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The Pseudoautosomal Region and Sex Chromosome Aneuploidies in Domestic Species

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Aneuploidy · Domestic species · Pseudoautosomal region · Sex chromosomes · X-monosomy · X-trisomy

Abstract
The pseudoautosomal region (PAR) is a unique and specialized segment on the mammalian sex chromosomes with known functions in male meiosis and fertility. Detailed molecular studies of the region in human and mouse show dramatic differences between the 2 PARs. Recent mapping efforts in horse, dog/cat, cattle/ruminants, pig and alpaca indicate that the PAR also varies in size and gene content between other species. Given that PAR genes escape X inactivation, these differences might critically affect the genetic consequences, such as embryonic survival and postnatal phenotypes of sex chromosome aneuploidies. The aim of this review is to combine the available information about the organization of the PAR in domestic species with the cytogenetic data on sex chromosome aneuploidies. We show that viable XO individuals are relatively frequently found in species with small PARs, such as horses, humans and mice but are rare or absent in species in which the PAR is substantially larger, like in cattle/ruminants, dogs, pigs, and alpacas. No similar correlation can be detected between the PAR size and the X chromosome trisomy in different species. Recent evidence about the likely involvement of PAR genes in placenta formation, early embryonic development and genomic imprinting are presented.

The pseudoautosomal region (PAR) is a short region of sequence homology between the sex chromosomes and is involved in sex chromosome pairing, recombination and segregation in meiosis of the heterogametic sex. The region has been found in many plant and animal species, including mammals [Charlesworth et al., 2005; Ming and Moore, 2007].

The mammalian PAR was discovered almost 80 years ago through studies of male meiosis in rats, where a synaptonemal complex between the X and Y was detected [Koller and Darlington, 1934]. Similar structures were soon found between the terminal ends of the X and Y chromosomes in several other eutherian species [Pathak and Elder, 1980], but not in marsupials [Sharp, 1982]. These observations have later been validated through detailed molecular genetic studies both in eutherian [Martin, 2006; Oliver-Bonet et al., 2006; Kauppi et al., 2011] and marsupial [Page et al., 2005, 2006] mammals.

Whole or partial genome sequence data are available for almost all main domestic species – alpaca, cat, cat-

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tle, dog, horse, pig, and rabbit (Ensembl: http://www.ensembl.org/index.html; UCSC: http://genome.ucsc.edu/). For a few species, such as dog [Lindblad-Toh et al., 2005], cattle [Bovine Genome Sequencing and Analysis Consortium et al., 2009] and horse [Wade et al., 2009], annotated sequence draft assemblies have been published, while the data for the remaining species are composed of partially annotated sequence scaffolds. The sequence information is supported, validated and chromosomally anchored by high-resolution whole genome linkage, radiation hybrid and/or cytogenetic maps which are available for most of the domestic species, viz., cat [Davis et al., 2009], dog [Breen et al., 2004], horse [Raudsepp et al., 2008], cattle [Everts-van der Wind et al., 2004], pig [Humphray et al., 2007], and rabbit [Chantry-Darmon et al., 2006]. Despite these outstanding achievements, information about the PAR remains scarce. In most sequence assemblies, the region is missing or represented only partially. Furthermore, most animal genome sequencing projects have used DNA from female individuals, thus obtaining diploid data for the X chromosome, but no sequences for the Y. Thus, even though map data are available for the X chromosome, lack of information for the Y sets limitations to properly demarcate the PAR. Despite these difficulties, recent mapping efforts indicate that the PAR varies in size and gene content between eutherian species [Raudsepp and Chowdhary, 2008; Van Laere et al., 2008; Young et al., 2008; Das et al., 2009]. Given that PAR genes escape X inactivation [Bondy and Cheng, 2009], these differences might critically influence the genetic effects caused by changes in sex chromosome numbers. Therefore, the aim of this review is to discuss the possible association between the organization of the PAR and the occurrence and phenotypic implications of sex chromosome aneuploidies in domestic species. We will first summarize the knowledge about the human and mouse PARs because these are the only mammalian PARs that have been studied in detail. Thereafter, we will focus on the PARs of the domestic species and discuss the available information in conjunction with the cytogenetic data on sex chromosome aneuploidies. Possible functions of the PAR genes in mammalian biology will be discussed.

Specific Features of the Mammalian Pseudoautosomal Region

The PAR is a unique region of true sequence homology (98–100%) between the eutherian X and Y chromosomes [Skaletsky et al., 2003; Galtier, 2004; Ross et al., 2005; Blaschke and Rappold, 2006; Mangs and Morris, 2007; Flaquer et al., 2008]. The physical domain of the PAR lies between the terminal ends of the sex chromosomes and the pseudoautosomal boundary (PAB) (fig. 1) – a border across which the sequence homology between the X and the Y chromosomes decreases, recombination ceases and regions specific to individual sex chromosomes begin [Galtier, 2004; Ross et al., 2005]. The PAB is typically demarcated by the insertion of transposable elements, like SINEs, which initiate the suppression of X-Y recombination [Ellis et al., 1989; Perry and Ashworth, 1999; Van Laere et al., 2008]. Also, most of the mammalian PABs studied so far are spanned by a gene which is truncated on one of the sex chromosomes [Ellis et al., 1989; Perry and Ashworth, 1999; Van Laere et al., 2008] (fig. 1). Loci located within the PAR behave similar to autosomal loci: they are diploid, undergo recombination in males and females and are not subject to dosage compensation by X inactivation in females [Ellis and Goodfellow, 1989; Brown and Greally, 2003; Bondy and

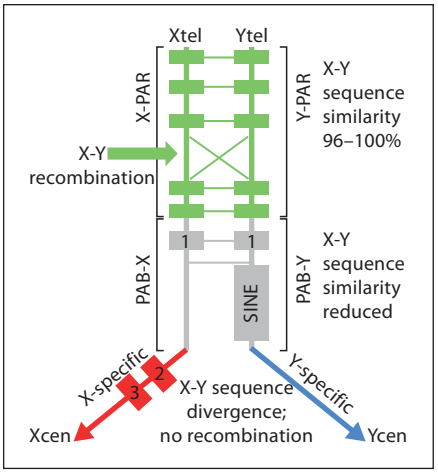

Fig. 1. A schematic illustrating the most characteristic structural features of the mammalian PAR. The PAR is shown in green, the PAB in grey, the X chromosome in red and the Y chromosome in blue colors; horizontal lines between the X and Y chromosomes demarcate sequence homology; crossed lines show a recombination site; filled rectangles stand for X-Y homologous genes; filled rectangles with numbers – 1, 2, 3 – demarcate the three exons of one gene: exon 1 is located in the PAB and is present on both sex chromosomes, while exons 2 and 3 are present only on the X chromosome; a SINE element has been transposed into the PAB-Y suppressing the X-Y recombination; Xtel and Ytel, and Xcen and Ycen demarcate telomeric and centromeric regions of the sex chromosomes, respectively. The figure does not represent the PAR of any particular species.

Cheng, 2009; Prothero et al., 2009; Urbach and Benvenisty, 2009]. These features led to naming of the region as 'pseudoautosomal' [Burgoyne, 1982], primarily to indicate the autosome-like properties, despite being on the sex chromosomes.

While the physical boundary of the PAR is demarcated by the PAB, functionally the region is defined by recombination. Because the PAR is a small region and because there is one obligatory cross-over in male meiosis, the overall recombination frequency in the PAR is high, exceeding the genome average 10–20 times [Filatov, 2004; Flaquer et al., 2009].

These almost canonical facts are exclusively based on the studies of human [Skaletsky et al., 2003; Ross et al., 2005] and mouse [Ellison et al., 1996; Palmer et al., 1997; Gianfrancesco et al., 2001; Perry et al., 2001] PARs, while only limited information is available for other mammals, including the domestic species. Ironically, though the mammalian PAR was first discovered in rats [Koller and Darlington, 1934], the size and gene content of the region in rats is still not determined.

The Human and Mouse PARs

The *human* (*Homo sapiens*, HSA) PAR is undoubtedly the best characterized due to the availability of annotated sequence data for both the X [Ross et al., 2005] and the Y chromosome [Skaletsky et al., 2003]. Notably, human is thus far the only eutherian species known to have 2 PARs. The PAR1 [Ellis and Goodfellow, 1989; Ellis et al., 1989], at the tip of HSAXp/Yp, shares similarity with other eutherian PARs, while PAR2 at HSAXq/Yq is strictly human-specific and is not found even in chimpanzee [Ciccodicola et al., 2000; Charchar et al., 2003; Hughes et al., 2010]. Since the PAR2 has no homology in other mammals and because only 2 of the 4 PAR2 genes escape X inactivation [De Bonis et al., 2006], the region has little relevance to genetic changes associated with sex chromosome aneuploidies and is not included in further discussion.

The physical boundary of the PAR1 is demarcated by the *XG* blood group gene at 2.67 Mb [Pritchard et al., 1987; Goodfellow et al., 1988; Ellis et al., 1989; Galtier, 2004; Ross et al., 2005; Blaschke and Rappold, 2006]. The PAR1 contains 24 genes and shows relatively higher gene density (10 genes/Mb) than the rest of HSAX (7 genes/Mb) [Ross et al., 2005] or HSAY (3 genes/Mb) [Skaletsky et al., 2003]. However, given that 20% of PAR1 sequence is not yet available [Ross et al., 2005], the proposed size and gene density for the human PAR1 are rough estimates.

Interestingly, the PARs in other primates differ from human PAR1 in size and gene content. For example, the Alu repeat is present at the PAB of human and great apes, but not in the Old World monkeys [Ellis et al., 1990]. In lemurs, the PAR has moved to the tip of the Xq and incorporates genes that are X-specific in human [Gläser et al., 1997, 1999].

The *mouse* (*Mus musculus*, MMU) PAR is the second most studied after human and, remarkably, shares no homology with the human PAR1 or any other eutherian PARs. The region is approximately one-quarter the size (~700 kb) of the human PAR1 and contains only 3 known protein coding genes [Ellison et al., 1996; Gianfrancesco et al., 2001; Peterlin et al., 2004]. Similar to humans, the mouse PAB is spanned by a gene, *Mid1,* which is truncated on MMUY [Palmer et al., 1997; Perry et al., 2001]. As far as known, the murine PAR is the smallest and the gene poorest among eutherians.

The PAR in Domestic Species

The remarkable differences between the human and mouse PARs and the observed variation between the PARs in primates pose outstanding questions: is the variation in PAR size and gene content a common feature among mammals; what is the extent of the variation, and what could be the genetic consequences of these differences? Some answers come from the recent PAR studies in domestic species.

The PAR has been mapped to the ends of both sex chromosomes in almost all domestic species, viz., dog [Olivier et al., 1999; Young et al., 2008], horse [Shiue et al., 2000; Raudsepp and Chowdhary, 2008], bovids-caprids [Iannuzzi et al., 2000a; Di Meo et al., 2005; Das et al., 2009], pig [Quilter et al., 2002], cat [Murphy et al., 2007; Pearks Wilkerson et al., 2008], and alpaca [own unpublished data]. On the X chromosome, which is evolutionarily conserved among mammals [Ohno, 1967; Raudsepp et al., 2004a], the PAR is typically located at Xpter (fig. 2), as is PAR1 in humans. The only known exceptions are bovids where, due to X chromosome rearrangements, the PAR has moved to the end of the long arm (Xq). The location of the PAR on the Y chromosome, which is not evolutionarily conserved [Raudsepp et al., 2004b], varies more and differs even between closely related species, e.g. the ruminants (fig. 2). The location of the PAR on the long or short arm of the sex chromosomes does not affect X-Y pairing, but might have genetic implications in case of structural chromosomal re-

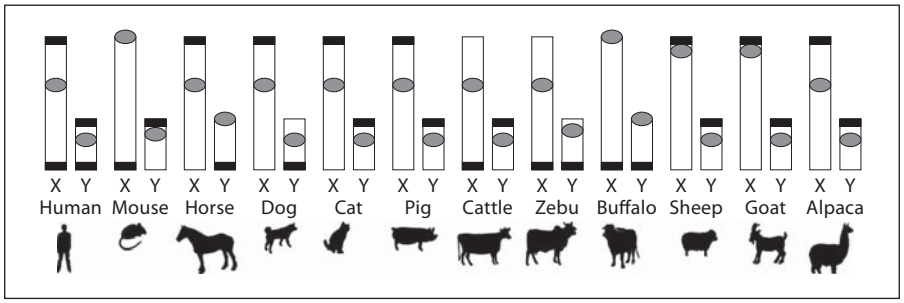

Fig. 2. A schematic showing the location of the PAR on the sex chromosomes of human, mouse and 10 domestic species. Black rectangles mark the PAR; grey ovals show the position of the centromeres. The information is retrieved from the following sources: human [Skaletsky et al., 2003; Ross et al., 2005], mouse [Perry et al., 2001], horse [Raudsepp and Chowdhary, 2008], dog [Olivier et al., 1999; Lindblad-Toh et al., 2005], cat [Murphy et al., 2007; Pearks Wilkerson et al., 2008], pig [Quilter et al., 2002], cattle, zebu, river buffalo, goat, and sheep [Iannuzzi et al., 2000a; Di Meo et al., 2005; Das et al., 2009], and alpaca [own unpublished observations].

arrangements. For example, isochromosome formation might result in complete deletion or duplication of the region on one of the sex chromosomes [see Das et al., 2011, this issue].

Dog and Cat

Despite the evolutionary conservation of the mammalian X chromosome, the location of the PAR alone, without demarcation of the PAB, provides no information about the actual size and gene content of the region. For example, sequence draft assembly of the dog X chromosome has been available since 2005 [Lindblad-Toh et al., 2005]. However, the canine PAB and, thus, the physical domain of the PAR was determined only recently [Young et al., 2008]. Notably, the canine PAR is ~6.6 Mb in size, thus more than two times larger than human PAR1. It extends proximal to *SHROOM2* and contains at least 34 protein coding genes (Ensembl: http://www.ensembl.org/index.html) [Young et al., 2008]. Though sequence assembly for the cat X chromosome is not complete (Ensembl website; UCSC: http://genome.ucsc.edu/cgi-bin/hgGateway), radiation hybrid mapping suggests that the cat PAB is also located between *SHROOM2* and *WWC3* genes [Murphy et al., 2007]. The PARs of the 2 species are, thus, very similar in gene content but might differ in size because in dog X chromosome, *SHROOM2* is located at 6.4 Mb and in cat at 8.0 Mb (UCSC website).

Dog is so far the only domestic species with a complete sequence map available for the PAR. In other species where whole genome draft assembly is available, like horse [Wade et al., 2009] and cattle [Bovine Genome Sequencing and Analysis Consortium et al., 2009], the PAR sequence is incomplete (horse) or largely missing (cattle). Therefore, the PARs of other domestic species have been characterized through various mapping efforts.

Horse

A high-resolution BAC contig map is available for the horse PAR and shows that the region is about 1.8 Mb in size, thus the smallest among domestic species, and contains 18 genes [Raudsepp and Chowdhary, 2008]. Interestingly, while the equine PAR and the human PAR1 are largely collinear on the X chromosome, the ~0.9 Mb smaller horse PAR contains 12 genes that are X-specific in humans. The horse PAB is located between *PRKXY* and *NLGN4X* in the X chromosome, and between *PRKXY* and *EIF1AY* in the Y chromosome.

Cattle, Goat, Sheep, and Other Ruminants

The physical domain of cattle/ruminant PAR is demarcated by the *GPR143* gene which spans the PAB in cattle, zebu, bison, yak, banteng, and sheep [Van Laere et al., 2008]. Thus, *SHROOM2,* which is a PAR gene in cat and dog, is X-specific in cattle/ruminants. Furthermore, *PLCXD1*, the most terminal PAR gene in dog, human and horse, is located in the X-specific region in cattle [Das et al., 2009]. Despite containing fewer genes than the PARs in cat and dog, the physical size of the cattle/ruminant PAR might be larger, over 9 Mb, as estimated from homologous region in HSAXp [Das et al., 2009]. The observed discrepancy between the PAR size and gene content, as seen between dog/cat and cattle, and between human and horse, can be attributed to variations in the content of repetitive sequences in different species. As a result, sequences which are collinear in gene content are not necessarily equal in size.

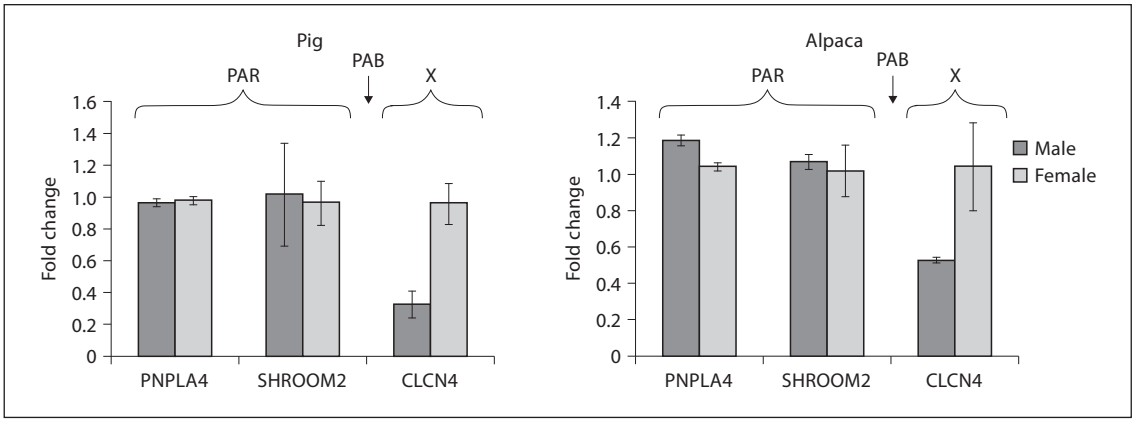

Fig. 3. The approximate location of the PAB in pig and alpaca X chromosomes. Genomic copy numbers were determined by quantitative real-time PCR (qRT-PCR): *PNPLA4* and *SHROOM2* with male/female copy number ratio 1:1 are located in the PAR; *CLCN4* with male/female copy number ratio 1:2 is located in the X-specific region.

Pig and Alpaca

Even though the pig genome is well studied, mapped and sequenced [see Raudsepp and Chowdhary, 2011], and the alpaca genome is not, the 2 species are quite equal regarding the knowledge about their PARs. Neither has a well-developed map or sequence information for the region. However, very recently, using quantitative real-time polymerase chain reaction, the putative PAB was demarcated in both species [own unpublished data]. Comparing the female-to-male copy number ratios which should be 1 for PAR genes and 2 for X-specific genes, the pig and alpaca PAB was mapped between *SHROOM2* and *CLCN4* (fig. 3) on the X chromosome. Thus, the 2 PARs might be more similar to those of carnivores than ruminants.

Taken together, the physical domain of the PAR has been determined in 6 domestic species (ruminants are considered as one), and notably, all 6 PARs differ from each other as well as from human and mouse PARs (fig. 4). This provides 2 important messages. First, while mouse PAR is an outlier among eutherians, the human PAR1 as well does not represent an average mammalian PAR. Thus, the salient properties of the PAR as revealed from human and mouse studies might not apply to all species. Secondly and most importantly, since the PARs differ in size and gene content, the number of functional genes that escape X inactivation and are the only truly diploid genes on both sex chromosomes, is also different between species. If so, does the size and gene content of the PAR influence the genetic effect of sex chromosome aneuploidies?

Sex Chromosome Aneuploidies

A variety of sex chromosome aneuploidies have been described in domestic species [Chowdhary, 1998; Chowdhary and Raudsepp, 2000; Ducos et al., 2007, 2008; King, 2008; Lear and Bailey, 2008; Villagomez and Pinton, 2008; Villagomez et al., 2009; Durkin et al., 2011; Raudsepp and Chowdhary, 2011]. The majority of those are in mosaic form, where chromosomally normal cells contribute to the phenotype together with cells containing an abnormal number of sex chromosomes, thus blurring the dosage effect of the genes that escape X inactivation. Among non-mosaic aneuploidies, there are those which cause haploinsufficiency for the PAR, such as X-monosomy, and those that increase the PAR dosage, such as XXX, XXY and XYY genotypes. However, in aneuploidies involving the Y chromosome, the phenotypic effects of PAR overdose might be masked by testis determining function of the *SRY* gene [Sinclair et al., 1990]. Therefore, in the following discussion, only non-mosaic cases of X-monosomy and X-trisomy in different species will be considered.

X-Monosomy

X-monosomy is a relatively common sex chromosome abnormality in humans, affecting approximately 1 in 2,500 live female births (0.04%) [Lynn and Davies, 2007; Bondy and Cheng, 2009]. The condition is over 200 times more frequent among conceptuses but seriously affects embryonic viability causing spontaneous abortions. Meta-analysis of over 10,000 human miscarriages shows that

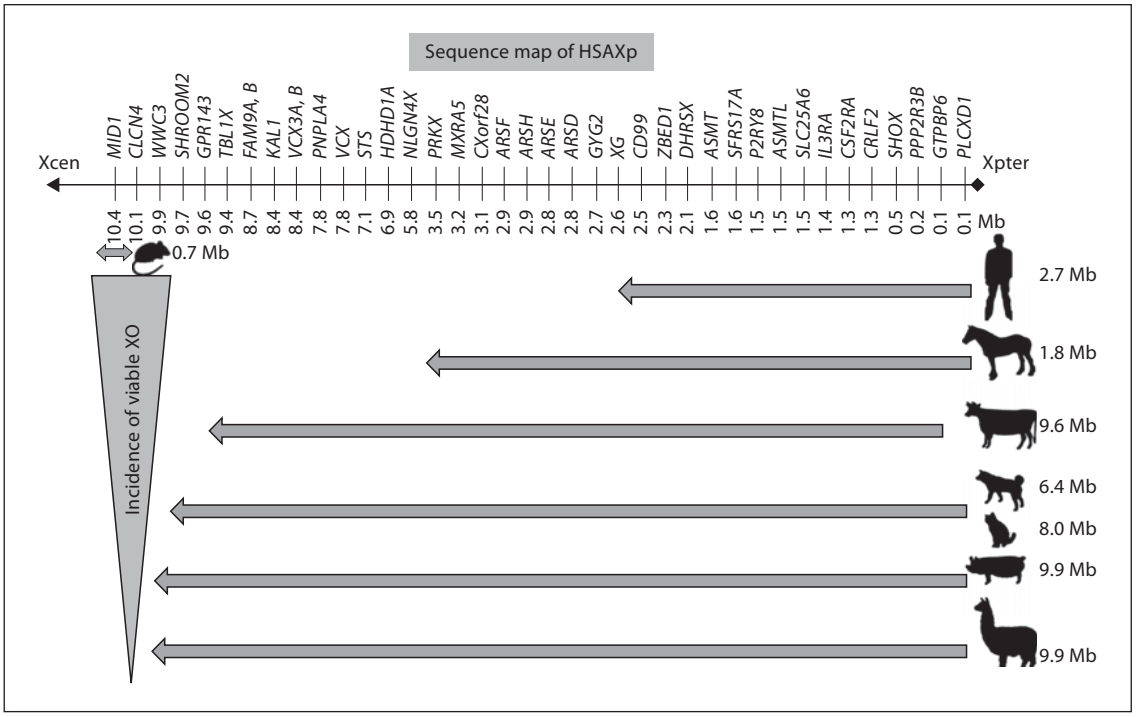

Fig. 4. Correlation between the incidence of viable X chromosome monosomy (left) and the size and gene content of the PAR in human, mouse and domestic species. Sequence map of HSAXp is shown at the top and serves as a reference for the PAR size and gene content for all other species. Bold grey arrows with species shapes at the right demarcate the span of their PARs; Mb at the right to each species depict the approximate size of their PAR; cattle/ruminant PAR starts at *GTPBP6* locus because *PLCXD1* is X-specific in these species.

about 10% have 45,XO karyotype [Menasha et al., 2005]. The few embryos that survive are depleted of oocytes and give rise to sterile females. Also, the XO human females have short stature and might suffer from cardiovascular and neuropsychiatric disorders [Lynn and Davies, 2007; Bondy and Cheng, 2009].

In contrast, X-monosomic mice grow and develop normally, are fertile and have no major congenital defects [Probst et al., 2008] except that the XO mice have less oocytes compared to normal XX mice and become prematurely sterile [Burgoyne and Baker, 1981]. Interestingly, XO mice also exhibit a distinct neurocognitive phenotype and are proposed as a model for the neurobiology of human XO syndrome [Lynn and Davies, 2007].

Apart from human and mouse, the only other species where XO syndrome has been reported frequently is the horse. Since 1968, when the first equine case of X-monosomy was detected [Payne et al., 1968], there have been at least 30 publications describing over 150 XO mares (table 1) [reviewed by Power, 1990; Chowdhary and Raudsepp, 2000; Lear and Bailey, 2008; Villagomez et al., 2009]. The XO syndrome is indisputably the most frequent chromosomal defect in horses accounting for approximately 36% of all sex chromosome abnormalities [Power, 1990; Chowdhary and Raudsepp, 2000; Lear and Bailey, 2008; Villagomez et al., 2009]. In a genotyping-based survey in a large population of newborn foals (n = 17,471), 63,XO karyotype was detected in 0.15% of female animals [Kakoi et al., 2005] suggesting that the incidence of viable X-monosomy in horse populations might be quite similar to those in humans. Likewise, all XO mares studied up till now were sterile. Other characteristic features of the equine condition, such as shorter than normal stature, small gonads lacking follicular development, and irregular or absent estrus cycle [Power, 1990; Chowdhary and Raudsepp, 2000] are also similar to the Turner syndrome in humans [Bondy and Cheng, 2009]. However, no information is available about the frequency of spontaneously aborted equine XO embryos.

In contrast to human and horse, reports about viable XO individuals among other domestic species are rare, less than 10 cases per species since the 1970s [Villagomez

et al., 2009] (table 1). Regardless of the species, all XO females studied so far are sterile. Because there are well-established cytogenetic survey systems for the main agricultural species in many countries worldwide [Ducos et al., 2008], and because the causes of meiotic nondisjunctions are not species-dependent, the low incidence of XO females in cattle/ruminants, pigs, dogs, cats, and alpacas might be due to genetic reasons. Indeed, not coincidentally, all species with low numbers of XO individuals have large, over 6 Mb in size, PARs (fig. 3). This implies that the loss of one X chromosome causes haploinsufficiency for a larger genomic segment and involves more genes than, for example, in mouse, human or horse. Though there are no statistics and cytogenetic surveys about spontaneous abortions in domestic animals, we theorize that such genetic losses are not compatible with viability. Therefore, it is anticipated that in species with larger PARs, the incidence of spontaneously aborted XO embryos is higher than the 10% reported for human miscarriages [Menasha et al., 2005].

X-Trisomy

While there seems to be a direct link between embryonic viability and the reduced dosage of PAR genes, only minor phenotypic effects are associated with the PAR overdose. Systematic studies of X chromosome trisomy in humans [Tartaglia et al., 2010] demonstrate that 47,XXX karyotype is the most common female chromosome abnormality affecting 1/1,000 female births. Survival of human fetuses with X-trisomy is about 99%. The phenotype varies considerably, ranging from almost normal fertile females to those having seizures, renal and genitourinary abnormalities, and premature ovarian failure. Because of relatively mild phenotypic effect, only 10% of the cases are ascertained clinically. Typical to almost all XXX individuals is tall stature, contrasting the short stature phenotype associated with the XO syndrome [Bondy and Cheng, 2009; Tartaglia et al., 2010].

In domestic animals, pure trisomy of the X chromosome is not frequent (table 1). In horses, only 11 cases have been reported, and the majority of 65,XXX mares are phenotypically normal but infertile [Chowdhary and Raudsepp, 2000]. Since infertility is usually the primary reason why horses are subjected to karyotyping, it is possible that more 65,XXX mares might be present in the general population, but due to normal fertile phenotype (like XXX humans) have escaped detection [Power, 1990]. Non-mosaic X-chromosome trisomy has also been found in cattle, river buffalo, dog, and alpaca (table 1). In cattle and river buffalo, some animals are fertile [Yadav and Balakrishnan, 1982] or subfertile [Swartz and Vogt, 1983], while others have impaired reproductive physiology and are sterile [Prakash et al., 1994; Moreno-Millan et al., 1987]. The single X-trisomy case found in dogs was associated with gonadal dysgenesis [Johnston et al., 1985]. Because of so few reported cases, no clear correlation between the occurrence of X-trisomy and the size of the PAR in different species could be pointed out. Nevertheless, in the horse, the species with the smallest PAR among animals, almost twice as many XXX reports have been published compared to other domestic species (table 1).

These data for XO and XXX conditions in domestic animals are in line with the cytogenetic analyses carried out between 2001–2011 at the Molecular Cytogenetic Laboratory, Texas A&M University [own unpublished data]. Among 216 female horses with various reproductive problems, 32 mares (15%) had 63,XO and one a 65,XXX karyotype. In contrast, chromosome analysis of over 30 cattle, sheep and goats, 36 pigs, 75 dogs, and 74 alpacas/llamas collectively identified just one 59,XO heifer. The animal was born as a result of embryo transfer and had cytogenetically normal siblings.

Taken together, the available information shows that viable XO individuals are relatively frequently found in species with small PARs, such as horses [Raudsepp and Chowdhary, 2008], humans [Ross et al., 2005] and mice [Perry et al., 2001], but are rare or absent in species where the PAR is substantially larger, as in cattle/ruminants [Van Laere et al., 2008; Das et al., 2009], dogs [Young et al., 2008], pigs, and alpacas [own unpublished data]. No similar correlation can be pointed out between the PAR size and the X chromosome trisomy in different species. This is probably because of a milder genetic effect of the PAR overdose compared to haploinsufficiency, due to which many XXX cases might remain undetected.

Why is embryonic viability more affected by the reduced dosage than the overdose of the PAR? What are the functions of the PAR genes? Are PAR genes critically involved in embryonic development? These are just some of the questions that arise from the above summarized observations. Yet, there are very few answers.

The Functions of the PAR Genes

Despite of extensive search for the molecular basis of sex chromosome aneuploidies, such as XO, XXX and XXY syndromes in humans [Tuttelmann and Gromoll, 2010; Urbach and Benvenisty, 2009] and mice [Lopes et al., 2010], surprisingly little is known about the expres-

Table 1. Summary of the published data about the occurrence of non-mosaic X chromosome monosomy and trisomy in domestic species

Species	XO references	No of XO cases	XXX references	No of XXX cases
Horse	Payne et al., 1968	1	Chandley et al., 1975	1
	Chandley et al., 1975	2	Bowling et al., 1987	5
	Hughes et al., 1975; Hughes and Kennedy, 1975	4	Stewart-Scott, 1988	1
	Taylor and Trommershausen-Smith, 1975	5	Moreno-Millan et al., 1989	1
	Hughes and Trommershausen-Smith, 1977	5	Power and Leadon, 1990	1
	Blue et al., 1978	1	Nie et al., 1993	1
	Bruère et al., 1978	6	Bugno et al., 2003a	1
	Metenier et al., 1979	1	Kakoi et al., 2005	1
	Miyake et al., 1979	3	de Lorenzi et al., 2010	1
	Trommershausen-Smith et al., 1979	12		
	Hughes et al., 1980	21		
	Cribiu and Losfeld, 1982	1		
	Buoen et al., 1983	1		
	Halnan, 1985	1		
	Makinen et al., 1986	1		
	Bowling et al., 1987	56		
	Long, 1988	1		
	Buoen et al., 1993	1		
	Breen et al., 1997	2		
	Makinen et al., 2001	1		
	Bugno et al., 2003b	1		
	Kakoi et al., 2005	13		
	Bugno et al., 2009	1		
	Di Meo et al., 2009	1		
Cattle	Prakash et al., 1995	1	Pinheiro et al., 1987	1
			Herzog et al., 1977	1
			Rieck et al., 1970	1
			Norberg et al., 1976	1
			Buoen et al., 1981	1
			Moreno-Millan et al., 1987	1
Sheep/Goat	Zartman et al., 1981	1	No reports	0
River Buffalo	Yadav et al., 1990	1	Yadav and Balakrishnan, 1982	1
	Prakash et al., 1992	1	Prakash et al., 1994	1
	Iannuzzi et al., 2000b	1	Iannuzzi et al., 2004	1
	Di Meo et al., 2008	2	Di Meo et al., 2008	1
Pig	Nes, 1968	1	No reports	0
	Lojda, 1975	1		
Dog	Lofstedt et al., 1992	1	Goldschmidt et al., 2006	1
	Mayr et al., 1991	1	Johnston et al., 1985	1
	Giger et al., 1989	1	Switonski et al., 2000	1
	Smith et al., 1989	1		
Cat	Johnston et al., 1983	1	No reports	0
Alpaca/ Llama	Hinrichs et al., 1997	1	Tibary et al., 2008	1
	Tibary et al., 2008	1		

sion profiles, the possible functions and genotype-phenotype correlations of PAR genes. For a long time, the human *SHOX* was the only known PAR-linked disease locus responsible for the short stature in XO Turner syndrome [Blaschke and Rappold, 2006; Mangs and Morris, 2007; Bondy and Cheng, 2009] and the tall stature typical for XXX [Tartaglia et al., 2010] and XXY Kleinfelter [Tuttelmann and Gromoll, 2010] syndromes. In addition, a susceptibility locus for bipolar affective disorder was recently discovered in human PAR1 [Flaquer et al., 2010]. These findings, however, do not explain the high rate of lethality of human XO embryos and differential survival of XO individuals in different species.

A breakthrough regarding the possible functions of PAR genes came recently from human stem cell studies showing that the only tissue where genes from human XX and XO embryonic stem cells are differentially expressed is placenta [Urbach and Benvenisty, 2009]. The authors suggest that genes in the PAR, as well as other genes that escape X inactivation, might have an important role in placental development. This explains the high rate of lethality (70–99%) of XO embryos in humans [Bondy and Cheng, 2009; Urbach and Benvenisty, 2009; Berletch et al., 2010]. If certain expression levels of PAR genes are critical in early development, changes in the dosage of these genes, especially haploinsufficiency, will seriously affect the survival of the developing embryo. Consequently, the size and gene content of the PAR might be decisive in determining the viability of embryos carrying sex chromosome aneuploidies in different species. Furthermore, recently discovered association of recombination hot spots with DNA methylation and imprinting [Luedi et al., 2007; Sigurdsson et al., 2009] suggest that PAR genes might be subject to genomic imprinting. Elevated expression of PAR genes in placenta [Urbach and Benvenisty, 2009] might be an evidence for this. Indeed, maternally and paternally imprinted loci were recently discovered in the PAR of pigs [Duthie et al., 2009], supporting the role of PAR genes in early development.

And this is not all. In humans, about 15%, and in mouse, about 3% of X-linked non-PAR genes escape X inactivation [Berletch et al., 2010], thus contributing to the dosage of functional genes in X chromosome aneuploidies. Though the escape genes have not yet been characterized in any of the domestic species, their role in the genetic consequences of sex chromosome aneuploidies cannot be ignored and should be a subject for immediate future studies.

Summary

The current body of knowledge regarding the PAR in domestic species, though limited, provides evidence that differences in the size and gene content of the region might critically implicate embryonic survival and postnatal phenotypes of the carriers of sex chromosome aneuploidies. Genetic causes of these effects are not fully understood, but there are indications that the PAR and other escape genes might be critically involved in placenta formation and genomic imprinting during early development. This implies that the functional significance of the PAR is not limited to sex chromosome segregation in male meiosis, encouraging the launch of systematic expression studies of PAR genes at different stages of development in domestic species.

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