in the mouse PAR (Disteche et al. 1992; Miyajima et al. 1995; D'Esposito et al. 1997; Ellison et al. 1997; Rao et al. 1997; Vermeesch et al. 1997). In fact, genes within human PAR1, when mapped in the mouse, are found on separate autosomes (Disteche et al. 1992; Miyajima et al. 1995; Ellison et al. 1997; Rao et al. 1997). Furthermore, the human ortholog of the only mouse PAR gene cloned, *Steroid sulphatase*, is located just proximal to the boundary within the X-unique portion (Yen et al. 1987). These observations are consistent with the idea that during the evolution of the sex chromosomes, several additions of autosomal material have occurred to the PAR, followed by continual attrition or loss of pseudoautosomal material from the Y chromosome (Graves 1995).

The pseudoautosomal boundary (PAB) is the point at which the PAR, where the X and Y chromosomes are identical, diverges into X-specific and Y-specific sequences and is therefore the proximal limit to legitimate X and Y recombination (Ellis and Goodfellow 1989). The PAB of the human short arm consists of 220 bp of incomplete sequence identity, after which the two chromosomes diverge into X-unique and Y-unique sequences. An *Alu* repeat element has been inserted into the Y chromosome between the PAR and the 220-bp region of reduced homology (Ellis et al. 1989). The structure of the PAR2 boundary is quite different from that of the PAB on the short arms of the X and Y. Here a LINE repeat is found on both the X and Y chromosomes, immediately adjacent to the breakpoint in homology between the long-arm PARs. It is

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Article and publication are at <http://www.genome.org/cgi/doi/10.1101/gr.203001>.

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Figure 4 Introduction of an I-SceI restriction site proximal to the pseudoautosomal boundary (PAB). (A) Targeting strategy for the insertion of an I-SceI restriction site proximal to the PAB: wild-type *Fxy* allele (i), *Fxy* targeting vector (ii), and targeted *Fxy* allele (iii). The region of the gene surrounding exon two (black box) of the *Fxy* gene (top panel) was replaced by a *LacZ* reporter gene (diagonal lines), which is in frame with the initiation codon (ATG), and a *neo* selection cassette (dark gray box) flanked by two LoxP sites (black triangles). An negative selection gene, Diphtheria toxin (dotted box), and an ampicillin resistance gene (light gray box), are located upstream of the 5' homology region. The bottom panel shows the correctly targeted allele and the position of two probes used for Southern hybridization (probes A and B). Restriction enzyme sites indicated are A, *Asc*I; B, *Bam*HI; Bx, *Bst*XI; En, *Eco*NI; I, I-SceI; N, *Not*I; and P, *Pac*I. (B) Analysis of targeted clones by Southern hybridization. Genomic DNA from wild-type (WT) and targeted embryonic stem cells (Perry and Ashworth 1999) digested with restriction enzymes and hybridized to probe A (i), probe B (ii), or a probe derived from the *neo* gene (iii). Sizes estimated from molecular weight markers are indicated on the right.

shown). The genomic structure of *Fxy* was investigated by using oligonucleotides derived from each exon of the gene to amplify interspersed introns by PCR on B6 and RPCI-23-306N24 genomic DNA. This analysis showed that the mouse *Fxy* gene has a similar structure to the human gene (Fig. 6). However, in general, the intron sizes of the mouse gene are smaller than those seen for the human gene (Quaderi et al. 1997; Perry et al. 1998).

Several markers, including *DXYMov15* (Harbers et al. 1990), *PAR-4* (Kipling et al. 1996b), and an interstitial telomeric repeat (TTAGGG)_n (Eicher et al. 1992), have been previously localized to the mouse PAR. In an attempt to clarify the physical organization of this region, these markers were hybridized to genomic DNA derived from the BAC clone RPCI-23-306N24 cut with restriction enzymes. All three markers hybridize to genomic DNA derived from RPCI-23-306N24 (data not shown). It therefore appears that the repeat unit contains *DXYMov15*, *PAR-4*, (TTAGGG)_n, as well as the seven 5' exons of the *Fxy* gene (Fig. 6). However, the possibility that these markers are also present in the remaining portion of the PAR cannot be ruled out.

DISCUSSION

The location and function of the PAR of mammalian genomes have resulted in the acquisition of unique genetic, physical, and evolutionary properties (Burgoyne 1982; Ellis and Goodfellow 1989; Rappold 1993; Graves 1995). Because of these properties, the only well-characterized PAR, that of humans, may not be typical of the PARs of other mammals. Here we describe the size and structural organization of the mouse PAR, which is evolutionarily independently derived from that of humans and has thus far not been characterized in detail.

By definition, the PAR is identical on both the X and Y chromosomes, but at the PAB, the X and Y chromosomes should diverge. After an extensive genomic walk (Fig. 1), we have identified the point of sequence divergence between the homologous X/Y PAR and X-unique sequences in the mouse (Fig. 2). However, the boundary is more complex than a simple transition from pseudoautosomal sequence into X-unique or Y-unique sequences. A variable tandem repeat array is located adjacent to this PAB on the PAR side. The number of repeat units appears to vary widely both between different strains of mice as well as between individuals from the same strain, according to estimates of copy number from Southern hybridization (Kipling et al. 1996a,b; Palmer et al. 1997; S. Palmer and A. Ashworth, unpubl.). At the PAB, the X chromosome diverges from the Y chromosome into X-unique sequence. However, at the point of divergence, what is expected

Figure 5 Direct sizing of the pseudoautosomal region (PAR). (A) Schematic representation of the genomic structure of the *Fxy* gene, indicating the position of the pseudoautosomal boundary (PAB) and the integrated I-SceI site. Exons are indicated by roman numerals, and the initiation and termination codons (ATG and TGA, respectively) are shown. (B) Southern analysis of the size of the PAR in 129 mice. Wild-type embryonic stem cell (ES) and targeted embryonic stem cell (Targeted) genomic DNA was incubated with (+) or without (-) the restriction enzyme I-SceI and were hybridized to the pseudoautosomal probes *Mov15* or *Fxy3*. Size, estimated from molecular weight markers (*Hansenula wingei* chromosomes), is indicated on the right.

Figure 6 The mouse pseudoautosomal region (PAR). (A) A physical map of the PAR of laboratory mice (129Sv) incorporating a previously reported study (Kipling et al. 1996a) as well as results presented here. The location of the *Fxy* gene is indicated by a gray line. PAB indicates the position of the pseudoautosomal boundary; TEL, of the telomere. The presence of two repeat units containing the 3' of *Fxy*, *DXYMov15*, *PAR-4*, and the interstitial telomeric repeat (TTAGGG)_n are also indicated. The positions of a *PacI* site and the *Steroid sulphatase* (*Sts*) gene have been taken from a study by Kipling et al. (1996a). (B) Schematic of the genomic organization of the *Fxy* gene in laboratory mice. Exons are indicated by gray boxes. The first three exons are X unique, whereas the remaining exons are pseudoautosomal. Intron sizes, where known, are indicated (kb). PAB indicates the position of the pseudoautosomal boundary.

to be a Y-specific sequence on the Y chromosome is in fact part of the repeat sequence present in the PAR array. These observations can be explained by proposing that the X- and Y-specific domains diverge from the repeat unit at different points within the sequence. So the PAB of laboratory mice appears to be the point of divergence of the X chromosome with the repeat unit on the Y chromosome. The variation in the copy number of the repeat suggests that this domain undergoes frequent alteration in size, which may be caused by recombination slippage and unequal exchange. Recombination slippage and unequal exchange would give rise to a range of allele sizes, and indeed, this region is known to undergo frequent alterations in structure (Kipling et al. 1996a,b). For example, *PacI* fragments hybridizing to the pseudoautosomal probes pMov15/1 and PAR-4 in B6 animals show variations between 0.6 and 2 Mb (Kipling et al. 1996a).

The sequence at the PAB, that is, the point of divergence between X and Y PARs, has no obvious distinguishing features. A search of the European Molecular Biology Laboratory and GenBank databases revealed no strong homology with any previously isolated sequence in any species. The sequences of the X-unique region and the repeat region, adjacent to the PAB, were compared using computer alignment, but no similarities were found. This lack of apparent residual sequence homology proximal with the boundary is unlike the situation for the human PAR1, in which there is evidence for a more proximal ancestral boundary (Ellis et al. 1989).

Although some progress has been made previously in identifying and mapping pseudoautosomal markers (Kipling et al. 1996a), this region of the mouse genome has remained largely uncharacterized. During the course of this investigation, we identified a mouse BAC clone derived from the repetitive region of the mouse PAR. We investigated the composition of the repeat unit by Southern hybridization and PCR analysis of this BAC with known pseudoautosomal markers. This analysis indicated that the PAR repeat unit contains the markers *PAR-4*, *DXYMov15*, the 3' seven exons of the *Fxy*

gene, as well as an interstitial telomere repeat (TTAGGG)_n. Although the presence of additional copies of these markers outside the repeat unit cannot be ruled out, it appears that these markers are all present within the proximal repetitive part of the PAR (Fig. 6).

The major human PAR is 2.6 Mb in length. We wished to determine the size of the PAR in mice, as previously only rough estimates of the size of the mouse PAR, based on genetic and cytogenetic measurements, were available (Eicher et al. 1992). We targeted a restriction enzyme (*I-SceI*) recognition site not normally present in the mouse genome to a position just proximal of the mouse PAB in 129 ES cells. This provided an opportunity to estimate the size of the PAR by cutting off the end of the chromosome. We used pulsed field gel electrophoresis and Southern blot hybridization to estimate the size of the PAR in these cells as being ~700 to 720 kb. The uncertainty in this figure is based on our estimate of the distance between exon 2 of the *Fxy* gene (position of *I-SceI* integration) and the PAB as being 30 to 50 kb. Our estimate is much smaller than the previous tentative estimates of 3 to 4 Mb (Eicher et al. 1992). This difference is most likely to be owing to the genetic methods used previously, which may have been confounded by the frequent cross-over and, indeed, double cross-over events that occur in this region (Harbers et al. 1986; Keitges et al. 1987; Soriano et al. 1987). Furthermore, our estimate of 700 to 720 kb is also much less than the PAR1 of humans, which is 2.6 Mb.

We noted above that the PAR proximal region contains a repeat unit of which an estimated two copies are present in the ES cell line that we analyzed. However, the repeat unit has been shown to vary in copy number (Kipling et al. 1996a,b; Palmer et al. 1997) between strains and may be completely absent in some, as in the inbred strain FVB, or present in multiple copies, numbering as many as 24, as seen in a C57BL/10 individual (Palmer et al. 1997). Although the size of the repeat unit is not known, it is estimated to be at least 16 kb and may therefore cause some variation in the overall size of the PARs of inbred strains. Therefore, the size of the PAR we described here is unlikely to be accurate for all mouse strains, as the number of repeats present varies.

In addition to being substantially smaller than the human PAR1, the mouse PAR appears to share little sequence similarity. This is a reflection of the distinct evolutionary origin of these two regions, as the human PAR1 has evolved by the addition of separate autosomal segments that have not occurred in the mouse lineage (Graves 1995). Furthermore, sequences within the PARs of both mice and humans appear to be subject to an accelerated evolution. Genes within the PAR appear to evolve more rapidly than their nonpseudoautosomal counterparts in humans or mice. Two human PAR genes, *GM-CSFR α* and *IL3R α* , have been shown to be considerably diverged from their autosomal mouse orthologs (Ellison et al. 1996). In addition, the mouse PAR gene, *Steroid sulphatase*, shares little sequence similarity with the human *Steroid sulphatase* gene located within Xp22.3 (Yen et al. 1987; Salido et al. 1996). A clear illustration of this accelerated divergence can be seen in the *Fxy* gene from laboratory mice, which spans the PAB in this species of mouse. We recently showed that the 3' portion of this gene was estimated to evolving ~170-fold faster than the corresponding region in SPE mice, which is X unique (Perry and Ashworth 1999). We attributed this finding to the high rate of recombination. Therefore, one would expect a very different sequence composition for the mouse (and human PARs). However, large-

scale rearrangements have also taken place (Graves 1995). This is revealed by the analysis of laboratory mice (*Mus musculus*) PAR sequences in *Mus spretus* (Fig. 3).

The PAR markers derived from within the repeat unit are clearly not pseudoautosomal in SPE but rather are X unique. The distal X chromosomal location of these markers in SPE suggests that the PAB in this species of mice must be distal to that of laboratory (*Mus musculus*) strains. It is already known that the distal X differs in these two species with respect to the presence of two genes, *Cln4* and *Fxy*. *Cln4*, a chloride channel gene, is present on the distal X chromosome in SPE, whereas the gene is present on chromosome 7 in all of the *Mus musculus* subspecies (Palmer et al. 1995; Rugarli et al. 1995). The *Fxy* gene is also differentially located in laboratory and SPE mice, being wholly X unique in the latter and spanning the PAB in the former (Perry and Ashworth 1999). These findings may be related. A possible hypothesis explaining these observations is that *Cln4* is very close to the ancestral and SPE boundary, and a single, probably complex rearrangement, event not only transferred the gene onto an autosome in laboratory mice but also destabilized the boundary and its surrounding region. This translocation event may also have resulted in *Fxy* being brought into a position spanning the boundary in these mice.

Taken together, these data indicate that the distal X chromosome of laboratory mice has undergone substantial rearrangements since its divergence from SPE mice ~3 Myr ago (Ferris et al. 1983). Hence, the PAR of these mice may represent a rearranged or deleted version of the PAR compared with that of other species of mice. The F₁ males produced by intercrossing these two species are infertile, very probably as a consequence of heterozygosity in the XY pairing region leading to the nonpairing of the X and Y, which is a prerequisite for spermatogenic survival through the meiotic process (Burgoyne et al. 1992). Clearly, the altered position of the boundary must be a contributory factor in the lack of sufficient pairing capacity. The determination of the position of the PAB in other mouse species such as *Mus musculus musculus* and *Mus castaneus* may clarify the extent to which the *Mus musculus domesticus* PAR is representative of that of other mouse species. Furthermore, the introduction of a means to separate the PAR from the nonrecombining portions of the sex chromosomes opens up the possibility of detailed sequence analysis of the region.

METHODS

STS PCR Markers and YAC Libraries

YAC clones were isolated from either the MRC HGMP combined mouse YAC library, from which the YACs I_U18, II_H24, and VII_B20 were isolated, or the MIT mouse YAC library (Research Genetics), from which all the other YACs were obtained. The BAC clone RPCI-23-306N12 was isolated using bioinformatic techniques as described in Results and is derived from the RPCI-23 Female (B6) Mouse BAC Library. The process of library screening and the isolation of *DXYCb1*, *DXYCb2*, *DXYCb3*, and *DXCb1* have been described previously (Palmer et al. 1997). The marker *DXYCb4* is derived from exon four of the *Fxy* gene using the oligonucleotides AATGCATCCCGTCAAGAAGC and GCCTTCTTAATCTTTGTCC. *DXYMov15* (Harbers et al. 1990), *PAR-4* (Kipling et al. 1996b), and the interstitial telomeric repeat (TTAGGG)_n (Eicher et al. 1992) have all been described previously. The sequences of the other markers generated during the walk are available on request.

Physical Mapping

For conventional agarose gels, genomic DNA was digested with restriction enzymes and electrophoresed on 0.8% agarose gels. The DNA was transferred to nylon membranes and hybridized overnight by the method of Church and Gilbert (1984) or for shorter periods using Rapid-Hyb (Amersham). For pulsed field gels, DNA embedded in agarose was prepared from ES cells and digested with restriction enzymes as described (Birren and Lai 1993). Samples were fractionated on a 1% agarose gel using a CHEF DRII (Bio-Rad) pulsed field gel electrophoresis apparatus according to the manufacturer's instructions. Molecular weight markers were *Hansenula wingei* chromosomes (Bio-Rad).

ES Cell Culture

Male 129 ES cells (Go Germline, Genome Systems) were grown under 5% CO₂ in ES cell medium, containing leukemia inhibitory factor (ESGROTM, GIBCO BRL). ES cells were grown in tissue culture dishes on a feeder layer of mitotically inactivated mouse embryonic fibroblasts derived from a 12-day embryo transgenic for the neomycin resistance gene. ES cells used for isolation of genomic DNA were passaged without the feeder cells at least twice and grown in dishes treated with 0.1% (w/v) gelatin. For ES cell transfection, 2 × 10⁷ cells were electroporated with a Bio-Rad GenePulser II at 0.270 V (500 μFA with 20 μg of linearized pFXKO vector), transferred to 10 cm² dishes, and allowed to recover in ES cell medium overnight. After 24 h, cells were treated with selection media consisting of 400 μg/mL G418 (200 μg/mL active concentration) for the next 6 d. Surviving clones were isolated and tested for correct integration of pFXKO by PCR and Southern blotting.

ACKNOWLEDGMENTS

This work was supported by the Wellcome Trust, The Medical Research Council, the Mary-Jean Mitchell Green Foundation, and Breakthrough Breast Cancer.

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Received June 28, 2001; accepted in revised form July 15, 2001.

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Genome Res. 2001 11: 1826-1832

Access the most recent version at doi:[10.1101/gr.203001](https://doi.org/10.1101/gr.203001)

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