Transcriptomic signatures of sexual dimorphism in the subcutaneous adipose tissue of obese individuals

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Introduction:

There is biological evidence of sex differences in many human traits. Sexual dimorphism in body shape, fat distribution, obesity and related diseases are are noticeable throughout different ethnicities. Gonadal hormones can partially account for those differences; men accumulate more visceral than subcutaneous adipose tissue in the abdominal region while premenopausal women store more fat in subcutaneous depots. However, sex differences in body size and composition appear before the exposure to gonadal hormones, evidencing some gonadal-independent mechanisms. Additionally, it is still unclear whether or not this sexual dimorphism also persists in the metabolism and function within the abdominal subcutaneous adipose tissue.

Hypothesis and Objetives:

Although men and women have almost identical genomes, sexually dimorphic traits likely result from differential expression of genes present in both sexes. In this work we have examined sex differences on subcutaneous adipose tissue gene expression and metabolic health in a cohort with a wide range of body mass indexes (BMI).

Methods:

INDIVIDUALS:

Biopsies from the abdominal subcutaneous adipose tissue (SCAT) from patients free of cancer or inflammatory diseases and undergoing elective surgery were obtained in the Hospital Universitario Miguel Servet (HUMS) and the Hospital Royo-Villanova (HRV), both in Zaragoza (Spain).Bloodwork was performed at the Clinical Biochemistry Service (HUMS) using state of the art analyzers in compliance with the ISO 15189:2012. This study has been approved by the by the Regional Institutional Review Board of Aragón

STUDY INDIVIDUALS´CHARACTERISTICS

	MEN N=18	WOMEN N=27	p
Age (years)	50.3 (8.79)	45.3 (9.33)	0.072
BMI (kg/m2)	37.1 (8.52)	40.1 (7.01)	0.235
Hypertension	11 (61.1%)	8 (29.6%)	0.074
Hyperlipidemia	5 (27.8%)	8 (29.6%)	1.000
Diabetes	7 (38.9%)	3 (11.1%)	0.064
CRP (mg/dl)	0.66 (0.74)	0.86 (1.18)	0.510

Data are mean (SD) or n (%) for continuous and categorical variables, respectively

RNA-SEQUENCING:

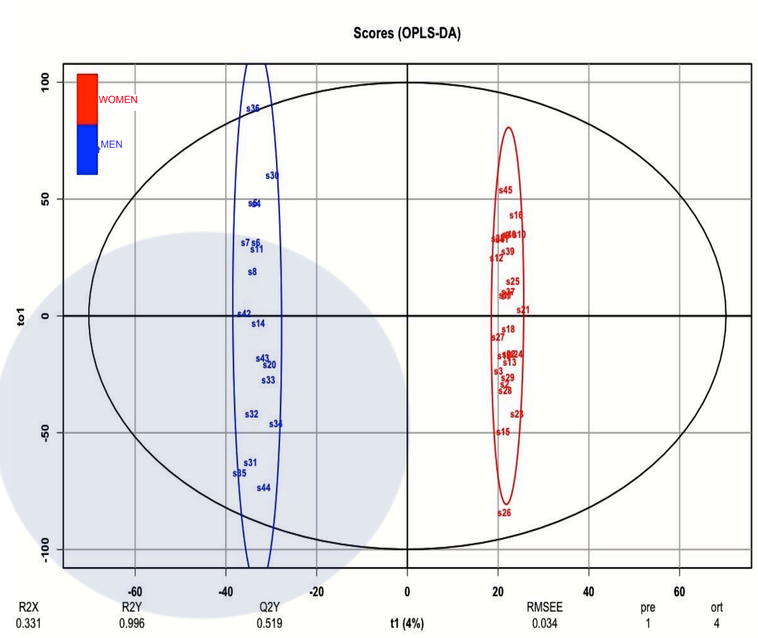
SCAT RNA-Seq analysis was performed using the Ion AmpliSeq™ Transcriptome HumanGene Expression Kit (AmpliSeq) on an Ion Proton System for next-generation sequencing (Life Technologies).

IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES (DEGs):

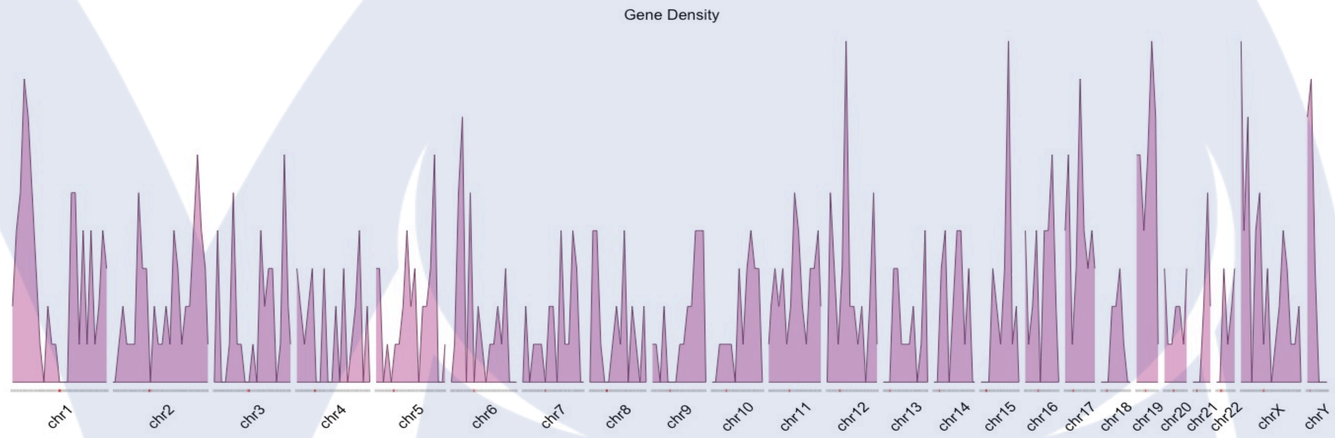
The Ion Proton reads were analyzed using the AmpliSeqRNA analysis in the Torrent Suite Software (Life Technologies).The resulting counts, representing the gene expression levels for over 20,800 different genes present in the AmpliSeq Human Gene Expression panel, were used for differential gene expression analysis by orthogonal partial least square modeling and discriminant analysis (OPLS-DA). Variable importance in projection (VIP) and detection of outliers were calculated with the R/ Bioconductor package ROPLS (http://www.bioconductor.org/).

Results

A The OPLS- DA analysis aims at finding out a set of gene transcripts (i.e. variables) most effective in discriminating men from women. The percentage of response variance explained by the predictor component only (t1) is indicated in parentheses. R2X (respectively R2Y): percentage of predictor (respectively response) variance explained by the full model. Q2Y: predictive performance of the model estimated by cross-validation. For the classification model (SEX), the ellipses corresponding to 95% of the multivariate normal distributions with the samples covariances for each class are shown.



B The variable importance in the projection or VIP in the OPLS-DA model represents an appropriate quantitative statistical parameter ranking DEGs according to their discrimination ability between men and women. A sex-specific response was observed for 599 genes (VIP values >2) expressed throughout the chromosomes.



Chromosome distribution of differentially expressed genes with VIP>2.

C Significant numbers of DEGs (VIP>2) from the adipose tissues were enriched in various GO terms of the developmental process and their KEGG pathway analysis showed differentially expressed genes between men and women.

FUNCTIONAL ANNOTATION OF DEGs

Term	Count	PValue	Genes
hsa00280:Valine, leucine and isoleucine degradation	9	<0.001	ACAA2, EHHADH, MCCC1, DLD, ACAT1, PCCA, HIBADH, ALDH9A1, HADHB
hsa01212:Fatty acid metabolism	9	<0.001	ACADVL, ACAA2, EHHADH, FADS1, TECR, ACSL3, ACAT1, MECR, HADHB
hsa01200:Carbon metabolism	14	<0.001	ACO1, EHHADH, HK2, ADH5, ACAT1, AGXT, IDH3A, SDHA, DLD, RGN, PDHA1, CAT, PSAT1, PCCA
hsa00071:Fatty acid degradation	8	0.002	ACADVL, ACAA2, EHHADH, ADH5, ACSL3, ACAT1, ALDH9A1, HADHB
hsa00062:Fatty acid elongation	6	0.003	ACAA2, ELOVL7, TECR, MECR, ACOT4, HADHB
hsa00630:Glyoxylate and dicarboxylate metabolism	6	0.005	ACO1, DLD, CAT, AGXT, ACAT1, PCCA
hsa01220:Degradation of aromatic compounds	3	0.005	AKR1A1, ADH5, RGN
hsa00010:Glycolysis / Gluconeogenesis	8	0.022	LDHB, AKR1A1, DLD, PGM1, ADH5, HK2, PDHA1, ALDH9A1
hsa04512:ECM-receptor interaction	9	0.029	COL4A2, COL4A1, ITGB4, ITGA1, SV2A, LAMC1, COL5A2, COL4A6, COL4A5
hsa00020:Citrate cycle (TCA cycle)	5	0.035	SDHA, ACO1, DLD, PDHA1, IDH3A
hsa00600:Sphingolipid metabolism	6	0.046	SPHK1, KDSR, SGMS1, B4GALT6, ASAH1, DEGS1
hsa00500:Starch and sucrose metabolism	5	0.048	PYGL, PGM1, GYS1, HK2, UGP2

Conclusion:

The transcriptomic milieu of the abdominal subcutaneous adipose tissue differs between the sexes. Given the increased burden associated with excessive fat accumulation, it is of paramount importance to focus on sexually dimorphic traits to develop sex-specific therapies that reduce metabolic alterations associated to obesity.

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