The Human Pseudoautosomal Region (PAR): Origin, Function and Future

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Abstract: The pseudoautosomal regions (PAR1 and PAR2) of the human X and Y chromosomes pair and recombine during meiosis. Thus genes in this region are not inherited in a strictly sex-linked fashion. PAR1 is located at the terminal region of the short arms and PAR2 at the tips of the long arms of these chromosomes. To date, 24 genes have been assigned to the PAR1 region. Half of these have a known function. In contrast, so far only 4 genes have been discovered in the PAR2 region. Deletion of the PAR1 region results in failure of pairing and male sterility. The gene *SHOX* (short stature homeobox-containing) resides in PAR1. SHOX haploinsufficiency contributes to certain features in Turner syndrome as well as the characteristics of Leri-Weill dyschondrosteosis. Only two of the human PAR1 genes have mouse homologues. These do not, however, reside in the mouse PAR1 region but are autosomal. The PAR regions seem to be relics of differential additions, losses, rearrangements and degradation of the X and Y chromosome in different mammalian lineages. Marsupials have three homologues of human PAR1 genes in their autosomes, although, in contrast to mouse, do not have a PAR region at all. The disappearance of PAR from other species seems likely and this region will only be rescued by the addition of genes to both X and Y, as has occurred already in lemmings. The present review summarizes the current understanding of the evolution of PAR and provides up-to-date information about individual genes residing in this region.

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THE X AND Y CHROMOSOMES

The human sex chromosomes (X and Y) originate from an ancestral homologous chromosome pair, which during mammalian evolution lost homology due to progressive degradation of the Y chromosome [1]. The X-chromosome in placental mammals represents approximately 5% of the haploid genome and the gene content is almost completely conserved amongst species. To ensure dosage compensation, most genes on the X are subject to X inactivation in females. The Y chromosome is much smaller than the X, being only 2–3% of the haploid genome, and is largely composed of repeated sequences. Most genes on the Y have relatives on the X chromosome and these are not subject to X inactivation. The degeneration of the Y chromosome has been researched and reviewed extensively [2-6].

THE PSEUDOAUTOSOMAL REGIONS

The pseudoautosomal regions (PAR1 and PAR2) are short regions of homology between the mammalian X and Y chromosomes. The PAR behave like an autosome and recombine during meiosis. Thus genes in this region are inherited in an autosomal rather than a strictly sex-linked fashion.

PAR1 comprises 2.6 Mb of the short-arm tips of both X and Y chromosomes in humans and other great apes [7, 8] and is required for pairing of the X and Y chromosomes during male meiosis. All characterized genes within PAR1 escape X inactivation. X-Y pairing in the PAR is thought to serve a critical function in spermatogenesis, at least in humans and mouse [9-11]. PAR2 is located at the tips of the long arms and is a much shorter region, spanning only 320 kb [12]. PAR2 exhibits a much lower frequency of pairing and recombination than PAR1 and is not necessary for fertility [13-15].

GENES IN HUMAN PAR1 AND PAR2

The sequence of the human X chromosome is nearly complete [16]. This has shown that PAR1 contains at least 24 genes. About half were identified almost a decade ago, while some, like *PLCXD1*, *P2RY8* and *DHRSX*, have been identified more recently. As well, many novel transcripts were recently assigned to the PAR1 region [16]. The function of known genes in PAR1 is summarized in Table **1**. One, designated *XE7* when it was described initially [17, 18], but which is now termed *CXYorf3*, had at that time no function ascribed to it. *CXYorf3* is located 1760 kb from the telomere in PAR1 and generates two protein isoforms [18]. The shorter one arises from the insertion of an alternative exon containing a stop codon that results in a truncated protein [17, 18]. The longer isoform has a C-terminal region rich in arginine and serine residues, reminiscent of the RS (arginine/serine) domain present in RNA binding/spliceosomal proteins. The protein, XE7, also termed 721P/B-lymphocyte surface antigen [19], had been identified initially in a spliceosomal screen [20]. Only recently have functional studies been carried out. In these we found that XE7 is an alternative splicing regulator which binds to two important splicing proteins, ASF/SF2 and ZNF265 [21]. Fig. (**1**) shows the localization of *XE7*/*CXYorf3* amongst other PAR1 genes. Interestingly, exon 3 of *XE7/CXYorf3* is identical to exon 1A of another pseudoautosomal gene, *ASMTL* (acetylserotonin

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Table 1. PAR1 Genes and Protein Function. Only Genes that have been Cloned or Otherwise Characterized are Shown

Gene symbol	Alternative name/symbol	Protein	Ref.
PLCXD1: phospatidylinositol-specific phospholipase C, X domain containing 1	*FLJ11323*	Function not known.	[70, 71]
GTPBP6: GTP binding protein 6 (putative)	*PGPL*	Function not known.	[72]
PPP2R3B: Protein phosphatase 2, regulatory subunit B	*PPP2R3L*, *PR48* protein	Exerts regulatory control over the initiation of DNA replication. Over-expression of PR48 causes G1 cell cycle arrest.	[73]
SHOX: short stature homeobox	*PHOG*, *GCFX*, *SS*, *SHOXY*	Homeobox-containing gene, thought to be a transcription factor related to short stature syndromes.	[34, 36]
CRLF2: cytokine receptor-like factor 2	*CRL2*, *TSLPR*	The receptor for TSLP, a cytokine that enhances the maturation process of dendritic cells and promotes the proliferation of $CD4^+$ T cells.	[74-77]
CSF2RA: colony-stimulating factor 2 receptor, alpha	*CD116*, *GMCSFR*	The alpha subunit of the receptor for the granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is important for the growth and differentiation of eosinophils and macrophages in the bone marrow, and also regulates cell viability in human embryos.	[55-57, 78-80]
IL3RA: interleukin 3 receptor, alpha	*CD123*	The alpha subunit of the receptors for interleukin 3.	[81, 82]
SLC25A6: solute carrier family 25, member A6	*ANT3*, *ANT3Y*, *MGC17525*	A member of the ADP/ATP translocase family, which has a potential role in Th cell survival and immune cell homeostasis.	[83-85]
ASMTL: acetylserotonin O-methyltransferase-like	*ASMTLX*	Function not known.	[22]
P2RY8: purinergic receptor P2Y, G-protein coupled, 8	*P2Y8*	A member of the purine nucleotide G-protein coupled receptor gene family.	[86]
CXYorf3	*XE7*, *XE7Y*, *DXYS155E*, *MGC39904*, B lymphocyte surface antigen 721P, X-escapee, *CCDC133*	Alternative splicing regulator.	[17, 18, 21]
ASMT: acetylserotonin O-methyltransferase	*HIOMT*, *ASMTY*, *HIOMTY*	Catalyzes the final reaction in the synthesis of melatonin.	[84, 87]
DHRSXY: dehydro-genase/reductase (SDR family) X-linked	*DHRS5X*, *DHRS5XY*, *DHRSY*, *DHRS5Y*	Encodes an oxidoreductase of the short-chain dehydrogenase/reductase family.	[88]
ZBED1: zinc finger, BED-type containing 1	*TRAMP*, *ALTE*, *KIAA0785*	Has been suggested to be involved in the transposition of other transposable elements.	[89]
CD99: CD99 molecule	*MIC2*, CD99 antigen, "antigen identified by monoclonal antibodies 12E7, F21 and O13"	Is a cell surface molecule involved in T-cell adhesion processes. Activation of a distinct domain of CD99 activates a caspase-independent death pathway in T-cells.	[90-92]
XG: XG blood group	*PBDX*, "XG blood group, pseudoautosomal boundary-divided on the X-chromosome"	The blood group gene XG generates a cell-surface antigen 48 % homologues to CD99.	[93, 94]

methyltransferase-like) [22]. *ASMTL* represents a unique fusion product of two distinct genes of different evolutionary origin and function [22]. The N-terminal part is homologous to the bacterial *mafl orfE* genes and the rest shows 60% homology to the *ASMT* gene and its encoded protein. Taken together the data suggest that exon duplication and shuffling, as well as gene fusion, may represent common features in the origin of the pseudoautosomal region. Indeed, gene duplications have been shown for other genes in this region. *CD99 (MIC2)* is 73% homologous to the pseudogene *MIC2R*, and its protein shows 48% homology with XG, while CSF2RA and IL3RA are 54% homologous at the amino acid level. The exon structure in both *MIC2/MIC2R* and *ASMT/ASMTL* are also similar [22]. Due to the crossing-over event in each male meiosis between X and Y in the PAR region [23], the recombination rate is 20-fold higher compared with the rest of the genome. This does not, however, fully explain the high rate of gene duplication in PAR.

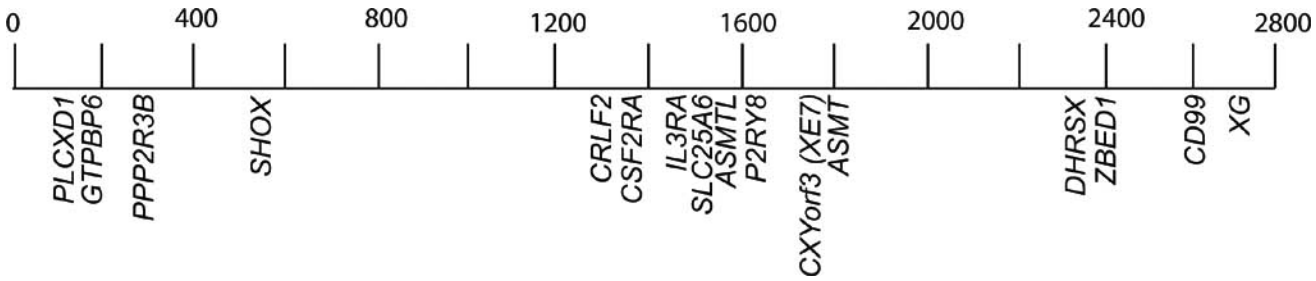

Fig. (1). Localization of genes in PAR1. Only characterized genes that are discussed in the text are shown. Their relative position and distance from the telomere is shown in Kb.

In the case of the PAR2 region, 4 genes have been identified to date: *SPRY3, SYBL1, IL9R* and *CXYorf1*. Of these, only *SYBL1* and *IL9R* have a known function, and these, together with SHOX from the PAR1, are discussed below.

PAR1/PAR2 AND DISEASE

SYBL1 is located in PAR2 but differs from most other PAR genes in that it undergoes both X and Y inactivation. It is a highly conserved gene [24] that codes for a member of the synaptobrevins implicated in cellular exocytosis. In a subset of families with bipolar affective disorder (BPAD), the absence of father-to-son transmission suggested that a susceptibility gene existed on the sex-linked portion of the X chromosome. Saito *et al.* [25] screened *SYBL1* and found a polymorphism (G to C transversion at the intron 7/exon 8 junction) with a statistical trend toward an association with BPAD in males. In addition, Muller *et al.* [26] observed a significantly increased frequency of genotypes homozygous for the C allele in females with BPAD in comparison with controls, thus strengthening the role of the *SYBL1* gene as a candidate gene for BPAD. *IL9R* (also known as *CD129*) belongs to the hematopoietin receptor subfamily and PAR2 expresses this gene in both membrane-bound and soluble forms [27]. A role for *IL9R* in the development of asthma has been suggested [28, 29]. The sDF2*10 allele of *IL9R* is more frequently transmitted than untransmitted to asthmatic offspring and the allele was found to be homozygous more often than expected in asthma patients [29]. Also, a specific X-chromosome haplotype (sDF2*10-sDF1*6) was found to be associated with asthma [29]. In support of the involvement of IL9R in allergic diseases, a specific IL9R haplotype appears to protect against wheezing in boys [30]. In addition, it has been shown that IL9R is expressed in samples from asthmatic airways but not those from normal subjects [31-33].

The *SHOX* (Short stature HOmeoboX-containing) gene resides in PAR1 and was first suggested to be involved in the short stature of Turner syndrome by Ellison *et al.* [34], although they named the gene *PHOG* for "pseudoautosomal homeobox-containing osteogenic gene". Turner syndrome is one of the most common chromosomal abnormalities in humans with an incidence of at least 1 in 1850 live female births [35]. It is characterized by features such as short stature, cubitus valgus, short metacarpals, Madelung deformity, high arched palate and short neck. Further data supported the involvement of *SHOX* in the growth failure of Turner patients and identified a mutation in the *SHOX* gene in patients with idiopathic growth retardation [36]. It has also been shown that *SHOX* haploinsufficiency can cause not only short stature but also Turner skeletal anomalities such as short fourth metacarpals, cubitus valgus and characteristics of Leri-Weill dyschondrosteosis (LWD) [37]. LWD is an inherited skeletal dysplasia characterized by disproportionate short stature, mesomelic limb shortening and Madelung deformity of the arm. Later studies have found submicroscopic deletions in the *SHOX* gene in 34% to 81% of affected families and point mutations in the *SHOX* gene in 19% to 39% of LWD families studied [38-46]. Patients with SHOX haploinsufficiency could benefit from early growth hormone treatment, so early screening of children with unexplained short stature has been suggested [47, 48]. A second PAR1 region has been implicated lately in the pathogenesis of LWD. This involved identification of a novel class of PAR1 deletions which did not include *SHOX* [49]. The finding indicated the presence of distal regulatory elements of *SHOX* transcription in PAR1 or the existence of an additional locus involved in the control of skeletal development [49]. More recently PAR1 deletions downstream of SHOX have been reported to represent a higher proportion of mutations than SHOX deletions and mutations implicated in LWD [50].

PRE-mRNA SPLICING AND PAR

Alternative splicing generates several mRNA products and thus protein isoforms from a single gene. This is one of the most important mechanisms regulating gene expression. Alternative splicing can lead to the production of protein isoforms with changed binding properties, intracellular localization, enzymatic activity, protein stability, or posttranslational modification (such as phosphorylation) and cell type/tissue-specific expression. Alternative splicing can also introduce a stop codon, which, if a pre-mature stop codon, can lead to nonsense-mediated decay (NMD) of the mRNA. Changes in splice site selection can also cause disease, or might be a consequence of disease. Several genes in PAR1 and PAR2 generate multiple protein isoforms as a result of alternative splicing.

SHOX can produce two protein isoforms, SHOXa and SHOXb, of 292 and 225 amino acids, respectively. *SHOX* consists of 6 exons. The two isoforms diverge after exon IV. Both SHOXa and SHOXb are expressed in skeletal muscle and bone marrow fibroblasts, while SHOXa is also expressed in placenta, pancreas and heart. SHOXb, on the other hand, is also expressed in fetal kidney, but the highest expression has been found in bone marrow fibroblasts [36].

The significance of the two isoforms is at present not known. An insertion in exon 6a in a man with Langer mesomelia dysplasia has led to the conclusion that the SHOXa isoform is essential for normal skeletal development [51].

XE7/*CXYorf3* also generates two isoforms. This is a result of the insertion of an additional exon (exon 5), which, as described above, leads to a truncated protein [18]. As mentioned earlier, we have shown that the longer isoform of XE7 is an alternative splicing regulator that affects the splicing of CD44, Tra2β1 and SRp20 [21]. The significance of the shorter isoform is at present not known, but it has been speculated that this isoform undergoes NMD. This could be a way of regulating the expression of XE7 in different cell types or developmental stages according to need.

CD99 serves as a marker for the Ewing sarcoma family of tumors and has been found recently in primary cutaneous melanoma [52]. CD99 exists in two isoforms, type I and II. An 18 bp insertion between exons 8 and 9 introduces a premature stop codon, generating a truncated protein, as in the case of XE7. The longer isoform of CD99 has been shown to regulate the adhesion of lymphocytes via the LFA-1/ICAM-1 pathway. In contrast, overexpression of the shorter isoform reduces the level of LFA-1 expression and regulates CD99-mediated and spontaneous aggregation of lymphocytes [53]. Type I is expressed in most tissues studied, while type II has been detected at lower levels in a cell-specific manner [53], suggesting that the alternative splicing of CD99 serves a biological functional role.

IL9R exists in two distinct isoforms and this too is due to alternative splicing. Isoform 1 [27] is the longer isoform and is 76% homologous to isoform 2 reported by Chang *et al.* [54]. Isoform 2 contains an insertion of 125 base pairs in the N-terminal region, and this results in a frameshift. Other base pair changes in the coding region, compared to isoform 1, generate an isoform with distinct N and C-termini and other internal differences. It is at present unknown if a difference in expression of each isoform is related to an association with asthma.

CSF2RA encodes the alpha subunit of the heterodimeric receptor for colony stimulating factor 2, a cytokine controlling the production, differentiation, and function of granulocytes and macrophages. Alternative splicing produces at least 5 isoforms, some being membrane-bound and others being soluble [55-59].

ORIGIN OF HUMAN PAR1 AND PAR2

Marsupials and eutherian mammals diverged about 130 million years ago (Mya), and monotremes and eutherians 170 Mya. The sex chromosomes of marsupials and monotremes differ quite substantially. Marsupials have a small X and an even smaller Y and these do not undergo homologous pairing, while the monotremes have a large X and Y which pair over the entire short arm of the X and the long arm of the Y.

The PAR of placental mammals varies greatly. The mouse and human PAR region are completely non-homologous and even within primates the gene content of the PAR deviates. Cloning and mapping dog and sheep homologues of human Xp22.3 genes *PRKX* and *STS*, as well as PAR1 genes *ANT3* and *CSF2RA*, showed that they are all pseudoautosomal in these mammals and must have been part of the sex chromosomes for at least 80 million years [60]. This means that the ancestral eutherian PAR was larger than the present human PAR. Mapping of *STS*, *ANT3* and *CSF2RA* genes in marsupials showed that these are autosomal in marsupials and colocalized with 7 other human Xp genes within a single autosomal cluster in marsupials (61). This implies that the eutherian PAR was part of a larger autosomal addition to the X and Y 130–80 Mya [61]. *ANT3* mapped separately on another wallaby autosome, so it may represent a region added independently to the eutherian PAR or a region that has been rearranged in marsupials [61]. The mouse sex chromosomes have a 2 Mb PAR region, but contain only one active gene, *Sts* [62, 63]. One other gene, *Fxy*, spans the pseudoautosomal boundary on the mouse X and has a truncated partner at the boundary of the Y PAR [64, 65]. The human homologue resides near the PAR on the X but does not exist on the Y. A recent revelation is that PAR1 resides within a 9 Mb block that has been removed from the X chromosome of a common murine ancestor of mouse and rat [16]. It thus seems that independent additions to PAR1 by gene translocation from autosomes seem to have occurred in eutherians, macropodid marsupials and monotremes, while loss of PAR1 genes is evident in mouse. By comparing human genes in or near PAR1 with those of other mammals it is evident that mutation and loss of genes on the differentiating Y chromosome reduced the homologous region to a different extent in different lineages [60].

Of the four PAR2 genes, only *SYBL1* is located on the X chromosome in all species, including marsupials, so it must have been part of the ancient X chromosome. *SPRY3* is localized to the X chromosome in all eutherians, but not marsupials, consistent with it having been added to the X after the divergence of eutherians and marsupials 130 Mya, but before the eutherian radiation 80 Mya [66]. Neither *SPRY3* nor *SYBL1* map to the Y chromosome in primates and mouse. Each are inactive on the Y and subject to X inactivation in humans [67]. *CXYorf1* on the other hand is on the X and autosomes in both primate and mouse [68], but is autosomal in the wallaby [66], so it must have been added 70–130 Mya. *IL9R* is located on the X only in primates [66], so it seems to be the latest addition to PAR2, occurring 60–70 Mya. Human *CXYorf1* and *IL9R* are expressed from the Y chromosome and are not subject to X inactivation [67]. There are multiple copies of *IL9R* and *CXYorf1* on the autosomes, so gene duplication has been suggested as playing a role in the evolution of these two genes [66]. Since the order of the genes on human PAR2 is *SPRY3*, *SYBL1*, *IL9R*, followed by *CXYorf1*, the evolution of this region must have required two inversion events on top of the three independent additions of genes.

FUTURE OF PAR

As mentioned earlier, X-Y pairing in PAR serves a critical function for spermatogenesis in humans and mice [9-11]. PAR is, however, absent in marsupials and the absence of homologous pairing of the X-Y chromosomes in this species causes no disruption to segregation at meiosis [8]. It is at present unclear what has replaced homologous pairing and recombination in marsupials. The mouse PAR also seems to

be at the last stage of degradation. The PAR region will only be saved if further additions of genes take place to both X and Y. This has already happened in the case of one mammal, the lemming [69]. The fact that the gene content of PAR in different species is so inconsistent argues for PAR not playing a sequence-dependent role in fertility. It does, however, seems to be an excellent genetic playground.

ABBREVIATIONS

PAR	=	Pseudoautosomal region
RS	=	Arginine/serine
BPAD	=	Bipolar affective disorder
LWD	=	Leri-Weill dyschondrosteosis
NMD	=	Nonsense-mediated decay
Mya	=	Million years ago

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