



## Data in Brief

# Transcriptome profiling of white adipose tissue in a mouse model for 15q duplication syndrome



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## ABSTRACT

Obesity is not only associated with unhealthy lifestyles, but also linked to genetic predisposition. Previously, we generated an autism mouse model (*patDp/+*) that carries a 6.3 Mb paternal duplication homologous to the human 15q11–q13 locus. Chromosomal abnormalities in this region are known to cause autism spectrum disorder, Prader–Willi syndrome, and Angelman syndrome in humans. We found that, in addition to autistic-like behaviors, *patDp/+* mice display late-onset obesity and hypersensitivity to a high-fat diet. These phenotypes are likely to be the results of genetic perturbations since the energy expenditures and food intakes of *patDp/+* mice do not significantly differ from those of wild-type mice. Intriguingly, we found that an enlargement of adipose cells precedes the onset of obesity in *patDp/+* mice. To understand the underlying molecular networks responsible for this pre-obese phenotype, we performed transcriptome profiling of white adipose tissue from *patDp/+* and wild-type mice using microarray. We identified 230 genes as differentially expressed genes. *Sfrp5* – a gene whose expression is positively correlated with adipocyte size, was found to be up-regulated, and *Fndc5*, a potent inducer of brown adipogenesis was identified to be the top down-regulated gene. Subsequent pathway analysis highlighted a set of 35 molecules involved in energy production, lipid metabolism, and small molecule biochemistry as the top candidate biological network responsible for the pre-obese phenotype of *patDp/+*. The microarray data were deposited in NCBI Gene Expression Omnibus database with accession number [GSE58191](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58191). Ultimately, our dataset provides novel insights into the molecular mechanism of obesity and demonstrated that *patDp/+* is a valuable mouse model for obesity research.

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Specification	
Organism/cell line/tissue	<i>Mus musculus</i> /white adipose tissue (WAT)
Sex	Male
Sequencer or array type	Agilent Whole Mouse Genome Microarray 4x44K G4122F (GPL4134)
Data format	Raw CEL files; Normalized data: SOFT, MINiML and TXT
Experimental factors	<i>patDp/+</i> vs WT
Experimental features	Microarray gene expression profiling to identify differentially regulated genes in WAT of <i>patDp/+</i> mice compared with WT mice
Consent	N/A
Sample source location	Wako, Saitama, Japan

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## 1. Direct link to deposited data

The deposited data can be found at: <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58191>.

## 2. Experimental design, materials and methods

## 2.1. Experimental design

Chromosome 15q11–q13 is not only a recombination hotspot in the human genome, but also a well-known imprinting locus. Genomic alterations of this region are associated with several disorders, including autism spectrum disorder (ASD), Prader–Willi syndrome and Angelman syndrome [1–3]. In particular, the duplication of this region is the most common cytogenetic abnormality leading to ASD, a neurodevelopmental

disorder characterized by social impairments, restricted interest and repetitive behaviors [4].

In an effort to understand the molecular and neurobiological basis of 15q11–q13 related disorders, we previously generated a mouse model (*patDp/+*) carrying a 6.3 Mb paternal duplication of mouse chromosome 7 syntenic to the human 15q11–q13 region using chromosome engineering techniques [5]. This mouse model recapitulates various aspects of human autistic phenotypes. Detailed analyses of *patDp/+* mice demonstrated that the paternal duplication is involved in social behavior and serotonin metabolism [6–8]. The duplication also caused neuro-anatomical changes, including smaller dentate gyrus and medial striatum, in the brains of *patDp/+* mice [9].

In addition to autistic-like abnormal behaviors, we noticed that *patDp/+* mice are highly susceptible to obesity and sensitive to a high-fat diet despite having similar levels of energy expenditure and food intake as wild-type (WT) mice [10]. Moreover, we also observed an enlargement of white adipocytes in young *patDp/+* mice relative to those in WT mice. The weight of these young *patDp/+* mice did not significantly differ from that of young WT mice, suggesting the pathophysiological process to obesity was initiated in *patDp/+* mice before the onset of obesity.

In this experiment, we conducted microarray gene expression profiling on RNA isolated from the WAT of *patDp/+* and WT mice to identify differentially expressed genes (DEGs) that may be responsible for the pre-obese phenotype in *patDp/+* mice.

## 2.2. Animals

The *patDp/+* mice were generated as previously described [5] and were backcrossed to C57BL/6J more than 10 generations. Three *patDp/+* and three WT mice were used in this study. All mice were male and were in the young adult stage (9–10 weeks old). Mice were housed in a 12-hour light/dark condition (light on 8:00 a.m. and off on 8:00 p.m.).

## 2.3. RNA extraction

Total RNA from epididymal WAT was extracted with TRIzol reagent (Life Technologies, Inc.), treated with DNaseI (Promega, Madison, WI, USA) and purified by columns to remove contaminating genomic DNA. We measured the RNA concentration using the NanoDrop ND-1000 spectrometer (NanoDrop Technologies, Wilmington, DE, USA), and examined the RNA quality with Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA).

## 2.4. Microarray

The Agilent Whole Mouse Genome 4x44K G4122F Array was used in this study. For each sample, 200 ng of total RNA was used to synthesize

double-stranded cDNA. cDNA was then transcribed into cRNA by using T7 RNA polymerase, and labeled with Cy3 (Low Input Quick Amp Kit for one color, Agilent Technologies). The cRNA was fragmented and prepared for one-color based hybridization (Gene Expression Hybridization Kit, Agilent Technologies). The cRNA samples were hybridized at 65 °C for 17 h on Whole Mouse Genome 4x44K microarrays. Microarray were washed with Gene Expression Wash Buffers (Agilent Technologies) and dried up. Fluorescent signal intensities were detected with the Agilent DNA microarray scanner. The scanned images were analyzed to generate raw files saved as CEL files using Agilent's Feature Extraction software version 9.5.

## 2.5. Data analysis

The Limma package (3.18.2) from R Bioconductor was used to identify DEGs [11]. The raw signal intensities were corrected by “backgroundCorrect” function of the Limma package, between-arrays normalization was performed using the quantile method. The signals in replicate spots were averaged with the “avereps” function. Linear model was fitted for each probe; finally the empirical Bayes moderated t-statistics were applied to assess differential expression. The R script for the analyses was available in the public repository ([https://github.com/psytky03/Microarray\\_Analysis\\_R](https://github.com/psytky03/Microarray_Analysis_R)). The pathway analysis was performed to identify the relevant biological networks using Ingenuity Pathway Analysis software (IPA, QIAGEN Redwood City, [www.qiagen.com/ingenuity](http://www.qiagen.com/ingenuity)).

## 3. Results

A total of 230 coding genes were found to be differentially expressed in the WAT of *patDp/+* compared to WT mice with criteria of P value  $\leq 0.05$  and fold change  $\geq 1.3$ . Of these, 145 genes were up-regulated and 85 were down-regulated in *patDp/+* mice (Table 1). Notably, *Sfrp5* – a gene whose expression is positively correlated with adipocyte size [12], was observed to be up-regulated in *patDp/+*. In addition, among the top up-regulated DEGs, paternally expressed genes *Ndn*, *Snurf* and *Snrpn* were located within the chromosome engineered duplicated region, demonstrating that the DEGs list was reliable. *Fndc5*, the precursor of a newly identified hormone – irisin, was identified as the top down-regulated gene. *Fndc5* has been proposed as a potent inducer of brown adipogenesis [13], and is of considerable interest for metabolism research. Finally in the pathway analysis, a set of 35 molecules involved in energy production, lipid metabolism, and small molecule biochemistry was subsequently highlighted as the top candidate gene network (Table 2). Leptin, a hormone that plays a critical role in appetite and weight control, and the protein kinase Akt were recognized as the central hub molecules of this network.

**Table 1**

List of differential expressed genes (DEGs) with P value  $\leq 0.05$  and fold changed  $\geq 1.3$  from microarray analysis.

145 up-regulated genes	85 down-regulated genes
1110059M19Rik, Acta1, Has1, Ccl7, Snrpn, Ndn, Ccl2, Tmem45b, Sfrp4, Xlr3c, Thbs1, Bmp3, Sfrp5, Snurf, Xlr4b, Ctgf, Timp1, Pamr1, Grb14, Cela1, Egr2, Duoxa1, Adamts12, Dact2, Cryab, Krt79, Cd44, Gfpt2, Sirpb1b, Slc1a1, Atp10a, Pdlim7, Spink2, Npr3, Arid5a, Krt1, Bhlhe40, Wnt2, Chsy1, Nol3, Socs3, F10, Timp4, Sct, Mgam, Pthlh, Synpo2, Rassf4, Tnfrsf6, Mutyh, Mkrn3, Dnm1, Ccl5, Slc16a3, Pdlim1, Fbn1, Tph2, Dpysl3, Uchl1, Ube3a, Ccl4, Lep, LOC100038947, Rasl11a, Cd8a, Fn1, Col14a1, Bmp7, Ldlr, Slc41a2, Kcnc1, Creb5, Esd, Vgll3, Prepl, Mag, Hdgf1, Nuak2, Lsp1, Expi, Lbp, Pla1a, Inhbb, Sybu, Wnt11, Slc22a2, Mefv, C1qtnf7, Gamt, Has2, Lrrc25, Herc2, Efhd1, Ms4a6d, Tmem100, Dact1, Rnd1, Tnfrsf11b, Thy1, Lgmn, Cxcr7, Hist1h1c, Mafb, Ranbp3l, Dnajb13, Rgs14, Tll10, Syp, Fcna, E030010A14Rik, Nov., Adh4, Anxa1, Pprc1, Nipal3, Ugt3a2, Prdm8, Al467606, Emilin2, Smg6, Tspan17, Myo1g, Vdr, S100a6, Maff, Vcan, Sncg, Batf, Pcolce2, Apbb1ip, Cdk1na, Mtap7, Itgam, Lrrc20, 1700019D03Rik, a, Pdlim4, Fxyd5, Csf1, Cmtm7, Myh2, Peli1, Nek6, Cdk6, Ccbb2	Fndc5, Mmd2, Cyp2f2, Rgs2, Ms4a1, Spon1, H2-Q10, Tst, Traf4, Ptgsd, Serpina3b, Hpca, Ly6d, Sfrp1, Cd79b, Apod, Faim3, Pappa, Acacb, Prnd, 1500015010Rik, Cpxm2, Nmb, Sox9, Agpat9, Slc5a6, Dennd2d, 4930524B15Rik, 2900062L11Rik, Igfbp2, Ppargc1a, Avpr1a, Drd1a, Btl9, Tbx3, Lrig1, Rnf144b, Gulp1, Aplnr, Ly6g6e, Ppargc1b, Gm7455, Pdgfr1, Dio3, Smpd3, Lrm1, Itm2a, Bcat2, Slc27a1, Prr1, Arl4a, Lpin1, 2010001M09Rik, Vnn3, Celf6, Rhbh, Trim9, Mogat1, Slc44a5, Chdh, Dock9, Pcsk6, BC031353, Il15ra, Acs1, Gdf10, Rab15, Mlxip1, Ppa1, Acot1, Alas1, Penk, Crispd2, Rcl1, Gria1, Nrg4, Baiap2l2, Itpka, Asp9, Slc22a23, Spink8, Col6a6, Mgst2, Bmf, Klhl2

**Table 2**  
Top biological network associated with pre-obese phenotypes based on pathway analysis.

Molecules in network	Diseases and functions
ACACB, ACSL1, ADH4, Akt, ALAS1, Alp, AMPK, BCAT2, BMF, CD79B, CTGF, CYP2F1, cytochrome C, FN1, HERC2, HIST1H1C, IGF2BP2, LDLR, LEP, LPIN1, NPR3, Pka, PPARGC1A, PPARGC1B, PTGDS, SFRP4, SLC27A1, SNRPN, SOCS3, SOX9, TNFRSF11B, UBE3A, VLDL-cholesterol, WNT11, ZBTB20	Energy production, lipid metabolism, small molecule biochemistry

#### 4. Summary

Here we described a dataset of transcriptome gene expression profiling of WAT in *patDp/+* and WT mice. Based on this data, we identified hundreds of DEGs and the biological networks that might be associated with the obese phenotype of *patDp/+*. We believe that this dataset will be particularly valuable for future studies on obesity.

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