Natural helix 9 mutants of PPARγ differently affect its transcriptional activity

Marjoleine F. Broekema^{1,2}, Maarten P.G. Massink^{1,3}, Cinzia Donato^{1,2}, Joep de Ligt^{1,3}, Joerg Schaarschmidt⁴, Marieke G. Schooneman⁵, Diana Melchers⁶, Martin N. Gerding⁷, René Houtman⁶, Alexandre M.J.J. Bonvin⁴, Amit R. Majithia⁸, Houshang Monajemi^{9,10}, Gijs W. van Haaften^{1,3}, Maarten R. Soeters⁹, Eric Kalkhoven^{1,2*}.

- Center for Molecular Medicine, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands.
- Department of Molecular Cancer Research, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands.
- Department of Genetics, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands.
- 4. Bijvoet Center for Biomolecular Research, Faculty of Science, Utrecht University, Utrecht, The Netherlands.
- Department of Internal Medicine, Amsterdam University Medical Centers, Amsterdam, The Netherlands.
- 6. PamGene International B. V., 's-Hertogenbosch, The Netherlands.
- 7. Deventer Hospital, Deventer, The Netherlands.
- 8. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
- 9. Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, Amsterdam, The Netherlands.
- 10. Rijnstate Hospital, Arnhem, The Netherlands.

* Corresponding author: Eric Kalkhoven, Center for Molecular Medicine, Department of Molecular Cancer Research, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. Telephone: +31-88-75-54258; E-mail: <u>e.kalkhoven@umcutrecht.nl</u>

Supplemental Methods

R script to determine the association of common genetic variants with partial lipodystrophic phenotype.

```
library("ggplot2")
setwd("53SNPs")
# Read relevant data
dosage <- read.table("UKHLS.dosage.txt.assoc.dosage",sep=",header=F, stringsAsFactors=F,
col.names=c("CHR","SNP","BP","A1","A2","FRQ","INFO","OR","SE","P"), skip=1)
head(dosage)
gts <- read.table("plink.ped",sep=' ',header=F, stringsAsFactors=F)
head(gts[,1:10])
snpinfo <- read.table("SNPdata.txt",sep='\t',header=T, stringsAsFactors=F)</pre>
colnames(gts) <- c("sample","family","pat","mat","gender","phenotype",as.character(snpinfo$SNP))
# Selecting females only
gts <- subset(gts, gender=="2")
# Determine where reference alle != non-risk allele
snpinfo$flip <- snpinfo$Effect.Allele!=dosage$A1
# Convert genotypes to risk scores
scores <- gts[,7:ncol(gts)]</pre>
scores[scores==0]<-NA
scores[scores==11]<-0
scores[scores==12]<-1
scores[scores==21]<-1
scores[scores==22]<-2
# Adjust risk scores for 'flipped' positions
scores[,snpinfo$SNP[snpinfo$flip]] <- scores[,snpinfo$SNP[snpinfo$flip]]-2
scores <- abs(scores)</pre>
# Determine missing genotypes to prevent over scoring
liponas <- apply(scores, 1, function(x) sum(is.na(x)))
liporisk <- rowSums(scores, na.rm=T)
liporiskfrac <- liporisk/((53-liponas)*2)</pre>
rownames(scores) <- gts$sample
```

scores\$liporiskfrac <- liporiskfrac</pre>

scores\$riskalleles <- scores\$liporiskfrac*106</pre>

Plot results of patient relative to population

pdf(file="LipoRiskDistribution_Paper.pdf",width=6,height=10,useDingbats=F, pointsize=10)

```
aplot <- ggplot(scores, aes(x=riskalleles)) + geom_histogram(binwidth=1, fill="#4396F0", color="#4396F0", alpha=.5)
```

```
bplot <- aplot + ylab("UKHLS controls, n") + xlab("Number of risk alleles") + theme_bw() +
theme(panel.border = element_blank(), panel.grid.major = element_blank(), panel.grid.minor =
element_blank(), axis.line = element_line(colour = "black")) +
scale_x_continuous(breaks=round(seq(40,80,by=5),1)) +
scale_y_continuous(breaks=round(seq(0,900,by=100),1))</pre>
```

cplot <- bplot + theme(axis.text = element_text(size=15)) + theme(axis.title = element_text(size=20))

```
print(cplot + geom_vline(xintercept=53, color="red"))
```

dev.off()

Calculate z-score

```
pop_sd <- sd(scores$riskalleles)*sqrt((length(scores$riskalleles)-1)/(length(scores$riskalleles)))
```

```
pop_mean <- mean(scores$riskalleles)</pre>
```

```
zscore <- (53 - pop_mean)/pop_sd
```

print(zscore)

Supplemental figures

Supplemental figure 1. Structural based sequence alignment of the amino acid residues surrounding PPARy L451P between human PPARs and other members of the nuclear hormone superfamily. Human PPARy (NP_056953.2), human PPAR α (CAG30433), human PPAR δ (Q03181), chimpanzee PPARY (XP_001153669.1), mouse PPARY (NP_035276.2), rat PPARY (NP_037256.1), cow PPARY (NP_851367.1), dog PPARY (NP_001019803.1), chicken PPARY (NP_001001460.1), and zebrafish PPARY (NP_571542.1). THRA, thyroid receptor alpha (NP_003241.2); THRB, thyroid receptor beta (AAI06931.1); GR, glucocorticoid receptor (NP_000167.1); MR, mineralocorticoid receptor (NP_000892.2); AR, androgen receptor (P10275.2); FXR, farnesoid X receptor (NP_001193908.1); VDR, vitamin D receptor (AAH60832.1); HNF α , Hepatocyte nuclear factor 4A (CAA61133.1). Residues analogous L451 and V318 are designated in yellow and bold. Residues analogous to 314, 316, S317, K347, and K422 are indicated in pink and bold. PPARY2 nomenclature. Dashes (-) represent the gaps included for appropriate alignment of the nuclear hormone receptors. The boundaries of the α -helices 9, and 10 are also shown.

Supplemental figure 2. Proline substitutions in helix 9 impair transcriptional activity of PPAR γ . U2OS cells were transiently cotransfected with expression vectors encoding PPAR γ WT or PPAR γ mutants respectively, and 3x peroxisome proliferator response element (PPRE)-Tk-Luc reporter. Activation of the luciferase reporter, in the absence or presence of 1 µM 15d-PGJ2, is expressed as fold induction over that with empty vector (EV). Results are averages of at least three independent experiments assayed in duplicate ± SEM. *P<0.05 cells transfected with mutant *vs.* WT. Expression levels of the different proteins were confirmed by Western blot analysis using a PPAR γ specific antibody. The arrow indicates PPAR γ and the asteriks indicates an unknown non-specific band. WT, wildtype.

Supplemental figure 3. Cofactor peptide binding profiles for GST-PPARγ LBD WT and L451P. GST-proteins were incubated with DMSO or 10 μM rosiglitazone. Images of all arrays were quantified and binding (AU; arbitrary units) was plotted. The experiments were performed in triplo.

Supplemental Table 1. SNP genotype of PPARy L451P index patient.

PCR was performed in the index patient to genotype the lead SNPs in 53 genomic regions that were previously identified to impair peripheral adipose tissue storage (51). The index patients harbors 53 risk alleles.

Supplemental figure 1. Strucutre sequence alignment of the amino acid residues surrounding PPARy L451P between human PPARs and other members of the nuclear receptor superfamily

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		NH2 —)		BD)	LBD			соон				
		L	γ 2 Α		Hinge				4F-2					
					C									
							· · · · · · · · · · · · · · · · · · ·		••••••					
				Helix 3			Helix 4				Helix 9		Helix 10	;
Homo sapiens Homo sapiens Homo sapiens	PPARγ PPARα PPARδ	 	319 273 246	FQGCQF RSV EAVQ FHCCQC TSV ETVI FYRCQC TTV ETVF	2 331 285 258	339 275 302	LNDQVTLL <mark>R</mark> Y LNDQVTLL <mark>R</mark> Y LNDQVTLL <mark>R</mark> Y	348 284 311	 	445 408 381	LELQI <mark>XI</mark> N LRLHI <mark>QS</mark> N LEFHI <mark>QA</mark> N	HPESSQ HPDDIF HPDAQY	LFAKLL LFPKLL LFPKLL	464 427 400
Pan troglodytes Mus musculus Rattus norvegicus Bos taurus Canius lupus Gallus gallus Danio rerio	ΡΡΑ Κγ	 	319 319 319 319 319 289 341	FQGCQFRSVEAVQ FQGCQFRSVEAVQ FQGCQFRSVEAVQ FQGCQFRSVEAVQ FQGCQFRSVEAVQ FQGCQFRSVEAVQ FHSYQSRSAEAIS	331 331 331 331 331 331 331 331 331 331 331 331 331 353	339 339 339 339 339 339 309 361	LNDQVTLINY LNDQVTLINY LNDQVTLINY LNDQVTLINY LNDQVTLINY LNDQVTLINY LNDQVTLINY	348 348 348 348 348 318 370	 	445 445 445 445 445 415 467	LELQL <mark>KI</mark> N LELQL <mark>KI</mark> N LELQL <mark>KI</mark> N LELQL <mark>KI</mark> N LELQL <mark>KI</mark> N LELQL <mark>KI</mark> N	HPESSQ HPESSQ HPESSQ HPESSQ HPESSQ HPESSQ HPDSLQ	LFAKLL LFAKVL LFAKVL LFAKLL LFAKLL LFAKVL	464 464 464 464 464 434 486
PPARγ THRα THRβ GR MR AR FXR VDR		 	319 224 278 569 775 710 297 236	FQGCQFRSVEAVQ FSEFTKIITPAIT FSHFTKIITPAIT MTTINMIGGRQVI LSTINRIAGKQMI LSSINFIGERQLV FLIITEMATNHVQ LPHIADIVSYSIQ	2 331 2 236 2 290 5 581 7 787 309 2309 2 248	339 244 298 589 795 730 317 256	LNDQVTLI X CEDQIILIXG CEDQIILIXG LDDQMTLIQY LEDQITLIQY VDDQMAVIQY HEDQIALIXG SEDQIVLIXS	348 253 307 598 804 739 326 265	··· ··· ··· ···	445 349 403 696 903 838 419 363	LELQL KI N FEHYU NH R FEHYI NY R LGKAIVIK LRKMVIK LDRIIACK LQKLCKIH LQTYIRCR	HPESSQ KHNIPH KHHVTH EGNSSQ PNNSGQ RKNPTS QPENPQ HPPPGSHL	LFAKLL FWPKLL FWPKLL NWQRFY SWQRFY CSRRFY HFACLL LYAKMI	464 468 422 716 922 857 438 384
HNF4α			184	VC SMKEOLI	196	204	LDDOVALIRA	213		310	LEDYINDR	OYDSRG	RFGELL	329





Supplemental figure 3. Cofactor peptide binding profiles for GST-PPARy LBD WT and L451P.

TS88135 1 39895460 A G GA 1 rs17386142 1 50815783 C T CC 2 rs11577194 1 10500175 T C CC 0 rs4846565 1 219722104 G A G GG 2 rs249105 2 65287896 A G AG 1 1 rs10196252 2 165513091 T C CT 1	Р	SNP	Chromosome	Position	Effect Allele	Other Allele	Genotype patient	Risk Allele score
	35	rs683135	1	39895460	A	G	GA	1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	6142	rs17386142	1	50815783	С	Т	СС	2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	7194	rs11577194	1	110500175	Т	С	CC	0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	291	rs9425291	1	172312769	A	G	GG	0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	565	rs4846565	1	219722104	G	А	GG	2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	105	rs2249105	2	65287896	Α	G	AG	1
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	5252	rs10195252	2	165513091	Т	C	СС	0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	00	s492400	2	219349752	Т	C	TT	2
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	645	s2943645	2	227099180	Т	C	CT	1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	71	rs308971	3	12116620	G	A	GG	2
rs295449 3 47375955 A G AG 1 rs11130329 3 52896855 A C AA 2 rs9881942 3 123082416 A G AG 1 rs645040 3 135926622 T G TT 2 rs2699429 4 3480136 C T CT 1 rs3822072 4 89741269 A G GG GA 1 rs4865796 5 53272664 A G AA 2 rs4976033 5 67714246 G A AG 1 rs4976033 5 118729286 C T T T 0 rs2434612 5 158022041 G A AG 1 rs4986544 5 173350405 G A AG 1 rs2434612 5 158022041 G AA 2 rs2434612 5 15803271	041	rs3864041	3	15185634	Т	С	CC	0
rs11130329 3 52896855 A C AA 2 rs9881942 3 123082416 A G AG 1 rs645040 3 135926622 T G TT 2 rs2699429 4 3480136 C T CT 1 rs3822072 4 89741269 A G GA 1 rs6822892 4 157734675 A G GG 0 rs459193 5 55806751 G A AG 1 rs682794 5 112711486 C T CT 1 rs6887914 5 112711486 C T T 1 rs1045241 5 118729286 C T T 1 rs12525532 6 35004819 T C CT 1 rs683738 6 139828916 G A AG 1 rs6937438 6 139828916 G A AG 1 rs2745553<	49	rs295449	3	47375955	Α	G	AG	1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0329	s11130329	3	52896855	А	C	AA	2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	942	s9881942	3	123082416	А	G	AG	1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	40	s645040	3	135926622	Т	G	TT	2
rs3822072489741269AGGGA1rs68228924157734675AGGG0rs4865796553272664AGAA2rs459193555806751GAAG1rs4976033567714246GAAG1rs68879145112711486CTCT1rs10452415118729286CTTT0rs24346125158022041GAAA1rs9665445173350405GAAA1rs12525532635004819TCCT1rs96937438643815364AGAA2rs27453536130398731CTCT1rs38613976139828916GAAG1rs17169104715883727GCCG0rs1011685819830769CTCC2rs74738141872469742GAAA0rs70059928126528955CGCG1rs102950411064869239GTTT0rs12316931163862612AGAG1rs12316931163862612AAAG0	429	s2699429	4	3480136	С	T	CT	1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	072	s3822072	4	89741269	А	G	GA	1
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rs4976033 5 67714246 G A AG 1 rs6887914 5 112711486 C T CT 1 rs1045241 5 118729286 C T TT 0 rs2434612 5 158022041 G A AG 1 rs966544 5 173350405 G A AA 1 rs12525532 6 35004819 T C CT 1 rs6937438 6 43815364 A G AA 2 rs2745353 6 127452935 T C TT 2 rs9492443 6 130398731 C T CT 1 rs3661397 6 139828916 G A AG 1 rs17169104 7 15883727 G C CG 1 rs2126259 8 9185146 T C CC 2 rs4738141 8 72469742 G A AA 0 rs4083	93	s459193	5	55806751	G	Ă	AG	1
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rs11231693 11 63862612 A G GG 0 rs17402950 12 14571671 G A AA	5441	s10995441	10	64869239	G	т	TT	0
rs17402950 12 14571671 G A AA O	1693	s11231693	11	63862612	A	G	GG	Ő
	2950	s17402950	12	14571671	G	Ā	AA	Ő
rs718314 12 26453283 G A AG 1	14	s718314	12	26453283	G	Â	AG	1
rs7973683 12 124449223 C A CC 2	683	s7973683	12	124449223	Ċ	A		2
rs7323406 13 111628195 A G GG 0	406	s7323406	13	111628195	Ā	G	GG	0
rs7176058 15 39464167 A G AG 1	058	s7176058	15	39464167	A	Ğ	AG	1
rs8032586 15 73081067 C T CG 1	586	s8032586	15	73081067	c	Ť	r.G	1
rs754814 17 4657034 T C CC 0	14	s754814	17	4657034	T	Ċ	CC CC	0
rs7227237 18 47174679 С т сс 2	237	s7227237	18	47174679	Ċ	Ť		2
rs8101064 19 7293119 T C C 0	064	s8101064	19	7293119	T	ċ		0
rs4804833 19 7970635 A G GG O	833	s4804833	19	7970635	Á	Ğ	66	õ
rs4804311 19 8615589 A G AA 2	311	s4804311	19	8615589	A	Ğ	ΔΔ	2
rs731839 19 33899065 G A AG 1	39	rs731839	19	33899065	G	Ă	AG	1
rs6066149 20 45602638 G A GG 2	149	s6066149	20	45602638	G	A	GG	2
rs132985 22 38563471 C T CC 2	85	s132985	22	38563471	c	Т		2
	-				-			53