

Genomic imprinting in Turner syndrome

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Abstract. The selective silencing of certain alleles depending on the parent of origin is known as genomic imprinting. Specific cognitive skills, statural growth and visceral adiposity have all been linked to the parental origin of the single normal X-chromosome in girls and women with Turner syndrome (TS). The putatively imprinted traits in TS reflect typical differences between eukaryotic males and females. This chapter reviews the evidence for parental X-chromosome imprinting in the TS phenotype. Published by Elsevier B.V.

Keywords: Parent of origin effect; Parental imprinting; Gender-specific; Atherosclerosis

1. Genomic imprinting and the X-chromosome

The terms parental, gametic and genomic imprinting refer to the epigenetic marking of specific genes or chromosome regions in the maternal or paternal germline, so as to inhibit expression of the locus when transmitted from that parent [1]. The epigenetic molecular marks include DNA methylation and histone modifications, which are reset during the next generation's gametogenesis. Disorders of imprinting affecting autosomal loci, such as Angelman syndrome, are well known [2]. The processes of X-inactivation and genomic imprinting are very similar mechanistically and may have evolved together [1,3]. Little is known, however, about possible parental imprinting of X-linked genes in humans. X-chromosome based imprinting effects are expected to demonstrate a complex, gender-specific phenotype since males express only a maternally-inherited X (X^M) in all cells, while females express both X^M and X^P . The process of random X-inactivation in females means that most tissues are composed of ~50% X^M active and 50% X^P active cells,

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Table 1
TS traits and parent of origin effects

Trait	Chromosomal association	Reference
Social cognition	Impaired in X ^M	Skuse et al. [6]
Verbal skills	Impaired in X ^P	Loesh et al. [7]
Visceral adiposity	Increased in X ^M	Van et al. [8]
Sensory hearing	Impaired in X ^P	Hamelin et al. [9]
Growth potential	Increased in X ^M	Chu et al. [5]; Hamelin et al. [9]

although skewed inactivation may occur in some tissues or when one X-chromosome is abnormal.

The study of girls and women with monosomy X, or Turner syndrome (45,X, TS) allows us to investigate potential parental imprinting of X-chromosome loci, since 45,X individuals are monosomic for X^M or X^P, and of course the single normal X is never inactivated. These studies have been difficult, because, among other reasons, of small numbers of X^P subjects. For these genotyping studies non-mosaic 45,X patients have been preferred, eliminating about 50% of available individuals. This pool is further reduced by availability of parental DNA. Finally, among 45,X individuals, only approximately one third have X^P [4,5], and the small size of the X^P group has been a critical limiting factor in most studies. The apparent reason for the 2:1 distribution of X^M:X^P genotypes is that mothers have two X-chromosomes to contribute to monosomic offspring, while fathers have only one (Y-monosomy is non-viable). Despite these limitations, several studies have found a selective association of various traits with either X^M or X^P in TS (Table 1).

2. X-imprinting and cognition

Because of the male predominance in psychiatric disorders involving defective social skills (autism, autism spectrum, attention deficit disorder and Asperger syndrome), Skuse et al. hypothesized that a gene or genes encoding factors promoting social cognition may be selectively expressed from the X^P. Supporting this view, an initial study found that parental reports of social skills were more positive for X^P vs. X^M girls [6]. The same study reported that verbal skills were better in X^P girls. These findings have not been replicated by other groups, however, and a larger, statistically more sophisticated study found better verbal skills in X^M TS females [7]. Brain imaging studies using diverse methodologies on small study groups with heterogeneous clinical backgrounds (e.g., age, socioeconomic status, variable estrogen, androgen and growth hormone exposure) have yielded variable findings on imprinting effect on brain structures [10–13]. In addition to small sample size, these studies have statistical issues with numerous endpoints, usually without adjustment for multiple comparisons, so inconsistent results are not unexpected. However, the risk of autism is reportedly 4-fold higher among girls with TS and all affected girls have had X^M, although the estimate is based on just 4 patients [6,14]. A very recent study found a significant increase in attention deficit hyperactivity disorder in TS, but did not find a parent of X-chromosome origin effect for this diagnosis [15]. It is doubtful, however, that the study was sufficiently powered to exclude such an effect. In fact, 7/20 girls with X^M and 1/7 with X^P had the ADHD diagnosis.

3. X-imprinting and statural growth

Height as an objective and quantifiable variable may provide a more robust endpoint for the study of X-imprinting effects than less well-defined aspects of social cognition or brain structure. Indeed, two independent studies have documented a relation between X^M and height in girls with TS [5,9]. Both studies showed that height in X^M girls was highly correlated with maternal but not paternal height, and the more recent study also showed that height increase in response to growth hormone treatment was significantly greater in X^M vs. X^P girls [9]. These findings are consistent with imprinting, or silencing of an X-linked gene that enhances growth potential when passed through the paternal germline, and may partially explain the typical taller stature in males (100% X^M) vs. females (only 50% X^M expression). This is an interesting possibility in view of the growth-associated phenotype of many parentally imprinted genes [1]. However, in autosomal imprinting, the growth phenotype is associated with paternal gene expression, while maternally expressed genes are involved in growth inhibition. Hamelin et al. suggest that the parental origin of the intact X-chromosome accounts for about 50% of the GH response in X^M girls, and thus should be considered a clinically significant factor in planning GH treatment [9].

4. X-imprinting and coronary artery disease

Compared to women, men have ~2-fold increased risk for death from coronary artery disease at all ages. Men typically have greater visceral fat and more atherogenic plasma lipids than women [16], contributing to their increased risk for ischemic heart disease. Traditionally, women's better metabolic profile and relative protection from coronary disease has been attributed to beneficial effects of estrogen, but this view has lost much support in recent years. Coronary disease is increased among women with TS [17], a finding which used to be attributed to the ovarian failure experienced by most women with the syndrome. To investigate the contribution of ovarian failure vs. X-chromosome monosomy to coronary risk factors in TS, we compared plasma lipids in young healthy women with TS and age- and BMI-matched women with karyotypically normal (46,XX) premature ovarian failure [18,19]. Both groups were normally on estrogen treatment but discontinued for the 2 weeks prior to study. Women with TS as a group had a more atherogenic lipid profile, with significantly higher LDL-cholesterol and triglycerides [18] and smaller lipid particle size [19] compared to the premature ovarian failure controls. These data suggest that X-monosomy confers an adverse effect upon lipid metabolism, apart from any effect of ovarian hormones.

We then hypothesized that possession of a X^M chromosome promotes visceral adiposity and atherogenic lipid profile typically seen in normal, X^M men. To test this hypothesis, we compared these features in X^M vs. X^P women with TS [8]. Age and BMI were similar in X^M and X^P groups (Table 2). However, triglyceride levels were 30% higher and LDL-cholesterol 20% higher ($P=0.001$) in X^M vs. X^P women.

Since excess visceral fat promotes an atherogenic lipid profile, we compared fat distribution in X^M vs. X^P groups (Table 2). The percentage of *total* body mass composed of fat determined by DXA was similar in the two groups. Total abdominal fat measured by CT was increased by 34% in X^M vs. X^P , and visceral fat was remarkably increased by 71% in the X^M group ($P=0.0005$).

Table 2
X-chromosome parental origin and metabolic profile

	X^M (N=62)	X^P (N=27)	P
Age (years)/S.D.	30.7/11	26.7/12	0.1
Body mass index (BMI; kg/m ²)/S.D.	27.6/7.5	25.2/ 6.2	0.2
Triglycerides (mg/dl)/S.D.	131/62	100/50	0.02
LDL-cholesterol (mg/dl)/S.D.	137/41	113/44	0.005
HDL-cholesterol (mg/dl)/S.D.	58/13	61/17	0.345
	N=40	N=16	
Total body fat by DXA (%)/S.D.	37.1/7.6	36.3/8.1	0.550
Total abdominal fat (ml)/S.D.	78.3/49.0	57.7/36.0	0.010
Visceral abdominal fat (ml)/S.D.	24.8/19.4	13.9/8.0	0.0005

The data are means/S.D. Group means were compared by one-way ANOVA/ANCOVA followed by Fisher's Protected Least Significant Difference test. Age and BMI were used as covariates in comparing metabolic measures. Only adults were eligible for CT measurement of fat. Adapted from Van et al. [8].

Thus, monosomy for a maternal X-chromosome is associated with greater visceral fat accumulation and a more atherogenic lipid profile than monosomy for X^P . The metabolic differences between X^P and X^M women are similar to metabolic differences between normal women and men, who are also monosomic for X^M . Men typically have about two-fold greater visceral fat than women, which contributes to their more atherogenic lipid profile and ischemic heart disease risk. This visceral adiposity is not due to testosterone, since male hypogonadism is actually associated with increased visceral fat, which is reduced with testosterone replacement. Both TS groups (X^P and X^M) had ovarian failure and thus differences due to sex steroids are not likely contributors to these metabolic findings. Taken together the observations in women with TS vs. age- and BMI-matched women with 46,XX premature ovarian failure, and the observations on differences between TS women with X^P vs. X^M support the view that monosomy for X^M predisposes to selective accumulation of visceral fat and dyslipidemia, independent of sex steroid effects. This could be explained by the imprinting or silencing of maternally transmitted X-linked gene(s) that prevent visceral fat accumulation or of paternally genes that promote visceral fat accumulation and dyslipidemia. These findings if confirmed would suggest that women with monosomy for X^M have an increased risk for dyslipidemia and coronary artery disease than women monosomic for X^P and 46,XX women, but similar to that of 46,XY males.

5. Summary

This brief review has touched on diverse phenotypic features of TS that seem to be influenced by parent of origin effects for the single normal, or intact X-chromosome. There are three major areas where X-imprinting effects seem to be found:

- cognitive function, particularly aspects of social cognition
- statural growth
- visceral adiposity and lipid metabolism

Interestingly, these three areas are all associated with typical male–female differences. For example, social cognition, or sensitivity to body language and other social cues, is generally enhanced in females compared with males, and susceptibility to disorders affecting social cognition, such as autism or ADHD, is clearly increased in males. Statural growth is typically greater in males, and visceral adiposity, atherogenic lipids and risk for coronary artery disease are all greater on average in males vs. females. Thus evidence from the study of X-chromosome imprinting in TS may provide insight into differences in normal physiology and pathophysiology between the sexes. While these are interesting observations that are potentially of considerable biological and medical importance, they are at present rather preliminary and require independent confirmation as well as further work to define the genetic and epigenetic mechanisms.

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