RESEARCH LETTERS

Maternal X Chromosome, Visceral Adiposity, and Lipid Profile

To the Editor: Men typically have more visceral fat and atherogenic plasma lipids than women,[1] contributing to an increased risk of ischemic heart disease. This pattern has been attributed to sex steroids, but other factors may be important. A disparity in X chromosome gene expression may influence sex-specific differences in lipid metabolism and coronary artery disease.[2]

Genomic imprinting involves the selective expression of certain genes determined by their parental origin, often associated with DNA methylation of imprinted, or silenced, alleles.[3] Genomic imprinting of X-linked genes could result in different gene expression in males and females, since females are normally mosaic for maternally and paternally inherited active X chromosomes (X^M and X^P), while men are monosomic for X^M. Genes imprinted (silenced) on X^M would still be expressed in females from cells in which the X^P is active, but not expressed at all in males. Evidence for the imprinting of genes involved in brain development has been found in monosomy X, or Turner syndrome.[4]

To determine whether imprinting of X-linked genes is associated with lipid homeostasis, we compared plasma lipids and regional fat distribution in women with Turner syndrome based on their X^M vs X^P status.

Methods. Patients with Turner syndrome were recruited on the National Institutes of Health (NIH) Web site and by newspaper notices between January 2002 and August 2005. The study was institutional review board–approved and participants provided written informed consent. All patients had 50-lymphocyte karyotyping performed. Inclusion criteria were age 14 years or older and karyotype either 45,X or 46,X,del(Xp). Patients with mosaic cell lines had to have at least 70% 45,X cells. Of the 130 potential participants, 41 could not provide parental samples and were not analyzed. They were significantly older than the 89 studied patients, with mean lipid levels similar to those of the combined X^M and X^P groups. All patients were self-identified as white.

The karyotype distribution in the study population was 45,X (63%); 46,X,del(Xp) or 45,X/46,X,del(Xp) (3.3%); 45,X/46,X,i(Xq) (12%); 45,X/46,X,r(X) (6.6%) and 45,X/46,XX (15%). The parental origin of the single normal X was determined using 7 or more highly polymorphic microsatellite markers distributed along the X chromosome.[5] Hormone therapy was being used by 75% of the patients in the X^P group and 89% in the X^M group but was discontinued 2 weeks before testing. Fasting glucose, insulin, and lipid levels were measured according to NIH standards.[6] Whole-body fat composition was measured by dual-energy x-ray absorptiometry (Hologic QDR-4500A, Bedford, Mass). Because excess visceral fat promotes an atherogenic lipid profile, women aged 18 years or older (n=56) underwent computed tomography to measure total abdominal adipose tissue and visceral adipose tissue in an L2/L3 abdominal transverse section.

Group means were compared by 1-way analysis of variance/analysis of covariance, followed by Fisher protected least-significant-difference tests; age and body mass index were covariates in metabolic and body fat comparisons. The sample size resulted in a power of at least 80% to detect a difference of 25 mg/dL (0.65 mmol/L) in low-density lipoprotein cholesterol and 10 mL in visceral fat, using a 1-sided α level of .05. For lipid and fat comparisons, 1-sided *P* values were calculated; for all other comparisons, 2-sided *P* values were calculated. $P<.05$ was considered statistically significant. Analyses were performed using Stat View software, version 5.0.1 (SAS Institute Inc, Cary, NC).

Results. Age, body mass index, and fasting glucose and fasting insulin levels were similar in the X^M and X^P groups (TABLE). Triglyceride levels were 31% higher ($P=.02$) and low-density lipoprotein cholesterol was 21% higher ($P=.005$) in X^M women compared with X^P women. High-density lipoprotein cholesterol levels were similar in the 2 groups.

Among women aged 18 years or older, the percentage of total body mass composed of fat as determined by dual-energy x-ray absorptiometry was similar in the X^M and X^P groups (Table). However, total abdominal fat as measured by computed tomography was increased by 36% in the X^M group compared with the X^P group ($P=.01$), and visceral fat was increased by 78% in the X^M group compared with the X^P group ($P<.001$).

Comment. In this study, monosomy for an X^M chromosome was associated with greater visceral fat accumulation and a more atherogenic lipid profile than monosomy for X^P. The differences between X^P and X^M women parallel the usual metabolic and adiposity differences between women and men, who are also monosomic for X^M. Increased visceral adiposity in normal men is not likely due to testosterone, since male hypogonadism is associated with increased visceral fat

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Table. X Chromosome Parental Origin and Metabolic Profile

	Mean (SD)		*P* Value*
	X^M	X^P	
All patients, No.	62	27	
Age, y	30.7 (10.9)	26.7 (11.6)	.11
BMI	27.6 (6.3)	25.2 (6.3)	.15
Fasting glucose, mg/dL	83 (10)	82 (7)	.68
Fasting insulin, μU/mL	8.2 (7.0)	8.1 (4.6)	.95
Triglycerides, mg/dL	131 (62)	100 (50)	.01
Total cholesterol, mg/dL	208 (40)	189 (43)	.02
LDL-C, mg/dL	137 (41)	113 (44)	.004
HDL-C, mg/dL	58 (13)	61 (17)	.17
Patients aged ≥18 y, No.	40	16	
Age, y	34.1 (9.3)	32.2 (10.1)	.51
BMI	28.6 (7.8)	27.4 (7.1)	.59
Total body fat by DXA, %	37.1 (7.6)	36.3 (8.1)	.27
Total abdominal fat, mL	78.3 (49.0)	57.7 (36.0)	.005
Visceral abdominal fat, mL	24.8 (19.4)	13.9 (8.0)	<.001

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; DXA, dual-energy x-ray absorptiometry; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; X^M, maternally inherited X chromosome; X^P, paternally inherited X chromosome.
SI conversions: To convert glucose to mmol/L, multiply by 0.0555; to convert triglycerides to mmol/L, multiply by 0.0113; to convert total cholesterol, HDL-C, and LDL-C to mmol/L, multiply by 0.0259.
*Group means were compared by 1-way analysis of variance/analysis of covariance followed by Fisher protected least-significant-difference tests. Age and BMI were used as covariates in comparing metabolic and adiposity measures. Two-sided *P* values were calculated for age, BMI, fasting glucose, and fasting insulin; all other *P* values are 1-sided.

that is reduced with testosterone replacement.[7] Because both Turner syndrome groups in this study had ovarian failure, sex steroids are not likely contributors to the present findings.

Limitations of this study include a relatively small sample size. As an observational study, results could be due to unmeasured confounders. The cross-sectional design limits inferences about causality. While interpretation of the *P* values should consider that there were 6 comparisons, the parallel increases in plasma lipids and abdominal adiposity are biologically consistent. Additional research is needed to confirm these findings and to extend them to X chromosome effects in normal men and women.

However, these results suggest a role of X chromosome gene dosage in metabolic regulation that could be explained by the imprinting (silencing) of maternally transmitted X-linked genes that normally prevent visceral fat accumulation, or imprinting of paternally transmitted X-linked genes that normally promote visceral fat accumulation. Identification of these putative imprinted X-linked genes and elucidation of the epigenetic mechanisms involved in their differential expression could have implications for cardiovascular health.

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Shyness, Social Anxiety, and Impaired Self-esteem in Turner Syndrome and Premature Ovarian Failure

To the Editor: Shyness and social anxiety are reported in women with Turner syndrome (TS).[1] Possible contributors include physical stigmata, such as short stature and neck-webbing, chromosomally-based deficits in social cognition, and premature ovarian failure with infertility. To investigate the potential role of premature ovarian failure and infertility, we compared measures of psychosocial distress in women with TS, women with spontaneous karyotypically normal premature ovarian failure (POF), and healthy controls.

Methods. Participants in this institutional review board–approved study were recruited through National Institutes of Health (NIH) Web sites and newspapers and provided written informed consent. Inclusion criteria for patients with TS and POF are described elsewhere.[2] Daily hormone therapy