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Monosomy for the X chromosome

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Abstract Dosage compensation serves to equalize X chromosome gene expression in mammalian males and females and involves extensive silencing of the 2nd X chromosome in females. If dosage compensation mechanisms completely suppressed the 2nd X chromosome, then actual physical loss of this "eXtra" chromosome should have few consequences. However, X monosomy has major effects upon normal development, fertility and longevity in humans and some other species. This article reviews observations and arguments attempting to explain the phenotypic effects of X monosomy in humans and other mammals in terms of X chromosome gene dosage.

Keywords Turner syndrome · X-monosomy · dosage compensation · X inactivation · pseudoautosomal gene · epigenetics · chromosomal interaction

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Abbreviations

TS	Turner syndrome
PAR	pseudoautosomal region
HSB	homologous synteny blocks
XM	maternal-derived X chromosome
XP	paternal derived X chromosome

Monosomy X or Turner syndrome (TS)

Loss of a sex chromosome due to non-disjunction during gametogenesis is a relatively common event that contributes to formation of zygotes monosomic for an X- or Y- chromosome as well as zygotes with supernumerary sex chromosomes. Monosomy for the rudimentary, gene-poor human Y chromosome is not compatible with survival, but embryos endowed with a single X chromosome are viable for the early stages of development and a small percent survive to term and into adulthood. Meta-analysis of the chromosomal constitution of >10,000 spontaneous miscarriages found monosomy X (45,X) in ~10% of cases, irrespective of the maternal or gestational age group (Menasha et al. 2005). Most 45,X fetuses apparently succumb to defects in lymphatic and cardiovascular development by mid-gestation (Miyabara et al. 1997). In the absence of Y-derived testis determining gene effects, monosomic embryos develop as phenotypic females. Cytogenetic screening of newborns shows that approximately 1/2500 live-born females is missing all or major parts

of the 2nd sex chromosome (Stochholm et al. 2006). Virtually all girls with complete or partial X monosomy have short stature and untreated, will fall short of their predicted adult height by ~20 cm. Many girls are now treated with growth hormone to increase final height by ~10 cm, although they are not growth hormone deficient (Quigley 2007). Most girls with TS experience depletion of oocytes from their ovaries during fetal development and early childhood. This results in infertility and absence of pubertal development, since without oocytes, the ovary regresses into a "streak" of fibrous tissue unable to produce estrogen. A small percentage of girls retain enough viable oocytes to trigger follicle development and estrogen production associated with spontaneous puberty, and a few go on to achieve natural pregnancy, although most all experience premature ovarian failure by age 30.

About 50% of girls and women with X monosomy have residual cardiovascular disease including hypertension and/or defects of the aortic arch and valve (Sybert and McCauley 2004; Ho et al. 2004) which are the major cause of premature mortality in TS (Matura et al. 2007). When we refer to the X monosomy or Turner phenotype in this article, we mean (a) high rate of fetal demise from defects in lymphatic and cardiovascular development; (b) short stature; (c) ovarian insufficiency; (d) persistent cardiovascular defects leading a high risk for aortic dissection or rupture. This article reviews observations and arguments elucidating the effects of X monosomy in humans in terms of X chromosome gene dosage.

Aneuploidy

Potential pathophysiological explanations for the phenotypic consequences of X monosomy have evolved over the years. In the era dominated by the Lyon hypothesis which saw the 2nd X as totally inert, aneuploidy *per se* was considered a possible cause of many if not all the features of TS (Mendez 1985; Ogata and Matsuo 1995). This view was influenced by observation of apparent similarities between TS and Down syndrome, e.g., neck webbing, congenital heart defects and short stature. On closer examination, however, these similarities are found to be superficial and not really consistent with common developmental defects. The neck webbing and variable distortion of eye lids and ears (Fig. 1) result from fetal lymphedema in both syndromes, but the defect is dilation of blind-ended jugular lymphatics in Down syndrome and generalized subcutaneous lymphedema due to delayed lymphatic development TS (Bekker et al. 2008). Likewise, the specific cardiovascular defects differ in the two syndromes. Venticuloseptal defects, patent ductus arteriosus and tetrology of Fallot are common in Down syndrome but not in TS, which exhibits mainly LV outflow tract abnormalities, e.g., aortic coarctation and aortic valve disease. Moreover, the short stature in TS is more dramatic and associated with specific skeletal anomalies (Ross et al. 2001) not found in Down syndrome. Finally, mental retardation is not a typical feature of TS. Focal neurocognitive characteristics including higher verbal vs. performance skills (non-verbal learning disorder) and selective visuospatial deficits are found in many girls with TS, but overall IQ is normal and educational performance is above average (Ross et al. 2006). An interesting historical note in this connection is that the girl seen in Fig. 1, (who had a 45,X karyotype confirmed many years after the photo) obtained a graduate degree in chemistry and worked as a chemist.

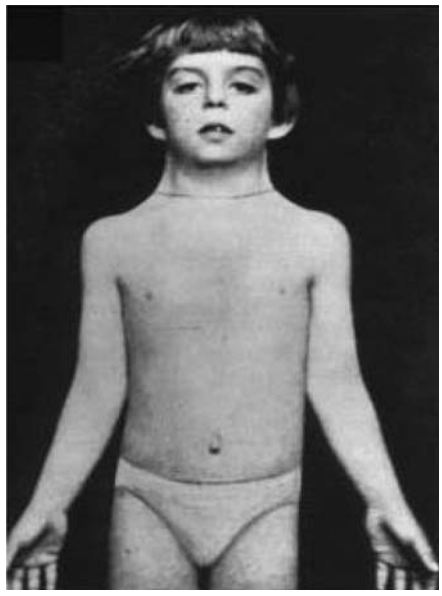

Fig. 1 A girl with classic features of what became known as "Ullrich-Turner", or simply "Turner syndrome" described in 1930 by Otto Ullrich (Ullrich 1930), used with permission. The webbed neck, low set ears, down-sloping features and shield chest are all secondary to fetal lymphedema. These features are found in a minority of girls diagnosed currently

Haploinsufficiency—pseudoautosomal genes

An alternative explanation for the Turner phenotype was based on an astute observation of a Turner-like phenotype associated with cytogenetically demonstrated *Yp* deletions. In a time before any actual gene had been identified and sequenced, Ferguson-Smith suggested that that monosomy for a gene or genes situated on the short arm of the X and Y chromosomes could cause the TS phenotype (Ferguson-Smith 1965). In the nearly half century since that initial haplo-insufficiency hypothesis, only one sex chromosome gene has been clearly implicated in the monosomy phenotype.

We now know that mammalian X- and Y-chromosome share so-called "pseudo-autosomal" regions containing homologous genes that engage in autosomal-like recombination. The human has two such loci located at the terminals of short (PAR1, ~2.6 Mb) and long (PAR2, ~320 kb) arms of both sex chromosomes, while most other species have only the PAR1. Since there has been dramatic attrition of most Y-chromosome coding regions over the course of evolution, a conserved region that promotes X-Y pairing and recombination is essential for male meiosis. This role is served by PAR1, which as a result has the highest recombination rate of any region in the human genome (Flaquer et al. 2008). The human PAR1 is not yet completely sequenced, but 24 genes have been annotated in this region (Ross et al. 2005).

PAR1 genes encode proteins implicated in transcriptional regulation (*ZBED* and *SHOX)*, RNA splicing (XE7), signal transduction, (*PPP2R3B* and *IL3RA)*, cell adhesion (*CD99)* and mitochondrial function (*SLC25A6*). These genes are expressed from both X chromosomes in females, and from X and Y chromosomes in males, suggesting that PAR1 gene dosage effects could be involved in phenotypic aspects of numerical sex chromosome anomalies (Zinn and Ross 1998). Elucidation of the developmental and physiological functions and disease associations of PAR1 genes has been hindered because this region is a blind spot in genetic linkage and association studies and because Xp deletions usually cause infertility or lethality in males. *SHOX* (short stature homeobox) is the only PAR1 gene with an established role in normal development. Microdeletions and mutations in *SHOX* have been convincingly associated with short stature and skeletal defects similar to the phenotype in girls with TS (Rao et al. 1997; Blaschke and Rappold 2000).

PAR1 was apparently added to ancient sex chromosomes about the time of divergence between mammals and marsupials, and has undergone selective attrition in rats and mice (Fig. 2). Perhaps as a result, X monosomy has relatively little effect in the mouse, which grows and develops normally and is fertile, without major congenital defects (Probst et al. 2008). There is however, a distinct neurocognitive phenotype in XO mice (Davies et al. 2007). In contrast, PAR1 is conserved and highly homologous in the human, dog and cat (Fig. 2 and Table 1). Probably not coincidentally, X monosomy in these animals is characterized by dwarfism, infertility and congenital defects similar to the human (Omoe and Endo 1996; Buoen et al. 1993). These observations suggest that major aspects of the Turner phenotype are due to haploinsufficiency for PAR1 genes not represented on the murine X chromosome. The PAR1 gene list in Table 1 includes only those well-known genes that have also been mapped in the dog; there are in addition at least 10 novel human PAR1 genes with completely unknown functions (Ross et al. 2005).

The second pseudoautosomal segment at X28 seems to be unique to humans and includes only a few genes: *SYBL1*encodes a synaptobrevin-like protein, *SPRY3* is a homolog of the Drosophila *sprouty, IL9R* encodes an interleukin 9 receptor, and *WASH6P* is a WAS protein family homolog 6 pseudogene. The first two genes appear to be silenced on both the inactive X and the Y chromosomes, while *IL9R* and *WASH6P* seem to escape X-inactivation and to be expressed from the Y-chromosome as well. However,

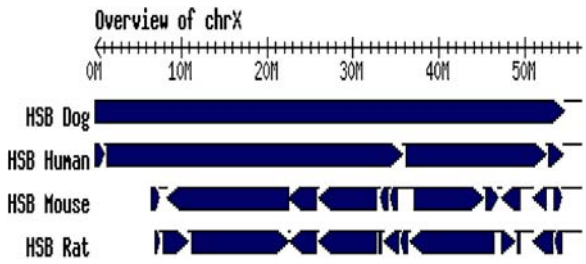

Fig. 2 X-Chromosome Homologous Synteny Blocks (HSB). The reference sequence is the *Felis catus* chrX (V12.2); 0–50 Mb. Downloaded April 2009 http://lgd.abcc.ncifcrf.gov/cgi-bin/gbrowse/cat/?name=chrX

Table 1 Xpter genes

Human	Mb Xpter	Dog
PLCXD1	**0.14**	*PLCXD1*
GTPBP6		*GTPBP6*
PPP2R3B		*PPP2R3B*
SHOX		*SHOX*
CRLF2		*CRLF2*
CSF2RA		*CSF2RA*
IL3RA		*IL3RA*
SLC25A6		*SLC25A6*
ASMTL		*ASMTL*
ASMT		*ASMT*
DHRSXY		*DHRSXY*
ZBED1		*ZBED1*
CD99		*CD99*
XG		*XG*
GYG2		*GYG2*
ARSD		*ARSD*
ARSE		*ARSE*
ARSH		*ARSH*
ARSF		*ARSF*
MXRA5		*MXRA5*
PRKX		*PRKX*
STS		*STS*
SHROOM2		*SHROOM2*
MID1	**10.45**	*MID1*

Data from UCSC Genome browser. Shaded areas show PAR extent.

the major phenotypic effects of X-monosomy are associated with haploinsufficiency for Xp, with no apparent defects found in females with terminal Xq terminal deletions encompassing PAR2 (Therman and Susman 1990).

Haploinsufficiency—pseudo-pseudoautosomal genes

We herein define "pseudo-pseudoautosomal" genes as sex chromosome genes with annotated X and Y homologs located outside PAR1 and PAR2. Theoretically, if biallelic expression of any of these X and Y homologous genes is necessary for normal development, then haploinsufficiency could contribute to the X monosomy phenotype. There are at least 26 such genes (Ross et al. 2005), but relevant information is available for less than half of them . Several pseudo-pseudoautosomal genes are subject to X-inactivation. *AMELX* encodes amelogenin, an extracellular matrix protein involved in tooth enamel development. Mutation of *AMELX* leads to amelogenesis imperfecta with a full phenotype in males and a mosaic phenotype in female "carriers" (i.e., striped or ridged dental enamel), consistent with random X-inactivation. Girls with TS have normal dental enamel, suggesting that expression of a single normal X allele is adequate for tooth development. The Y-homolog, *AMELY* (Yp11.2) is highly conserved and encodes an expressed amelogenin protein, which is apparently unimportant. *TGIFX2, PCDH11X and TMSB4X* and their expressed Y-homologs, are located in the Xq21.2/Yp11.2 homology block but are not known to escape X-inactivation. All three are situated on the X chromosome long arm (Xq21.3), while the Turner phenotype is commonly seen in girls with a major Xp deletion despite retaining Xq, and in girls with an isoXq chromosome, which consists of two long arms fused together with total deletion of the short arm. Finally, all three genes have murine X-linked orthologs, and given the lack of a somatic phenotype in the mouse, it seems unlikely that haploinsufficiency these genes contribute to the Turner phenotype in humans.

Other pseudo-pseudoautosomal genes appear to escape X-inactivation. *RPS4X&Y* encode functionally equivalent ribosomal components. The X-allele at Xq13.1 escapes inactivation and the Y-allele is expressed, suggesting that haploinsufficiency could

cause the Turner phenotype (Watanabe et al. 1993). However, individuals with an isoXq chromosome have a full Turner phenotype and abundant RPS4 (Geerkens et al. 1996). Moreover, species such as the dog and cat express a Turner-like XO phenotype but do not have a Y chromosome *RPS4* allele (Omoe and Endo 1996). *PRKX* and *TBLI1X* are situated on Xp and escape X-inactivation, but both have murine X-linked orthologs. Moreover, deletions of the human Y-alleles are relatively common and stably transmitted without an obvious phenotype (Jobling et al. 2007). *ZFX* encodes a zinc finger transcription factor recently implicated in stem cell renewal (Galan-Caridad et al. 2007). *ZFX* escapes X inactivation, and dosage compensation is apparently achieved by *ZFY* expression (Johnston et al. 2008). In mice, *zfx* deletion is associated with germ cell depletion (Luoh et al. 1997), although *zfx* is subject to X-inactivation. *EIF1AX* encodes an essential translation initiation factor that escapes X-inactivation and has a highly expressed Y homolog (Johnston et al. 2008), which seems consistent with an important role in human development. Mice have only an X-encoded *eif1a* gene.

Several additional pseudo-pseudoautosomal genes have interesting functional roles and complex expression patterns not inconsistent with a role in TS. *UTX* and *JARID1C* are histone demethylases likely involved in embryonic development by remodeling chromatin (Agger et al. 2007). Both Xp genes escape X inactivation and have expressed Y-homologs that appear to achieve dosage compensation, at least in lymphoblast cell lines (Johnston et al. 2008). Mutations in *JARID1C* are associated with X-linked mental retardation, indicating that the Y-linked *JARID1D* is not sufficient for normal brain development (Abidi et al. 2008). The murine *jarid1* and *utx* genes demonstrate sex-specific expression in brain, with higher expression of the X-linked alleles in females and under-expression of Y alleles (Xu et al. 2008). Thus it has been proposed that sexually dimorphic neurocognitive function and behaviors may be related to differential expression of these genes and their effects on chromatin conformation and gene expression during brain development (Xu et al. 2008). The *USP9X* encodes a deubiquitinase recently identified as an essential component in TGFbeta signaling (Dupont et al. 2009). *USP9X* escapes X-inactivation and *USP9Y* expression equals that of *USP9X* in lymphoblast cell lines from males (Johnston et al. 2008). *USP9Y* is located in a region of the Y chromosome implicated in azoospermia (AZFa, Yq11) but recent data indicate that an adjacent pseudo-pseudoautosomal gene, *DDX3Y,* is to blame (Tyler-Smith and Krausz 2009). *DDX3X* and *DDX3Y* encode RNA helicases with 92% sequence homology and appear functionally interchangeable (Sekiguchi et al. 2004). Similar to *USP9X&Y*, expression from the Y-allele appears to compensate for expression from both X chromosomes in humans (Johnston et al. 2008). Deletion of *DDX3Y* is associated with azoospermia in humans but not mice (Tyler-Smith and Krausz 2009).

Escape from X-inactivation

Experimental studies consistently show that, in contrast to the mouse, a significant portion of human genes escape X-inactivation (Brown and Greally 2003). About 15% of known transcripts are expressed from the inactive human X-chromosome in rodent-human hybrid cell lines, although at relatively low levels (Carrel and Willard 2005). Diverse array platforms also typically show higher X transcript levels in samples with multiple X chromosomes. Table 2 summarizes results from seven recent systematic studies of this issue, highlighting "consensus" escape genes. Interestingly, female vs. male gene expression profiles on whole genome arrays consistently report that X chromosome genes dominate the differentially expressed list (Johnston et al. 2008; Craig et al. 2004; Tan et al. 2008). The higher level expression of X-linked genes attributed to expression of 'escaping' X genes is in the range of 10–80% (Johnston et al. 2008).

Three fourths of the X chromosomes genes reported to escape silencing are located on Xp (<60 Mb from pter in Table 2), consistent with the short arm's more recent autosomal origin (Ross et al. 2005). Somewhat unexpectedly, only 20% of escape genes have known Y-homologues (in bold in Table 2). Haploinsufficiency for X-specific genes could, as a matter of speculation, contribute to differences between female and male development and physiology (e.g., immunological and behavioral characteristics), and to subtle aspects of the Turner phenotype. *Sts*, encoding steroid sulfatase, is an X-linked gene implicated in the

Table 2 Human genes escaping X-inactivation

X-GENE	Mb	1	2	3	4	5	6	7
ARSD	2.8	√		9 / 9				
PRKX	3.5			7 / 9		√	√	√
HDHD1A	7.0	√		8 / 9	√	√	√	√
STS	7.1	√		9 / 9		√	√	√
PNPLA4	7.8			9 / 9	√		√	
TBL1X	9.4		√	7 / 9				
CLCN4	10.0		√	5 / 9				
MSL3	11.7	√		3 / 9		√	√	
TRAPPC2	13.6	√	√	9 / 9				√
GPM6B	13.7	√		8 / 9				
CA5BL	15.6			9 / 9		√		
CA5B	15.7			9 / 9			√	
ZRSR2	15.7		√				√	√
AP1S2	15.8			9 / 9	√			
RBBP7	16.8			9 / 9		√		
PHKA2	18.8	√		2 / 9				
EIF1AX	20.1			9 / 9		√	√	√
ACOT9	23.6	√		2 / 9				
EIF2S3	24.0		√	9 / 9		√	√	
ZFX	24.1		√	9 / 9	√	√	√	
USP9X	40.8	√		9 / 9		√	√	√
DDX3	41.1	√	√	9 / 9		√	√	√
FUNDC1	44.3			8 / 9			√	
UTX	44.6	√	√	9 / 9	√	√	√	√
UBE1	46.9			9 / 9		√	√	√
PCTK1	47.0			7 / 7			√	
GATA1	48.5	√		1 / 9				
SYP	48.9		√	2 / 9				
JARID1C	53.2	√		9 / 9		√	√	√
SMC1A	53.4		√	7 / 9			√	√
SMC1L1	53.4	√		7 / 9				
ERCC6L	71.3		√	2 / 9				
RPS4X	71.4	√		9 / 9	√	√	√	√
ATP7A	77.1	√		4 / 9				
ITM2A	78.5	√		5 / 9				
ARMCX2	100.8	√	√	1 / 9				
TCEAL2	101.3		√	0 / 9		√		
TCEAL4	102.7		√	2 / 9				
PAK3	110.2	√		2 / 9				
ALG13	110.8			5 / 9			√	

◀ Human X chromosome genes thought to escape X inactivation based on evidence from at least two publications. Pseudoautosomal genes and *XIST* are excluded. Genes with Y-chromosome homologs are in bold text. The grey shading indicates genes that were over-expressed in over half these studies. All of the studies (1–7 described briefly below), listed in order of publication, employed a systematic approach to address this issue.

(1) Sudbrak et al. used custom X chromosome cDNA arrays compared gene expression in lymphoblastoid cell lines with 4–5 X's vs. 46XX and 46XY lines with 5 samples per group (Sudbrak et al. 2001).

(2) Craig et al. used Affymetrix HG133A arrays to compare fresh lymphocyte gene expression profiles from 6 male and 6 female subjects (Craig et al. 2004).

(3) Carrel and Willard used rodent-human hybrid fibroblast cell lines and RT-PCR to assay gene expression from human Xi. Results in this table are expressed as number of cell lines positive for transcript expression over number assayed (Carrel & Willard 2005).

(4) Talebizadeh et al. analyzed female/male gene expression ratio for 299 X-linked and 7795 autosomal genes from 11 different tissues using *in vivo* cDNA microarray database (Talebizadeh et al. 2006).

(5) Tan et al. compared male vs. female gene expression in lymphoblastoid cell lines from the CEPH population analyzed by Affymetrix Focus Arrays (~8500 genes in total and 397 X-linked genes represented). Among young subjects (57 males and 53 females) they found a total of 101 genes were differentially expressed, with the genes on top of the lists dominated by X-linked genes (Tan et al. 2008).

(6) McCrea et al used Affymetrix U133+2 arrays to compare gene expression profiles in lymphoblastoid cell lines from monozygotic twin pairs (10 male, 9 female). The effect of sex on gene expression levels was most noticeable on the X chromosome, which contained 15 of the 20 significantly differentially expressed genes (McRae et al. 2007).

(7) Johnston et al. analyzed male vs. female results from Illumina humanWG-6 v3.0 BeadChips repository data for lymphoblastoid cell lines from Utah, Han Chinese, Japanese and Nigerian HapMap populations (Johnston et al. 2008)

murine XO neurological phenotype (Davies et al. 2007). This gene is pseudoautosomal in mice, but has no Y-chromosome version in the human (Ross et al. 2005). Nevertheless, *STS* clearly escapes X-inactivation (Table 2) and is located at Xp22.31, a region implicated in the human neurological phenotype including visuospatial and attention deficits (Zinn et al. 2007).

Genomic imprinting effects

If certain X-chromosome genes were silenced by genomic imprinting, then the phenotypic effects of X monosomy may be influenced by parent of origin effects. The first study to suggest this possibility reported that girls monosomic for a maternal X-chromosome showed deficient social skills and lesser verbal scores compared to girls monosomic for a paternal X (Skuse et al. 1997), consistent with the authors' view that the maternal X preferentially promotes autistic spectrum tendencies, which are more common in boys. Since social and verbal skills are determined by so many different factors and the brain is the least accessible and most complex of tissues, it has been difficult to pursue this issue. More discrete aspects of the TS phenotype have been more tractable to analysis of potential imprinting effects. Under normal conditions, 46XY males are monosomic for XM, while 46,XX females are mosaic for XM and XP, with approximately 50% of cells expressing an active XM and 50% an active XP. Thus maternal imprinting (silencing) of an X-linked gene would virtually eliminate its expression in males while allowing expression in ~50% of female cells. Conversely, paternal imprinting would result in full expression in males but only ~50% of cells in females. Therefore, genomic imprinting of X-linked gene(s) is expected to affect sexually dimorphic characteristics. Verbal and social skills are generally better in females, consistent with imprinting of unknown genes affecting neurocognitive development, as suggested by Skuse and colleagues (Skuse et al. 1997). Somatic size and fat distribution are also sexually dimorphic, with men being taller on average and tending toward accumulation of abdominal fat while women are smaller and accumulate fat preferentially in the hips and extremities. Height is not significantly different in XM vs XP groups, but it appears that girls monosomic for XM may grow better in response to growth hormone treatment (Hamelin et al. 2006). Women monosomic for XM demonstrate selective accumulation of abdominal fat in a typical android pattern, while women monosomic for XP have a marked gynoid body habitus (Van et al. 2006). Non-sexually dimorphic aspects of development such as the cardiovascular and renal systems do not seem to be impacted by X-imprinting (Bondy et al. 2007).

An interesting and well-confirmed observation is that height in girls with TS is predicted by the maternal but not paternal height (Fig. 3), regardless of which parental X chromosome the individual carries (Hamelin et al. 2006; Bondy et al. 2007; Salerno and

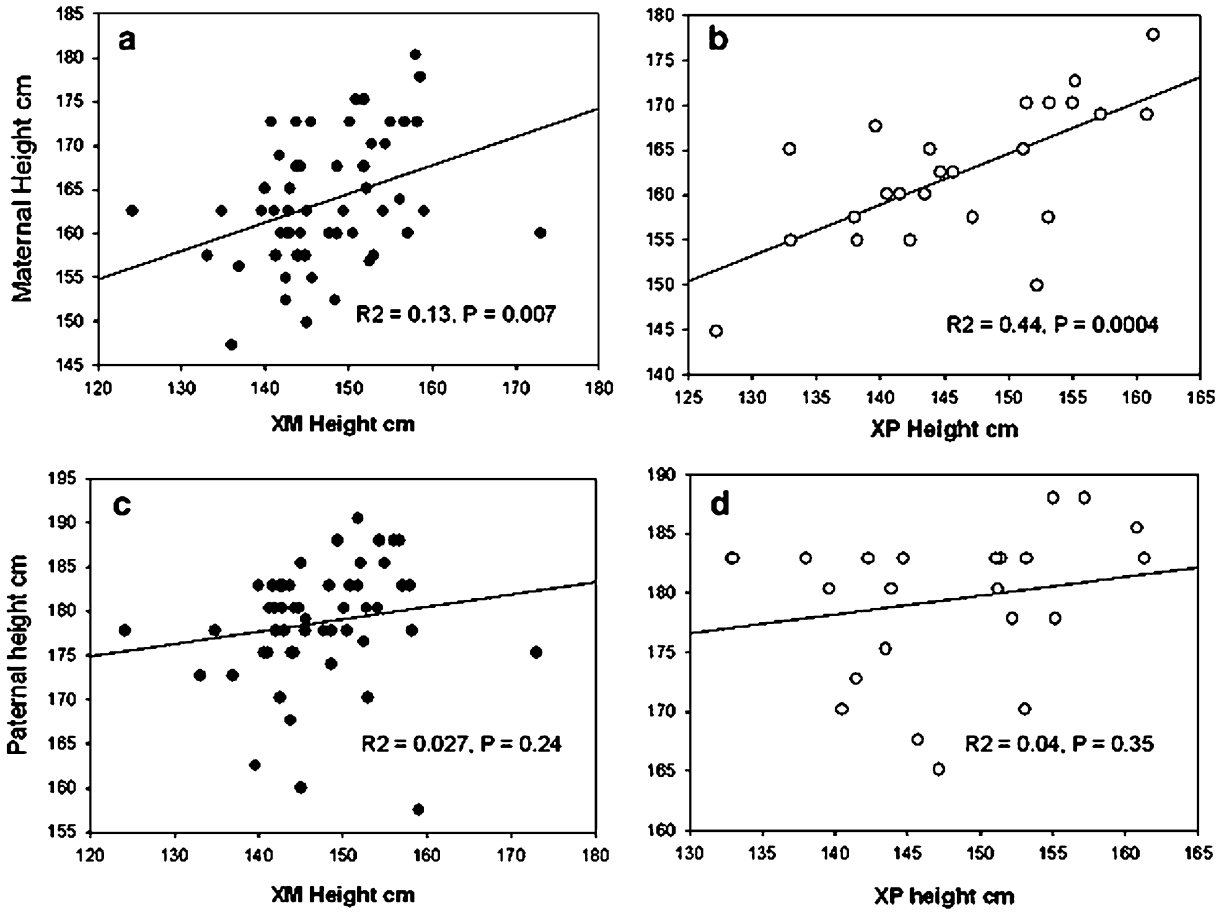

Fig. 3 Adult height correlates with maternal height for individuals monosomic for XM (**a**) and XP (**b**), but not with paternal height (c & d). X^M subjects (*solid symbols*) X^P subjects (*open symbols*). Adapted from Bondy et al. 2007

Job 1987; Chu et al. 1994; Kochi et al. 2007). One interpretation `of this finding is that X monosomy somehow alters the balance of autosomal imprints influencing stature (Bondy et al. 2007).

The X stands alone

We emphasized in this review the strong likelihood that haploinsufficiency for unknown PAR1 genes (in addition to *SHOX*) shared by human, canine, feline but not murine species contributes to the X monosomy phenotype, typified by major defects in lymphatic-cardiovascular development. In light of current evidence, we also think that haploinsufficiency for "pseudo-pseudoautosomal" gene(s) such as *JARIDC, UTX, USP9X, EIF1AX, DDX3* and *ZFX* must be considered as potential contributors to sexually dimorphic aspects of brain and germ cell development that are revealed in X-monosomy by neurocognitive deficits and infertility. But finally, we cannot exclude the possibility that the physical fact of monosomy affects development. We have reviewed the limited evidence that parental origin of the single X chromosome produces a distinct phenotype due to genomic imprinting of unknown maternal or paternal alleles. This possibility has interesting and important implications for understanding differences in normal male and female behavior patterns, body composition and risk for certain chronic diseases, although current evidence for this phenomenon is quite limited. However, the evidence that X monosomy *per se*

influences the parental contribution to growth potential is very strong (Fig. 3 and references noted about) and does not seem to be explained by haploinsufficiency for specific X-linked gene effects.

Our view of a Lyonized, inactive X chromosome has changed dramatically in recent years. We now see that the heterochromatic Barr body consists mainly of non-coding, highly repetitive DNA, with loops of coding sequence located externally (Chaumeil et al. 2006; Clemson et al. 2006) allowing "escaping" X-linked genes access to transcription machinery. Moreover, we have an expanded view of chromosomal domains and interactions, including a physical interaction between X chromosomes during the process of X-inactivation (Bacher et al. 2006; Xu et al. 2006). It seems possible that sex chromosome monosomy upsets the nuclear architecture potentially disrupting normal chromosomal interactions. Finally, we have recently learned that transcription from the active X is selectively up-regulated to equal the average output from a pair of autosomes (Nguyen and Disteche 2006). There is little knowledge of how this selective up regulation of active X gene expression is achieved, but one possibility is that ncRNAs produced from the 2nd sex chromosome are involved. If so, regulation of the single X chromosome may be altered in X-monosomic cells. This does not seem to be a major factor in mice, but the organization of the sex chromosomes, and mechanisms of X-inactivation and regulation of X-linked gene expression are significantly different in mice (Yen et al. 2007). Further investigation of these differences will be important in understanding the unique aspects of X chromosome functions in different species.

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