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Review article

The pseudoautosomal regions of the human sex chromosomes

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Abstract. In human females, both X chromosomes are equivalent in size and genetic content, and pairing and recombination can theoretically occur anywhere along their entire length. In human males, however, only small regions of sequence identity exist between the sex chromosomes. Recombination and genetic exchange is restricted to these regions of identity, which cover 2.6 and 0.4 Mbp, respectively, and are located at the tips of the short and the long arm of the X and Y chromosome. The unique biology of these regions has attracted considerable interest, and complete long-range restriction maps as well as comprehensive physical maps of overlapping YAC clones are already available. A dense genetic linkage map has disclosed a high rate of recombination at the short arm telomere. A consequence of the obligatory recombination within the pseudoautosomal region is that genes show only partial sex linkage. Pseudoautosomal genes are also predicted to escape X-inactivation, thus guaranteeing an equal dosage of expressed sequences between the X and Y chromosomes. Gene pairs that are active on the X and Y chromosomes are suggested as candidates for the phenotypes seen in numerical X chromosome disorders, such as Klinefelter's (47,XXY) and Turner's syndrome (45,X). Several new genes have been assigned to the Xp/Yp pseudoautosomal region. Potential associations with clinical disorders such as short stature, one of the Turner features, and psychiatric diseases are discussed. Genes in the Xq/Yq pseudoautosomal region have not been identified to date.

Historical perspective

Interest in the pseudoautosomal region (PAR) and in the phenomenon of incomplete sex linkage arose more than 70 years ago. Pairing between parts of the X and Y chromosomes in higher organisms was first observed in the rat (Koller and Darlington 1934), and incomplete sex-linkage first described in cyprinodont fishes and later in *Drosophila melanogaster* (Aida 1921; Philip 1935).

In one of the first attempts at linkage analysis in *man*, Haldane also claimed to find evidence for such partial linkage (Haldane 1936). The suggested candidates were genes that were preferentially handed down by a heterozygous male to his male offspring (genes for xeroderma pigmentosum, achromatopsia, retinis pigmentosa, Oguchi's disease and epidermolysis bullosa dystrophica). Unfortunately, all of the examples proved to be wrong. They illustrate the difficulty of differentiating pseudoautosomal inheritance from autosomal and X-linked inheritance with variable penetrance.

By examining spermatocytes in meiotic prophase, pairing was demonstrated to occur on the short arms of X and Y (Pearson and Bobrow 1970; Moses et al. 1975). Replication studies on premetaphasic sex chromosomes led to the postulation of functional homology between parts of the distal short arms of the X and Y (Müller and Schempp 1982). In 1982, two papers appeared proposing similar models for genetic homology and crossing over within the X-Y pairing region (Burgoyne 1982; Polani 1982). It was argued that a single obligatory crossover, restricted to this homologous pairing region, should exist between the X and Y chromosomes and it was concluded that it would therefore behave like an autosomal segment. The term "pseudoautosomal" has since found general acceptance. A prediction arising from this hypothesis is that sequences within this region should exhibit varying degrees of partial sex linkage, depending upon their physical location within the PAR. Evidence from molecular studies of X and Y chromosomes in humans and mice has subsequently been provided by identifying pseudoautosomal markers that recombine between the sex chromosomes, thus verifying these earlier predictions (Keitges et al. 1985; Cooke et al. 1985; Rouyer et al. 1986a, b; Goodfellow et al. 1986; Page et al. 1987a; Freije et al. 1992).

Evolution of the sex chromosomes and the origin of the pseudoautosomal region

Evolution of chromosome X and Y in mammals

It is a generally accepted view that the dimorphic sex chromosomes evolved from a homomorphic sex chromosome pair by gradual reduction of the Y, accompanied by a series of rearrangements (Ohno 1967). This view has

also found support from studies on reptiles and birds, subsequently used as model organisms (Ohno 1967; Singh and Jones 1985; Charlesworth 1991). The common past of the sex chromosomes is still noticeable, emphasized by the observation that different X-Y homologous regions with varying degrees of conservation have been found on both the long and the short arm of the human X and Y (Page et al. 1984; Cooke et al. 1984; Koenig et al. 1985; Page et al. 1987b; Brown et al. 1990; Fisher et al. 1990a).

The gradual process of X and Y chromosome differentiation has been accompanied by the spreading of X-inactivation into the newly unpaired regions of the X chromosome, an entirely mammalian innovation. Most of the human genes known today to escape X-inactivation (with the exception of XIST and (UBE1; Brown and Willard 1989; Brown et al. 1991), have a homologue on the Y chromosome. This homologue is either an actively expressed gene on the Y, as in the case of ZFX (zinc finger protein), and RPS4X (ribosomal protein S4) (Schneider-Gädicke et al. 1989; Fisher et al. 1990b) or a pseudogene on the Y, as in the case of STS (steroid sulphatase), KAL (leading to Kallmann Syndrome) and GS1 (Yen et al. 1987, 1992; Franco et al. 1991; Legouis et al. 1991). Thus, escaping X-inactivation seems to reflect a relic remaining from the ancestral homologous chromosome pair.

The observation that all X-Y homologous genes map to Xp (with the single exception of RPS4X) and escape inactivation has led to the hypothesis that these genes are of autosomal origin and have been acquired as later additions to the sex chromosomes. This view is supported by the fact that genes on Xp are clustered on two different autosomes in marsupials and monotremes (Spencer et al. 1991), which evolved from eutherians 150 and 170 million years ago, respectively (Graves 1987). It is therefore becoming increasingly evident that the long and short arm of the X chromosome have a different history (Watson et al. 1990; Spencer et al. 1991).

Origin of the PARs

Whereas the size and structure of human PARs are well established (2.6 Mb on Xp and 0.4 Mb on Xq), little information is available on the PARs of other mammals. Work on markers within the human Xp22.3 region, in particular on STS, has provided compelling evidence that a pericentric inversion on Xp22.3/Yq11.2 occurred about 40 million years ago, when the higher primates diverged from the prosimians (Yen et al. 1988). Studies on STS indicate that this gene, together with two other known murine pseudoautosomal markers, Mov15 and Sxr, and three new telomere-related markers behave pseudoautosomally in, for example, prosimians and mice (Keitges et al. 1985; Harbers et al. 1986; Yen et al. 1988; Eicher et al. 1992). However, human STS is X-linked and like KAL, possesses a Yq-linked pseudogene; both pseudogenes are in reverse order on Yq compared with the situation on Xp (Yen et al. 1991; Bardoni et al. 1991), as are other loci from this linkage group. The homology of Xp22.3 and Yq11.2 is still such that pairing and crossing over may occasionally occur, resulting in rare X-Y translocations (Ballabio et al. 1989; Yen et al. 1991). Interestingly, this linkage group of markers on Xp22.3 is immediately adjacent to the PAR. This observation led to the hypothesis that the present day PAR represents only a part of a previous considerably larger segment of homology that has been disrupted by pericentric inversion (the model of "shrinking" or "gradual reduction" of the PAR; Yen et al. 1988). So far, no markers from the PAR have been shown to have mouse pseudoautosomal homologues and no markers known from the mouse PAR are found within the human PAR. This suggests that there is complete divergence between the PAR of mice and humans. CSF2RA and ANT3 are highly conserved genes and it will be interesting to determine whether the murine homologues of ANT3 and IL3RA also map to an autosome, as has recently been shown for Csf2ra (Disteche et al. 1992).

The existence of a PAR has been shown in man (see above), in mouse (Keitges et al. 1985) and in chimpanzee (Weber et al. 1987). Marsupial X and Y chromosomes, however, do not undergo obvious homologous pairing and a chiasma has not been found (Sharp 1982). Nevertheless, the association of X and Y chromosomes at one or both of their ends suggests the existence of a common region that could be small.

In summary, the origin and the evolution of the PAR in different mammmalian species remains a major open question. This puzzle will, however, be resolved within the next few years with the availability of new, highly conserved pseudoautosomal markers and comparative mapping studies.

Structure of the PAR on Xp/Yp

The 2.6-Mb human PAR is located at the distal tip of the short arm of the X chromosome, band Xp22.3, and at the tip of the short arm of the Y chromosome, band Yp11.32. Characterisation of DNA within light and dark bands has revealed a series of interesting associations (Holmquist et al. 1982; Korenberg and Rykowski 1988; Bickmore and Bird 1993). Chromosomal band Xp22.3 is a Giemsa-negative band and displays the expected high density of CpG islands that serve as gene markers in all vertebrate species (Bird 1986, 1987). Because of the early replication of this region in the cell cycle (Schempp and Meer 1983), this band was thought not to be subject to random X-inactivation. A diagram of the CG richness of the pseudoautosomal region is shown in Fig. 1, with respect to five different enzymes of different CG classes (Bickmore and Bird 1993). One striking feature is the high density of cleavage sites within the most distal 500 kb of the PAR (Brown 1988; Petit et al. 1988; Rappold and Lehrach 1988). Most of the individual variation in different CG cleavage sites seems to occur in this CG-rich chromosomal subregion. To date, it is not clear whether this feature of the most distal region mirrors an extremely dense area of genes, similar to, for example, the mouse major histocompatibility complex, MHC (Steinmetz et al. 1987), or a stretch of noncoding, very GC-rich DNA with structural features possibly related to the initiation of pairing within this region close to the telomere.

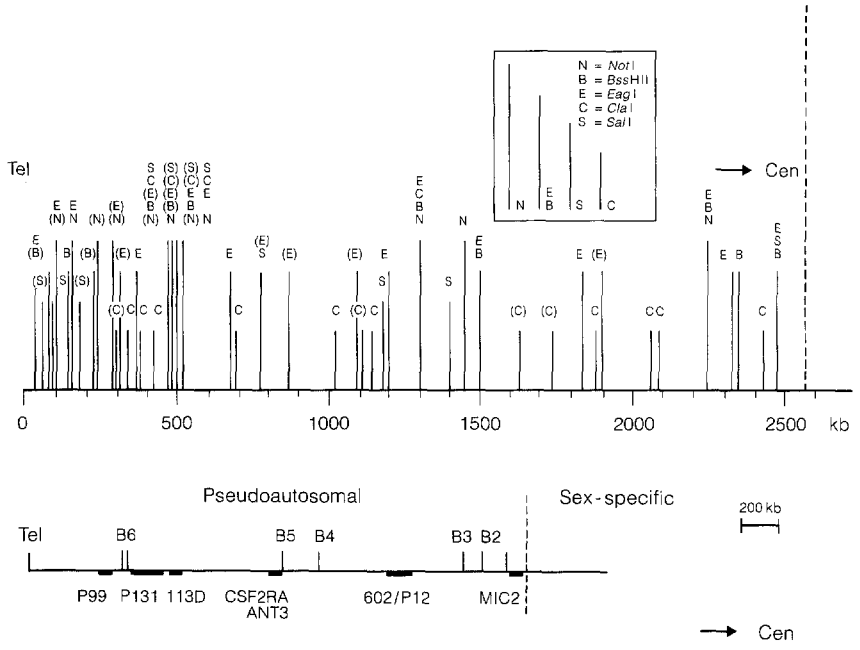

Fig. 1. Cleavage sites of rare cutting enzymes in the PAR. Enzymes *Not*I, *Bss*HII, *Eag*I, *Cla*I and *Sal*I are grouped into 4 different classes dependent on their frequency in CpG islands (Bickmore and Bird 1993) and are depicted as *shorter* or *longer lines* see *box above*). Partially methylated cleaveage sites are shown in *brackets*

Fig. 2. Physical map of the PAR. Five CpG islands *(B2–6)* are marked distal of *MIC2*. *ANT3* is associated with the CpG island *B5*. Physical locations were determined by pulsed field gel analysis (Brown 1988; Petit et al. 1988; Henke et al. 1991)

A closer evaluation of the rare cutter restriction cleavage sites within the PAR reveals at least five different CpG islands distal to MIC2 (see Fig. 2); we have named these islands B2–B6 because of the presence of at least one *Bss*HII cleavage site in each of the islands. B2 and B3, 120 and 220 kbp distal to the MIC2 gene respectively, were isolated from a chromosome *Bss*HII jumping library (Poustka et al. 1987) in two subsequent chromosomal jumps (G. Rappold, unpublished results). Methylation studies in different tissues indicated true CpG islands. Subsequent sequence analysis around the islands and screening of five different cDNA libraries, however, failed to reveal any transcribed products. We therefore concluded that this is attributable either to a narrow stage-specific or temporal-specific expression pattern of the potential genes involved, or to the existence of "dead islands" that are associated with recently inactivated genes or pseudogenes. The only well-known example of an unmethylated CpG island that is not associated with a functional gene is the ψα2 pseudogene at the human α-globin locus (Fischel-Ghodsian et al. 1987). Other non-processed pseudogenes have lost their CpG islands through methylation and mutation.

There is as yet no information available on the gene associated with the CpG island B4 at position 1500 kb from the telomere. CpG island B5, at position 1300 kb from the telomere, is associated with the gene encoding an ADP/ATP translocase (Schiebel et al. 1993; Slim et al. 1993b). B6 at position 470–520 kb from the telomere represents a cluster of potential CpG islands, or, as mentioned before, a structural CG-rich region whose function still has to be elucidated. A similar accumulation of rare cutter enzyme cleavage sites has been described in the HLA complex in man with five CpG islands within 50 kb (Ragoussis et al. 1991) and at the *surfeit* locus in mouse with four CpG islands within 32 kb (Huxley and Fried 1990). It will be interesting to determine whether this section of the PAR also represents such a gene-rich area.

Physical maps of the human pseudoautosomal region on Xp/Yp have been constructed using pulsed field gel analysis (Brown 1988; Petit et al. 1988; Rappold and Lehrach 1988; Henke et al. 1991). The PAR with its approximate physical length of 2.6 Mb represents 3%–5% of the human Y chromosome (because of Y heterochromatic variation) and 1.6% of the X chromosome. The physical extent of the pseudoautosomal region can be verified by a yeast artificial chromosome (YAC) contig covering the whole region. Pseudoautosomal YACs have been isolated from different libraries (Foote et al. 1992; Slim et al. 1993a; Ried et al., in preparation), and a high instability and chimaera rate was seen. Recombination studies on YAC clones in yeast have recently shown that the level of recombination (and gene conversion) is maintained as in its natural context on the chromosome (Ross et al. 1992). The high frequency of recombination in male meiosis and the presence of many minisatellite sequences in the PAR may therefore contribute to the high degree of instability and chimaerism of YACs from this region.

The interface between sex-specific and pseudoautosomal sequences is the pseudoautosomal boundary (PABY and PABX), defined as the proximal limit of recombination in the PAR (Ellis et al. 1989). In man, the pseudoautosomal boundary on Xp/Yp is marked by an Alu repeat, followed by a 220-bp stretch of reduced (78%) homology (Ellis et al. 1989). Sequences proximal to this block are non-homologous and sex-specific. Studies on Old World monkeys and great apes have indicated that the Alu repeat did not create the boundary seen in man, but instead was inserted at the pre-existing boundary after the Old World monkeys and great ape lineages diverged (Ellis et al. 1990). No information is available yet on the structure of the pseudoautosomal boundary on Xq/Yq.

The distal boundary of the PAR is the telomere. Telomeric DNA at the end of all chromosomes consists of the

simple repeated sequence $(TTAGGG)_n$ of variable length (Moyzis et al. 1988). In humans, the range is between 2 kb and 20 kb, with the telomeres in germ cells being considerably longer than those in somatic cells (Cooke and Smith 1986). Proximal to these conserved repeats, a complex mixture of chromosome-specific short repetitive sequences have been described for several chromosome ends, extending over several kb (Brown et al. 1990; Cross et al. 1990); however, there are no specific data as yet on these subterminal repeats of Xp and Yp.

Various lines of evidence suggest that the human PAR on Xp/Yp contains an especially high density of minisatellite sequences (Cooke et al. 1985; Simmler et al. 1985; Page et al. 1987a; Rouyer et al. 1990). It has been argued that minisatellites represent recombination hotspots involved in chromosome pairing, and/or play a role in the initiation of meiotic recombination, which would explain their prevalence in the PAR (Jeffreys et al. 1985; Steinmetz et al. 1987; Chandley and Mitchell 1988; Royle et al. 1988). Structural studies on several pseudoautosomal tandem-repeats show copy number variations between individuals. Loci DXYS14, DXYS20 and DXYS78, for example, exhibit a 0.3–3 kb, 10–50 kb and 5–30 kb variation range, respectively, between individuals (Page et al. 1987a; Inglehearn and Cooke 1990; Armour et al. 1990). It is conceivable that other VNTR (variable number of tandem repeats) loci in the PAR display similar features. Extrapolating from these observations, one may argue for a possible length polymorphism of the PAR as a whole. Whether heterozygosities of pseudoautosomal length differences have an influence on meiotic segregation remains to be shown.

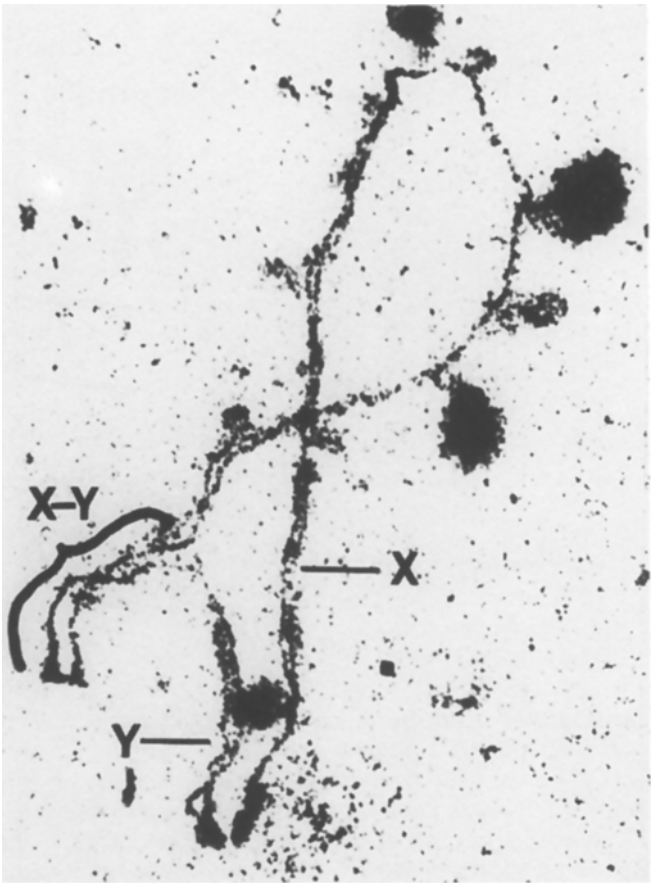

Fig. 3. Pairing of the human sex chromosomes X and Y in the early stages of pachytene, examined by electron microscopy (Chandley et al. 1984). The separation of the axial elements of X and Y in both chromatid strands has occurred and dense bodies, associated with the lateral elements, become visible. The synaptenomal complex of the pairing region of X and Y at this stage comprises approximately one third or more of the total length of the Y chromosome. Note the association of Xp and Yp, and of Xq and Yq. Courtesy of Drs. P. Goetz and A. Chandley

Genetics of the PAR

Pairing and recombination in meiosis

During meiotic prophase, physical contact between the homologous chromosomes results in pairing and synapsis, and consequently in the formation of a synaptenomal complex. Chromosome synapsis and genetic recombination are related events, and recent observations suggest that recombination provides the basis for pairing and not vice versa, as generally assumed (reviewed in Roeder 1990).

Pairing of human chromosomes usually starts at sites very close to the telomere (Laurie and Hultén 1985). On the sex chromosomes, the initiation of pairing and the obligatory crossover event take place within the pseudoautosomal region. Crossing over within the PAR was observed first cytogenetically (Hultén 1974; Solari 1980) and was then established with molecular probes following the segregation of restriction fragment length polymorphism (RFLP) alleles in pedigrees (Cooke et al. 1985; Simmler et al. 1985; Rouyer et al. 1986a, b; Page et al. 1987a; Freije et al. 1992). Pairing of the sex chromosomes has been noticed not only between the Xp and Yp regions, but occasionally also between Xq and Yq in electron-microscopic studies of meiotic prophase cells (Chandley et al. 1984; Speed and Chandley 1990; see Fig. 3). Only recently has the existence of a small second PAR with crossover events between Xq and Yq been demonstrated (Freije et al. 1992).

The extent of pairing between Xp and Yp is variable, including the PAR and most of the short arm of the Y chromosome (see Fig. 3), and extending in some cases into the long arm of the Y (Chandley et al. 1984). It is not known what causes the homologous parts to become precisely aligned; it seems probable, however, that pronounced homology over very long stretches of DNA is not required.

Errors in pairing and recombination

X-Y pairing has been hypothesised as a prerequisite for the completion of male meiosis (Burgoyne 1982). Burgoyne and others have argued that primary spermatocytes containing univalent X and Y chromosomes do not produce functional sperm. Meiotic and segregation data in mice from Sxr-carrier males and XY* males (these are mice which have a rearranged Y and in which the PAR occupies an interstitial position) showed that all functional sperm are derived from spermatocytes with sex

chromosomes that paired and that had an XY chiasma (Keitges et al. 1987; Cattanach et al. 1990; Hale et al. 1991). Whether X-Y pairing per se or X-Y recombination is a prerequisite for producing functional sperm is still an open question.

X-Y dissociation leads to sterility; in other words, the obligatory crossover is an indispensable condition for the reproduction of the individual. This was recently shown by a particulary striking example that involved crosses between two species of mice. These studies demonstrated a 95% dissociation rate on the hybrids, which were sterile, compared with a 3%–4% X-Y dissociation rate in the parental strains (Matsuda et al. 1991, 1992). Genetic divergence of the pairing region can thus contribute to reproductive barriers existing between species and to the process of speciation.

In humans, male individuals lacking X-Y pairing are also known to be sterile. A reduced recombination frequency leads to incorrect segregation, and to 47,XXX or 47,XXY individuals (Hassold et al. 1991). Occasionally, the obligatory X-Y crossover occurs outside the PAR (illegitimate recombination); in this case, the testis-determining factor (TDF or SRY), which is located just 5 kb proximal to the pseudoautosomal boundary on Xp/Yp (Sinclair et al. 1990) may be transferred to the X chromosome. This illegitimate crossover event results in 46,XX individuals who display a male phenotype (Page et al. 1985; Petit et al. 1987). The reciprocal product is a Y chromosome deleted for SRY, as found in some XY females with gonadal dysgenesis (Levilliers et al. 1989).

Segregation of pseudoautosomal minisatellite loci: the genetic map

Genetic map expansions have been observed in telomeric and subtelomeric regions of different human chromosomes, reflecting a higher recombination rate per physical length unit in these regions (reviewed in Rouyer et al. 1990; NIH/CEPH Collaborative Mapping Group 1992; Harris and Higgs 1993). The PAR exhibits these subtelomeric features in a particularly striking way. Recombination during male meiosis is markedly higher; an approximately 10-fold difference exists between the frequencies of recombination in male and female germ cells on Xp/Yp (Rouyer et al. 1986a, b; Page et al. 1987a; Henke et al. 1993) and an approximate 5-fold difference in the PAR on Xq/Yq (Freije et al. 1992). The molecular basis of these differences in recombination is not known. Previous genetic maps, using RFLPs from the PAR on Xp/Yp, have established a linear gradient of recombination with frequencies of approximately 50% at the X-Y telomeres and 0% at the pseudoautosomal boundary (Cooke et al. 1985; Rouyer et al. 1986a, b; Goodfellow et al. 1986; Page et al. 1987a). It has been proposed that the recombination frequency could be used to estimate the position of any locus within this region, implying that there is only one crossover event and that the genetic distances are strictly additive (Rouyer et al. 1986a, b). In contrast of the findings in the PAR of the mouse (Harbers et al. 1986; Soriano et al. 1987), no double crossover has been described as yet in the human PAR.

Whereas the entire PAR may be seen as a region prone to high recombination in male meiosis, this is definitely not the case in female meiosis. In the latter, the recombination rate in the overall PAR on Xp/Yp is comparable to the X chromosome average. A hot spot of recombination is, however, located between loci DXYS20 and DXYS78 within 20–80 kb from the telomere (Henke et al. 1993). In this telomere-adjacent region only, male and female recombination rates are very similar – an observation whose biological significance, if any, is as yet unknown.

A comparison of the genetic and the physical map allows us to correlate centimorgans with kilobases. On the PAR on Yp there are, on average, around 53 kbp of DNA per centimorgan (based on a physical and genetic map length of 2560 kbp and 48.5 cM in male meiosis) and 480 kbp correspond to 1 cM in female meiosis (Henke et al. 1993).

The reason for certain segments of the genome exhibiting highly elevated or low recombination rates remains an enigma. Extreme examples are seen in *Drosophila* males and silkworm females, with a complete absence of recombination. Recent experiments artificially altering the chromosome size of *Saccharomyces cerevisiae* have shown that chromosome length has a direct effect on the rate of recombination (smaller chromosomes lead to higher recombination rates) (Kaback et al. 1992). It has also been demonstrated that recombination differences are influenced by chromatin structure or by the binding of specific proteins at predetermined sites (White et al. 1991; Ponticelli and Smith 1992). In *D. melanogaster* and *S. cerevisiae*, for example, the frequency of meiotic recombination is altered by the proximity of certain chromosomal structural elements, such as the centromere or large blocks of heterochromatin. The movement of a hotspot from its original place to another location fails to enhance recombination (Ponticelli and Smith 1992). Eukaryotic hotspots are therefore more complex than can be explained by single sites, and the exact nature of the chromosomal context necessary for hotspot activity remain to be elucidated.

Minisatellites may also act as recognition sites for specific enzymes that directly or indirectly promote recombination (Rouyer et al. 1990; Chandley and Mitchell 1988; Wahls et al. 1990) and many of these are found within the pseudosomal regions. Yet, whatever the underlying reasons for recombination are, the PAR marks a unique area for investigating the structural components required for homologous recombination in mammals.

Genes in the pseudosomal region

Interest in the biological phenomena of the PAR has been a major impetus for the isolation of numerous sequences of this region. In particular, genes operating in the region of highly differential recombination rates between male versus female raise important questions. Six human (and one murine) pseudoautosomal genes have been described to date and their location with respect to the distance from the telomere is depicted in Fig. 4.

MIC2 is the first pseudoautosomal gene described in man (Goodfellow et al. 1983, 1984, 1986; Smith et al.

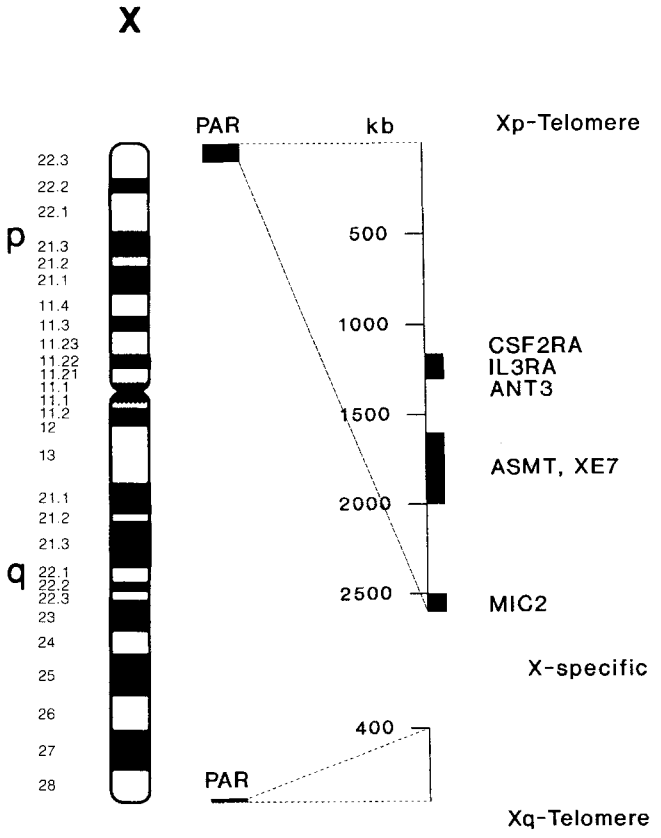

Fig. 4. The PAR at the Xp telomere extends for approximately 2.6 Mb, and at the Xq telomere for approximately 0.4 Mb. Six different genes have been assigned to the Xp/Yq PAR. All of these are physically mapped and CSF2RA, ASMT and MIC2 are also genetically mapped

1993). As it maps just 95 kb distal to the pseudoautosomal boundary, next to a CpG island, it constitutes an important reference point on the physical and genetic map. MIC2 is a ubiquitously expressed housekeeping gene. It encodes a cell surface antigen (defined by the monoclonal antibody 12E7) and is involved in cell adhesion processes, e.g. in the spontaneous rosette formation of erythrocytes (Gelin et al. 1989). Recently a second pseudoautosomal locus, cross-reacting with two exons of MIC2, has been described (Smith et al. 1993).

XE7 represents a pseudoautosomal gene, which was isolated from an inactive X cDNA library (Ellison et al. 1992). XE7 appears to be ubiquitously expressed and alternative splicing results in two very hydrophilic protein isoforms (Ellison et al. 1993). Presently there is no clue to its biological function. Its physical location within the PAR has been determined by a combination of YAC screening and PFGE (Ried and Rappold, unpublished results).

ASMT (acetylserotonin methyltransferase or hydroxyindole-O-methyltransferase) catalyses the final reaction in the synthesis of the hormone melatonin, which is secreted from the pineal gland. This enzyme was cloned by sequence homology to a bovine ASMT gene and has been genetically mapped within the PAR adjacent to the marker DXYS17 (Yi et al. 1993). It has been suggested as a candidate for psychiatric disorders (Yi et al. 1993) because of (1) its tissue-specific expression in brain and retina (and the interesting observation that individuals with bipolar illness or seasonal affective disorder exhibit an altered sensitivity to light) and (2) previous association and linkage studies of pseudoautosomal markers in schizophrenia patients (Crow 1988; Crow et al. 1989; Collinge et al. 1991; d'Amato et al. 1992).

ANT3 (adenine nucleotide translocase) represents a highly conserved gene from the ADP/ATP translocase family. It catalyses the exchange of ATP and ADP across the mitochondrial membrane and thus plays a fundamental role in the energy metabolism of the eukaryotic cell (Cozens et al. 1989). This pseudoautosomal gene was isolated by cross-hybridization with a microdissected clone from the chromosomal subregion Xp22.3 (Schiebel et al. 1993; Slim et al. 1993b). Sequencing of the cDNA revealed its identity with a previously characterised member of the translocase family (Cozens et al. 1989). Expression studies indicated that ANT3 is a housekeeping gene and that it escapes X-inactivation (Schiebel et al. 1993; Slim et al. 1993b). Interestingly, a homologue of ANT3, viz. ANT2, maps to the long arm of the X chromosome and undergoes X-inactivation. The two genes provide the first evidence of two closely related genes, one on Xp and the other on Xq, that show striking differences in their X-inactivation behaviour.

IL3RA (interleukin receptor subunit α) has properties characteristic of the cytokine receptor family. It maps close to and proximal to CSF2RA, distal to ANT3 (Kremer et al. 1993; Milatovich et al. 1993). Interestingly, IL3RA and CSF2RA share the same β subunit, whereas the α subunits are distinct.

CSF2RA (colony stimulating factor receptor α): Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a growth and differentiation factor that acts on the cells of the monocyte/macrophage lineage (Gough and Nicola 1990). The cell surface receptor for GM-CSF (CSF2RA) is composed of two subunits, α and β, of which the α-chain gene has been genetically and physically mapped to the PAR (Gough et al. 1990; Rappold et al. 1992; see Fig. 4). CSF2RA represents the most distally located pseudoautosomal gene so far functioning in a region with a 27% recombination frequency (Henke et al. 1993). Either the X or the Y chromosome is lost in about 25% of acute myeloid leukemias, suggesting that a recessive oncogene may be involved in the genesis of acute myeloid leukemia subtype M2 (Gough et al. 1990). Loss or X-inactivation of both copies of this gene would be expected to generate cells that are unresponsive to GM-CSF, as indeed has been found (Gough et al. 1990).

A summary of the available information on the six so far known human pseudoautosomal genes is given in Table 1. Does the genomic organisation of a pseudoautosomal gene reflect the unusual recombination rates in male meiosis? Are their exons considerably smaller than the average for mammalian genes, and their introns considerably larger? Are genomic gene sizes smaller than average? Are pseudoautosomal genes preferentially genes for which a certain degree of genetic divergence would have a selective advantage? Preliminary data suggest that

Table 1. References to gene isolation and characterisation are given in the text. Physical mapping within the PAR was done by PFGE using genomic DNA derived from lymphocytes of 46,XX individual AH and by YAC screening. Reference point is the telomere. Physical locations are based on a physical map length of the PAR of 2560 kbp (as determined for individual AH). The physical location of ASMT is taken from Slim et al. (1993a)

Gene	Physical location	Orientation	Genomic size [kb]	No. exons	cDNA	Expression
MIC2	2470	Tel-Cen	52	10	1.24	Ubiquitous
XE7	1600–2000	?	11	6	3.23	Ubiquitous
ASMT	1600–1850	?	>6	?	1.25	Pineal gland, retina
ANT3	1300	Cen-Tel	5.9	4	1.3	Ubiquitous
IL3RA	1180–1300	Tel-Cen	?	>4	1.5	Haemopoietic cells
CSF2RA	1180–1300	?	>45	>5	1.8	Haemopoietic cells

none of these is very likely. Gene sizes range from 5.9 kb (ANT3) to 52 kb (MIC2). Exon sizes are smaller than average in some genes (e.g. MIC2), but larger than average in others (e.g. ANT3 and XE7). There are no data as yet on the genetic divergence of pseudoautosomal genes.

The unusual mode of inheritance of pseudoautosomal genes, with varying degrees of partial sex linkage, also stimulated the proposal of a wide range of hypothesis concerning different diseases. Indeed, all traits that appear to be inherited in an autosomal fashion but that cannot be assigned to an autosomal linkage group may result from a pseudoautosomal gene.

Since this region escapes X-inactivation, some genes that it contains are thought to lead, in a dosis-dependent way, to some of the features seen in Turners syndrome (45,X). Association studies between short stature and terminal deletions of both Xp and Yp have pointed to a pseudoautosomal location of one of the growth genes (Ballabio et al. 1989; Henke et al. 1991; Ogata et al. 1992a, b). Short stature represents one of the cardinal and consistent features of Turner syndrome. Molecular studies on several patients with partial monosomies of the PAR (with or without short stature) suggest that the critical region for the putative growth gene is the region 50–1300 kb from the telomere (Henke et al. 1991; Ogata et al. 1992a, b). It will be interesting to find out which other diseases are associated with genes located in the PAR. Surprises are guaranteed over the next few years.

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