Supplemental File 1. Adipose tissue and body weight of female *wt/wt*, *P465L/wt*, *ob/ob*, and *P465L/ob* mice. Weight expressed in grams (g)

	WT		P465L		OB		P465L/OBOB	
Body Weight	23.59	±0.669	22.64	±0.486	54.13	±1.448	48.53	±1.844*
Inguinal	0.319	±0.038	0.284	±0.038	2.601	±0.134	2.377	±0.195
Retroperitoneal	0.124	±0.020	0.057	±0.008*	1.317	±0.082	1.304	±0.143
Mesenteric	0.204	±0.032	0.149	±0.022	1.305	±0.067	0.982	±0.077*
Gonadal	0.598	±0.070	0.411	±0.044*	5.531	±0.295	4.085	±0.313*
Gonadal/BW	0.024	±0.002	0.018	±0.002	0.102	±0.005	0.082	±0.004*

Data represent means ± SE of 12 animals per group.

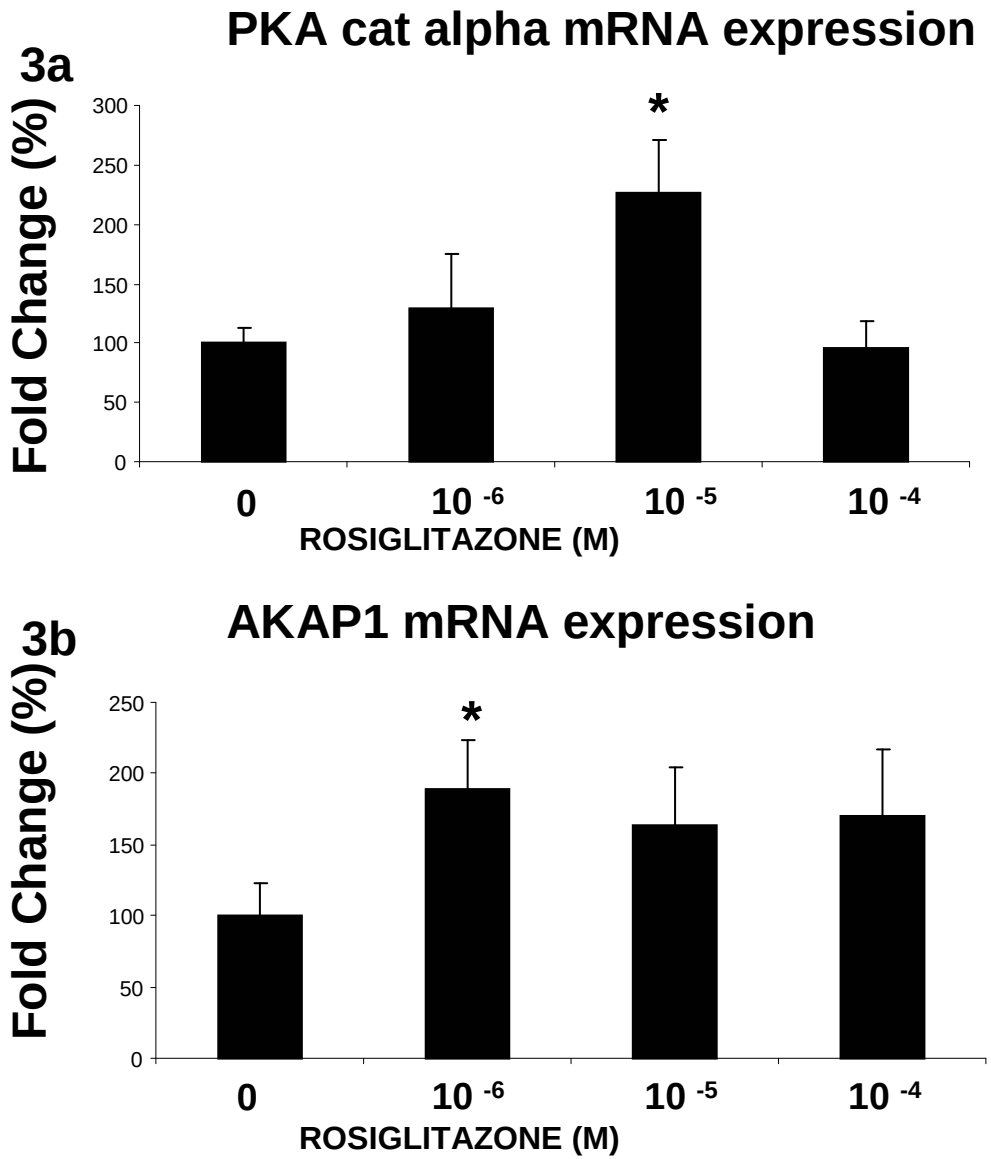
* wt vs. P465L; Student's *t*-test significance was $P < 0.05$.

Supplemental File 2
Cohort1. Biological characteristics of controls and morbidly obese patients

	Controls	MO-LowIR	MO-HighIR
Male/female, n/n	3/3	7/7	7/7
Age, years	52.17 ± 5.1	44.14 ± 3.43	39.00 ± 2.50
Weight, Kg	74.00 ± 0.71	153.36 ± 7.17	157.64 ± 7.48
Height, cm	162.60 ± 1.60	164.07 ± 2.01	167.00 ± 2.98
BMI, Kg/m^2	25.04 ± 0.55	56.72 ± 1.71	56.30 ± 1.65
Serum insulin, UI/ml	11.23 ± 1.58	15.42 ± 1.44	44.76 ± 3.17
HOMA-IR	3.51 ± 0.48	3.60 ± 0.32	12.76 ± 1.25
Serum glucose, mmol/l	6.03 ± 0.32	5.32 ± 0.23	6.16 ± 0.29
Serum cholesterol, mmol/l	4.68 ± 0.40	4.91 ± 0.26	4.93 ± 0.24
HDL cholesterol , mmol/l	0.97 ± 0.23	1.16 ± 0.08	1.05 ± 0.11
Triglycerides, mmol/l	1.08 ± 0.20	1.27 ± 0.13	1.57 ± 0.25

[1] Values are means ± SEM. HDL-c= High density lipoprotein-cholesterol

Supplemental File 3



Ex-vivo experiments using gonadal adipose tissue explants. Gonadal adipose tissue was obtained from wt mice. 10mg of tissue was incubated in absence or presence of different concentrations of rosiglitazone for 12h. Differences in expression between groups were assessed by student t Test. * vs. untreated The level of probability was set at $P < 0.05$.

Supplemental File 4

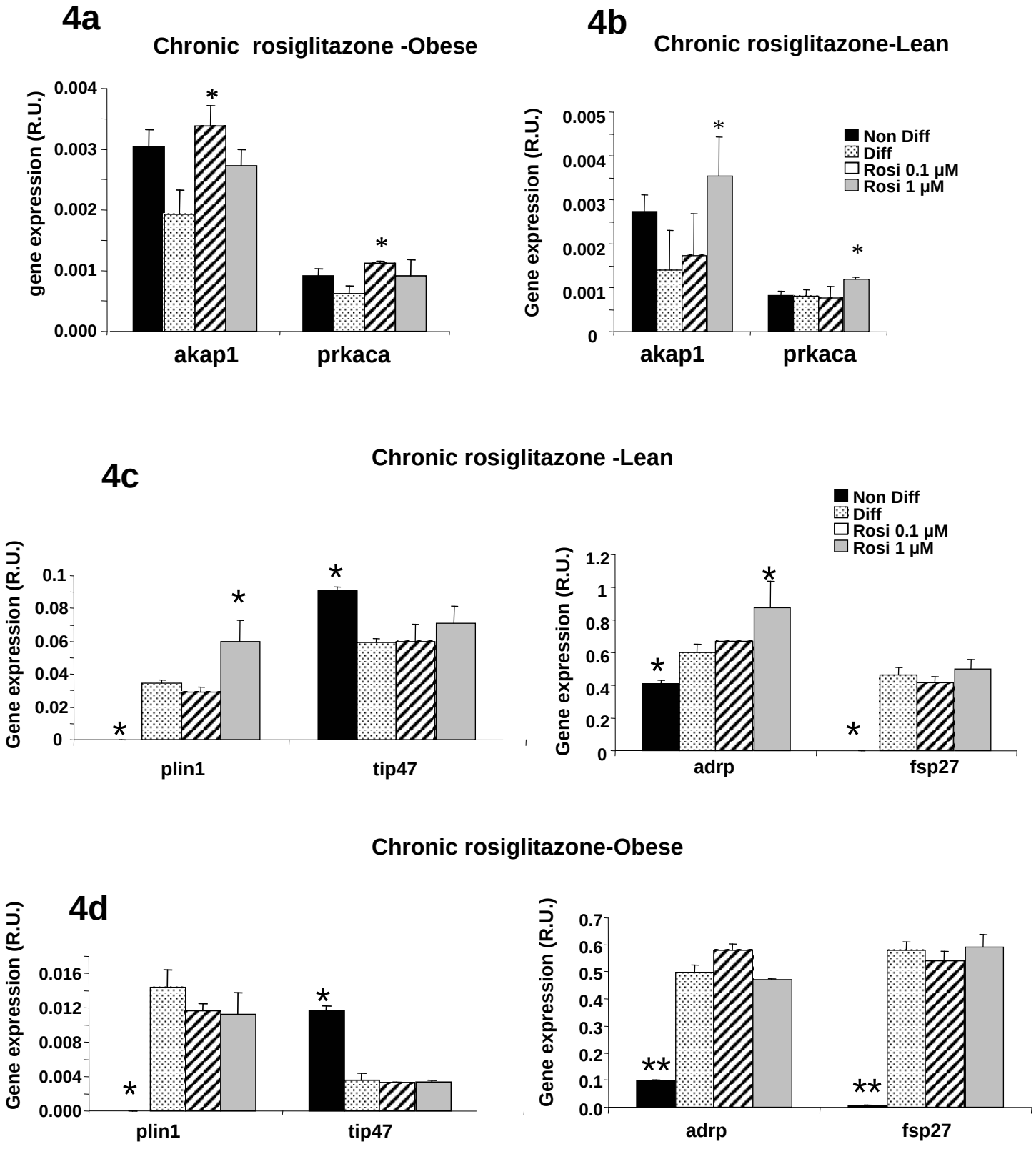
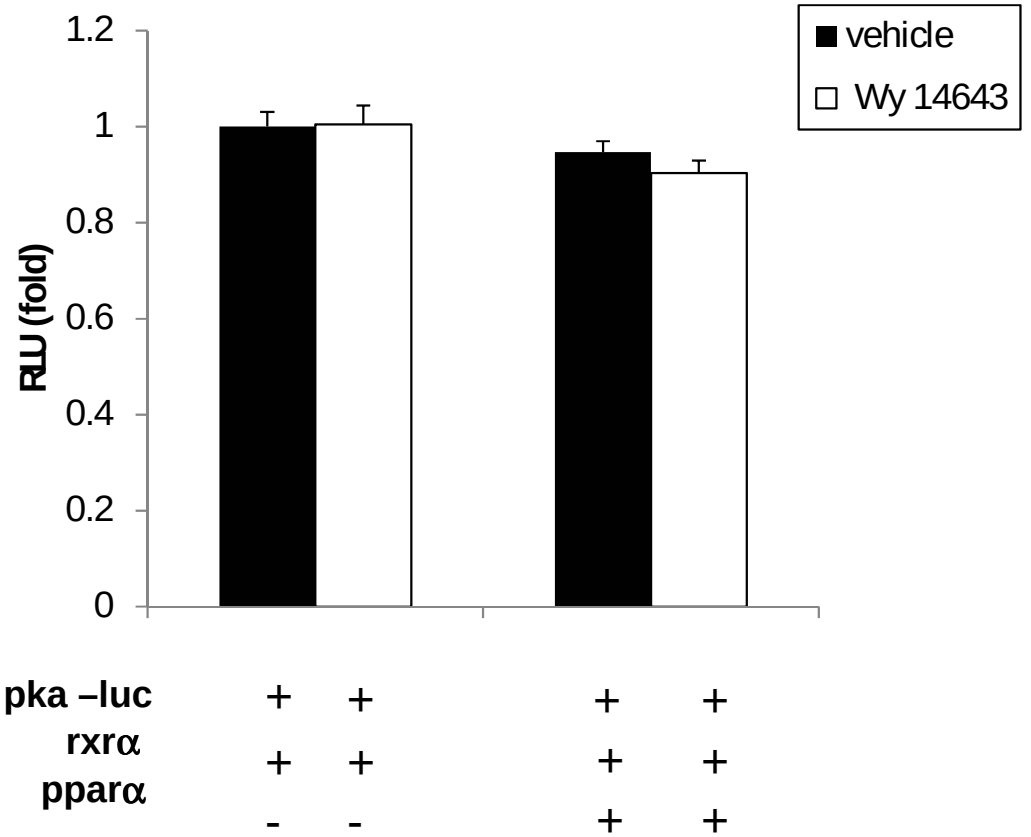


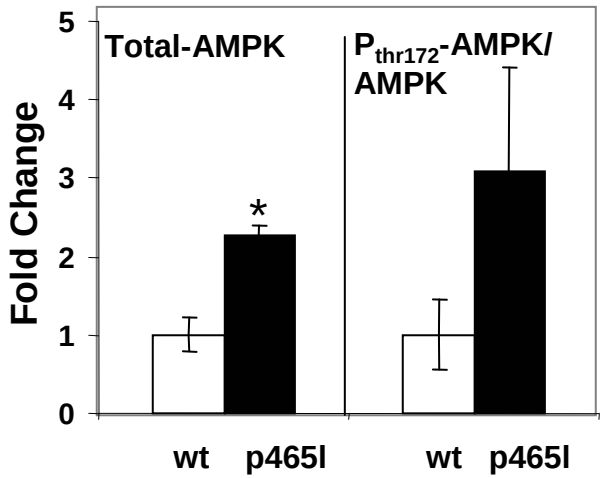
FIGURE 4. **a-d** prkaca and *d-akap1 and* lipid droplet proteins mRNA expression mRNA expression in adipocytes from lean and obese subjects after chronic exposure to rosiglitazone. Data represent means ± SE. Differences in expression between groups were assessed by ANOVA and student t Test. * differentiated adipocytes. The level of probability was set at *p<0.05 *vs* Diff, **p<0.005 *vs* Diff.

Supplemental File 5



Transactivation of the pka cat subunit promoter-luciferase reporter construct (*pka-Luc*) by PPARalpha in HEK293T cells. The pka-luc reporter plasmid was transiently co-transfected with plasmid expressing RXRa together with Pparalpha. At 24h post-transfection, cells were incubated with 5uM WY14643 (open bar) or vehicle (solid bar) and further incubated for 24h before being harvested and assayed for luciferase activity. Here we shows a representative experiment. Luciferase activity maesured in the cells transfected with pka-luc and RxRa and pGS5 as control for Pparalpha (basal consition) in the absence of WY14643 was set at 1.

Supplemental File 6



Western blot from isolated mature adipocytes blot. Differences in expression between groups were assessed by student t Test. * P465L vs. WT The level of probability was set at $P < 0.05$. n=3.

Supplemental File 7

Table I. Gene expression analysis of P465L mutant adipocytes from lean and obese mice vs. wt counterparts. mRNA levels of different genes determined by real-time PCR of in isolated mature adipocytes from 12-16-week-old wild-type fed a normal diet.

	WT		P465L		ob/ob		P465L/ob/ob		ANOVA
ADRENERGIC PATHWAY									
β3-AR	100.0	± 10.9	87.5	±8.8	13.0	±3.9°	17.2	±11.0°	**OB**
α2A-AR	100.0	±24.8	62.1	±15.6	201.9	±67.9	66.6	±18.4	
pd3b	100.0	±18.9	98.8	±12.8	32.5	±5.4°	30.8	±13.8°	**OB**
pd4a	100.0	±21.8	53.8	±6.0*	184.5	±46.9	83.3	±27.4	**G, OB**
pd4d	100.0	±16.8	102.4	±8.7	86.1	±19.6	52.1	±4.3°	**OB**
LIPASE INTERACTING PROTEINS									
CGI58/Abdh5	100	±12.8	81.2	±9.3	67.1	±12.9°	48.3	±9.9°	**OB**
FABP4	100	±15.7	98.5	±8.4	54.2	±9.5°	43.2	±7.3°	**OB**
REESTERIFICATION									
Pepck	100	±28.1	39.1	±12.7*	9.2	±1.9°	12.2	±7.3	**OB**
FFA TRANSPORT									
Cd36	100	±19.2	55.5	±9.7*	69.0	±11.6	56.0	±12.2	**G**
FATP1									**G, OB**
	100	±20.8	39.5	±5.1*	23.1	±3.4°	14.6	±3.8°	**G x OB**
LPL	100	±16.4	85.7	±11.8	62.2	±12.1°	44.9	±8.0°	**OB**
PPARGAMMA									
Pparγ1	100	±13.5	99.1	±16.9	84.4	±21.2	49.2	±11.6°	**OB**
Pparγ2	100	±35.9	235.0	±64.1*	41.6	±9.2	59.5	±22.7°	**G, OB**

Data represent means ± SE of 8–12 animals per group. Fold changes were established using wt as 100. Differences in expression between groups were assessed by ANOVA (G:effect of P465L mutation, OB: effect of obesity, G x OB: interactive effect) and student t Test. * P465L vs. WT and ° P465L/ob/ob vs. ob/ob. The level of probability was set at $P < 0.05$.