Published in final edited form as:
Diabetes. 2005 May ; 54(5): 1598–1602.

Variations in Peptide YY and Y2 Receptor Genes Are Associated With Severe Obesity in Pima Indian Men

Lijun Ma, **P. Antonio Tataranni**, **Robert L. Hanson**, **Aniello M. Infante**, **Sayuko Kobes**, **Clifton Bogardus**, and **Leslie J. Baier**
From the Diabetes Molecular Genetics Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Phoenix, Arizona.

Abstract

Peptide YY (PYY) and Y2 receptor (Y2R) may be important in the central regulation of body weight and food intake. To determine whether genetic variation in *PYY* and/or *Y2R* may contribute to morbid obesity in humans, these genes were sequenced in 83 extremely obese Pima Indians (BMI ≥50 kg/m^2). Sequencing of *PYY* identified three single nucleotide polymorphsms (SNPs) in the untranslated region. Sequencing of the *Y2R* coding region identified one missense (Ala172Thr) substitution and two silent substitutions. Eight additional SNPs in the 5′ untranslated region of *Y2R* were identified from public databases. These SNPs were genotyped in 489 full-heritage adult Pimas (362 severely obese and 127 non-diabetic, nonobese subjects), who are not first-degree relatives, for association analysis. The *PYY* variants were not associated with obesity, whereas four variants from two haplotype blocks in *Y2R* were marginally associated (P = 0.054–0.067) with obesity. However, if the analysis was restricted to men (n = 167, 100 obese and 67 lean), the *PYY* variants and two SNPs in *Y2R* that were in complete linkage disequilibrium were significantly associated with severe obesity (P = 0.001 and P = 0.002, respectively). Our data suggest that the PYY-Y2R pathway may influence body weight through a sex-specific mechanism, but this finding requires confirmation in other populations.

Peptide YY (PYY), a member of the neuropeptide Y (NPY) family, is a 36–amino acid peptide secreted from the L-cells of the gastrointestinal tract in response to food intake (1,2). It has been suggested that PYY plays a role in the development of obesity in rodents, but this remains controversial. Peripheral administration of PYY was first reported to decrease food intake in rodents in 1993 (3). PYY3-36, the active form of PYY, also markedly inhibits food intake in rodents (2), and it has been shown to cross the blood-brain barrier and act on the arcuate nucleus of the hyperthalamus (4,5). PYY3-36 has a high affinity for the Y2 receptor (Y2R) (2,6), and animal studies have shown that PYY3-36 inhibits hypothalamic NPY-expressing neurons by binding to Y2R (7). Mice lacking the *Y2R* gene have increased body weight, food intake, and fat deposition (8). In contrast to these studies, Tschöp et al. (9) recently reported that PYY3-36 does not decrease food intake in rodents.

It has also been suggested that the PYY/Y2R pathway plays a role in human obesity. Peripheral administration of PYY3-36 was reported to inhibit food intake in humans (10), and plasma PYY concentrations were decreased in obese compared with lean subjects (10). In addition,

Address correspondence and reprint requests to Leslie J. Baier, PhD, Diabetes Molecular Genetics Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 4212 North 16th St., Phoenix, AZ 85016, E-mail:lbaier@phx.niddk.nih.gov..

Additional information for this article can be found in an online appendix at http://diabetes.diabetesjournals.org.

NPY, neuropeptide Y; PYY, peptide YY; SNP, single nucleotide polymorphism; Y2R, Y2 receptor.

two synonymous amino acid substitutions have been identified in Y2R that are associated with obesity in British Caucasian men (11).

The Pima Indians of Arizona have a high prevalence of severe obesity, and BMI in this population is highly heritable (12,13). As part of our genetic studies to identify variation in genes that affect body weight in this Native-American population, *PYY* and *Y2R* were analyzed as obesity candidate genes. These genes were sequenced to detect variation in a group of 83 extremely obese Pima Indians, and variants were analyzed for association with obesity in a case/control study.

The human *PYY* gene (NCBI accession no. NM_004160) on chromosome 17q21.1 is composed of four exons and three introns that span 1.2 kb. Three variants were detected by sequencing the *PYY* gene in 83 extremely obese Pima Indian subjects (BMI from 50.5 to 79.6 kg/m^2) (Table 1). Two novel variants were positioned in the 5′ upstream flanking region, a C/T at −1746 bp (single nucleotide polymorphism [SNP]1) and a G/C at −1653 bp (SNP2), relative to the transcriptional start site. These two variants were in complete genotypic concordance among the 83 subjects and had a major allele frequency of 0.55. The third variant was a previously identified C/T in intron 3 (SNP3; rs162430), which was in tight linkage disequilibrium with SNP1/2 ($D' = 0.9999$, $\Delta^2 = 0.9999$). SNP1 (as the representative SNP for SNPs 1 and 2; SNP1/2) and SNP3 were genotyped in the case/control group of 489 full heritage, non–first-degree–related adult Pima Indians (Table 2) for association analysis. Genotypes of SNP1 and SNP3 were in Hardy-Weinberg equilibrium when analyzed in the case, control, and combined groups, respectively (Table 1). The allele frequency of these two SNPs did not differ between the case and control group (Table 3). However, since several obesity genes in animal models have sex-specific effects, the analysis was repeated in men and women separately. In the gender-restricted analysis, SNP1/2 and SNP3 were associated with severe obesity in men ($n = 167$, 100 obese and 67 lean; $P = 0.001$) using a logistic regression full model (Table 3).

The human *Y2R* gene (NCBI accession no. U36269) on chromosome 4q31 consists of two exons that span 4.5 kb. Three variants were detected by sequencing the coding region of *Y2R* in the same 83 extremely obese subjects described above (Table 1). A G/A polymorphism, predicting an alanine-to-threonine substitution, was identified at codon 172 (Ala172Thr; SNP9). Two additional variants, both C/T predicting a silent (isoleucine) substitution, were identified at codons 195 and 312 (SNP10 and SNP11, respectively). These three coding SNPs and eight additional variants (SNPs 1–8, across 34 kb) (Table 1), located in the 5′ untranslated region that was identified in the dbSNP (http://www.ncbi.nlm.nih.gov) and/or Celera databases (http://abassays.celera.com), were genotyped in the 489 case/control subjects. SNP10 and SNP11 (SNP10/11) were found to be in perfect genotypic concordance among the 489 case/control samples and therefore provided identical information. Genotypes of these 11 SNPs were in Hardy- Weinberg equilibrium in the case, control, and combined groups, except for SNP10/11, which deviated modestly in the control group ($P = 0.04$) (Table 1). SNPs 6, 7, and 10/11 in *Y2R* were marginally associated ($P = 0.054$–0.067) with severe obesity (Table 3). However, when the analysis was restricted by gender, SNP10/11 was significantly associated with severe obesity in men ($P = 0.002$) (Table 3).

To better understand the underlying genetic models for these associations, logistic regression analyses were also applied to the entire case/control group, and the gender-restricted groups in different genetic models (Table 3). The *PYY* variants (SNP1/2 and SNP3) appear to function under a dominant model, where men with the major allele (both homozygotes and heterozygotes) were more prevalent in the obese group, and men homozygous for the minor allele tended to be in the lean group ($P = 0.001$–0.002, odds ratio [OR] > 3.5). Variants in *Y2R* (SNPs 3, 6, and 7 in 5′ region, SNPs 10 and 11 in exon 2) were associated with severe obesity under a recessive model (Table 3). The strongest association in men was with

SNP10/11, where men homozygous for the C allele tended to be in the lean group, and men homozygous or heterozygous for the *T* allele tended to be more prevalent in the obese group ($P = 0.001$, $0.33 < OR < 0.4$).

A statistically significant interaction of genotype with sex was observed for several of these SNPs in both genes (*PYY* SNP1/2 and SNP3, $P = 0.001$ in dominant model; *Y2R* SNP10/11, $P = 0.018$ in recessive model) (online appendix Table 4 [available at http://diabetes.diabetesjournals.org]).

The genotypic information from 11 variants (SNPs 1–11) in *Y2R* was used to determine the haplotype structure of this gene (Fig. 1). Three haplotype blocks were identified. *Y2R* SNPs 2–4 represent the first haplotype block, SNPs 5–7 represent the second block, and SNPs 8–11 represent the third haplotype block. SNP9, the only coding missense substitution identified in *Y2R*, which was physically located in the third block, had a minor allele frequency that was too low for confident assignment to any haplotype block. In the association analysis, at least one variant in each of the three haplotype blocks of *Y2R* was modestly associated with severe obesity, but variants in the third haplo-type block (SNP10/11) show a greater difference in men.

The finding of associations between variants in *PYY* and *Y2R* and severe obesity was unexpected in men only and may represent false-positive associations. However, a recent study by Hung et al. (11) on the PYY-Y2R pathway in British Caucasians also described an association between *Y2R* SNPs and human obesity with two SNPs identical to these significant SNPs detected in our current study (SNP10/11, rs1047214 [nt585C/T], and rs2880415 [nt936C/T]), and this association was only present in men. They found that men homozygous for the C allele of SNP rs1047214 had lower BMI than men homozygous or heterozygous for the T allele in British Caucasians ($P = 0.017$) (11), and rs2880415 was almost in complete genotypic concordance with rs1047214 (11). These findings are consistent with our results in Pima Indians. Therefore, it is possible that *PYY* or *Y2R*, or a different gene in the pathway that is activated by their interaction, is hormonally controlled. For example, *NPY* (a family member of PYY) expression is increased in male sheep in a testosterone-dependent manner (14), and testosterone also contributes to age-related changes of *NPY* expression (15). Since PYY belongs to the same family as NPY, it is possible that PYY also has a sex hormone–regulated element or other indirect hormone-controlled factor regulatory sites. Based on the sequence analysis of the *PYY* putative promoter by MatInspector (release professional 7.2.2, http://www.genomatix.de), *PYY* SNP1 (PYY-1746) is located in the anchor site of the ribonucleoprotein-associated zinc finger protein (MOK-2) binding region, and *PYY* SNP2 (PYY-1653) is located in the c-Myb/v-Myb core binding region. MOK-2 is preferentially expressed in testis tissue (16), providing a plausible mechanism for sex-specific expression of *PYY*. c-Myb is a transcription factor expressed in the hematopoietic system and the gastrointestinal tract that regulates the exquisite balance among cell division, differentiation, and survival (17). Androgen can influence the c-Myb expression level in mice (18); therefore, c-Myb binding could also potentially regulate *PYY* expression in a sex-dependent manner.

A third explanation for our association to be observed only in men is that more significant, female-specific obesity genes mask the contribution of *PYY* and *Y2R* to obesity in women. For example, female-specific effects on BMI and/or obesity-related traits have been reported for variants in several genes, including *resistin* (19), *UCP3* (20), and *FOXC2* (21,22).

As the present association was detected in a case/control study of extremely discordant individuals, the significance of these findings on the population basis is not yet clear. Further genetic analysis of *PYY* and *Y2R* in other populations should help clarify the biological importance of these genes in the development of severe human obesity.

RESEARCH DESIGN AND METHODS

The subjects are part of an ongoing longitudinal study of the etiology of obesity and type 2 diabetes among the Gila River Indian Community in central Arizona. Eighty-three extremely obese Pima subjects (37 men and 46 women, BMI 60.0 ± 6.1 kg/m^2 [range 50.5–79.6 kg/m^2], age 35.0 ± 9.5 years [means ± SD]), who were not first-degree relatives, were selected for sequence analysis of the *PYY* and *Y2R* genes. Unique variants in *PYY* and *Y2R* were genotyped in 489 full-heritage adult Pima Indians (who were not first-degree relatives) for association analyses, where 362 subjects were severely obese, as defined by a maximum BMI >45 kg/m^2, and 127 subjects were nonobese control subjects as defined by BMI <30 kg/m^2 at >35 years of age and not having diabetes. Diabetic status was determined by the criteria of the World Health Organization (23). The 83 obese subjects who were used for sequence analysis were part of the 362 obese subjects who were genotyped for association studies.

Sequence variant identification and genotyping

Genomic DNA for sequencing and genotyping was obtained from peripheral lymphocytes. Sequence analysis of *PYY* included the entire four exons and three introns (1.2 kb), and 2 kb of the 5′ untranslated region. Sequence analysis of *Y2R* included only the coding region. The 5′ untranslated region of *Y2R* was not directly sequenced due to its large size (~34 kb, http://www.ncbi.nlm.nih.gov), but all SNPs in this region that were available in the NCBI public database (http://www.ncbi.nlm.nih.gov) were genotyped. Sequencing of DNA from 83 subjects was done using Big Dye terminator (Applied Biosystems, Foster City, CA) on an automated DNA capillary sequencer (model 3730; Applied Biosystems). Variants identified by direct sequencing or by searching databases were genotyped in DNA from 489 subjects using the TaqMan Allelic Discrimination Assay (Applied BioSystems). The TaqMan genotyping reaction was amplified on a GeneAmp PCR system 9700 (95°C for 10 min, followed by 40 cycles of 95°C for 30 s and 60°C for 1 min 30 s), and fluorescence was detected on an ABI Prism 7700 (Applied BioSystems). Sequence information for all oligonucleotide primers and probes is available upon request.

Statistical analysis

Statistical analyses were performed using SAS Institute (Cary, NC) software. Age and BMI are expressed as means ± SD. Differences of genotype frequencies were assessed with logistic regression between the lean and obese groups. For logistic regression modeling in the additive model, homozygotes for the major allele (aa) and heterozygotes (ab) and homozygotes for the minor allele (bb) were coded to a continuous numeric variable for genotype (0, 1, and 2). A dominant model was defined as contrasting genotypic groups aa + ab versus bb, and the recessive model was defined as contrasting genotypic groups aa versus ab + bb. Product terms were used to assess the interaction between genotype and sex. To examine pairwise linkage disequilibrium, haplotype frequencies were estimated with the EH program (Xie and Ott, http://linkage.rockefeller.edu/ott/eh.htm), and these haplotype frequencies were used to calculate D-prime and Δ^2. HaploView was used to place SNPs in haplotype blocks. The confidence interval method (24) was applied to define blocks (http://www.broad.mit.edu/personal/jcbarret/haploview/). *P* values < 0.05 were considered statistically significance.

Acknowledgements

The authors thank Dr. Michal Prochazka for his critical reading of this manuscript.

References

1. Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterolog 1985;89:1070–1077.

2. Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 2002;418:650–654. [PubMed: 12167864]

3. Okada S, Ohshima K, Mori M, Takemoto K: Peripheral not central administration PYY decreased high fat diet intake (Abstract 180). In *Program of the 75th Annual Meeting of the Endocrine Society, 1993, Las Vegas, NV*

4. Nonaka N, Shioda S, Niehoff ML, Banks WA. Characterization of blood-brain barrier permeability to PYY3-36 in the mouse. J Pharmacol Exp Ther 2003;306:948–953. [PubMed: 12750431]

5. Challis BG, Pinnock SB, Coll AP, Carter RN, Dickson SL, O'Rahilly S. Acute effects of PYY3-36 on food intake and hypothalamic neuropeptide expression in the mouse. Biochem Biophys Res Commun 2003;311:915–919. [PubMed: 14623268]

6. Grandt D, Schimiczek M, Rascher W, Feth F, Shively J, Lee TD, Davis MT, Reeve JR Jr, Michel MC. Neuropeptide Y 3-36 is an endogenous ligand selective for Y2 receptors. Regul Pept 1996;67:33–37. [PubMed: 8952003]

7. Korner J, Leibel RL. To eat or not to eat: how the gut talks to the brain. N Engl J Med 2003;349:926–928. [PubMed: 12954739]

8. Naveilhan P, Hassani H, Canals JM, Ekstrand AJ, Larefalk A, Chhajlani V, Arenas E, Gedda K, Svensson L, Thoren P, Ernfors P. Normal feeding behavior, body weight and leptin response require the neuropeptide Y Y2 receptor. Nat Med 1999;5:1188–1193. [PubMed: 10502824]

9. Tschöp M, Castaneda TR, Joost HG, Thone-Reineke C, Ortmann S, Klaus S, Hagan MM, Chandler PC, Oswald KD, Benoit SC, Seeley RJ, Kinzig KP, Moran TH, Beck-sickinger AG, Koglin N, Rodgers RJ, Blundell JE, Ishii Y, Beattie AH, Holch P, Allison DB, Raun K, Madsen K, Wulff BS, Stidsen CE, Birringer M, Kreuzer OJ, Schindler M, Arndt K, Rudolf K, Mark M, Deng XY, Withcomb DC, Halem H, Taylor J, Dong J, Datta R, Culler M, Craney S, Flora D, Smiley D, Heiman ML. Physiology: does gut hormone PYY3-36 decrease food intake in rodents? Nature 2004;430:165. [PubMed: 15241404]

10. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med 2003;349:941–948. [PubMed: 12954742]

11. Hung CC, Pirie F, Luan J, Lank E, Motala A, Yeo GS, Keogh JM, Wareham NJ, O'Rahilly S, Farooqi IS. Studies of the peptide YY and neuropeptide Y2 receptor genes in relation to human obesity and obesity-related traits. Diabetes 2004;53:2461–2466. [PubMed: 15331560]

12. Baier LJ, Hanson RL. Genetic studies of the etiology of type 2 diabetes in Pima Indians: hunting for pieces to a complicated puzzle. Diabetes 2004;53:1181–1186. [PubMed: 15111484]

13. Ravussin E, Bogardus C. Energy expenditure in the obese: is there a thrifty gene? Infusionstherapie 1990;17:108–112. [PubMed: 2191919]

14. Dobbins A, Lubbers LS, Jackson GL, Kuehl DE, Hileman SM. Neuropeptide Y gene expression in male sheep: influence of photoperiod and testosterone. Neuroendocrinology 2004;79:82–89. [PubMed: 15004430]

15. Sohn EH, Wolden-Hanson T, Matsumoto AM. Testosterone (T)-induced changes in arcuate nucleus cocaine-amphetamine-regulated transcript and NPY mRNA are attenuated in old compared with young male brown Norway rats: contribution of T to age-related changes in cocaine-amphetamine-regulated transcript and NPY gene expression. Endocrinology 2002;143:954–963. [PubMed: 11861518]

16. Arranz V, Kress M, Ernoult-Lange M. The gene encoding the MOK-2 zinc-finger protein: characterization of its promoter and negative regulation by mouse Alu type-2 repetitive elements. Gene 1994;149:293–298. [PubMed: 7959005]

17. Ramsay RG, Barton AL, Gonda TJ. Targeting c-Myb expression in human disease. Expert Opin Ther Targets 2003;7:235–248. [PubMed: 12667100]

18. Toda I, Sullivan BD, Wickham LA, Sullivan DA. Gender- and androgen-related influence on the expression of proto-oncogene and apoptotic factor mRNAs in lacrimal glands of autoimmune and non-autoimmune mice. J Steroid Biochem Mol Biol 1999;71:49–61. [PubMed: 10619357]

19. Mattevi VS, Zembrzuski VM, Hutz MH. A resistin gene polymorphism is associated with body mass index in women. Hum Genet 2004;115:208–212. [PubMed: 15221446]

20. Damcott CM, Feingold E, Moffett SP, Barmada MM, Marshall JA, Hamman RF, Ferrell RE. Genetic variation in uncoupling protein 3 is associated with dietary intake and body composition in females. Metabolism 2004;53:458–564. [PubMed: 15045692]

21. Ridderstrale M, Carlsson E, Klannemark M, Cederberg A, Kosters C, Tornqvist H, Storgaard H, Vaag A, Enerback S, Groop L. FOXC2 mRNA Expression and a 5′ untranslated region polymorphism of the gene are associated with insulin resistance. Diabetes 2002;51:3554–3560. [PubMed: 12453913]

22. Kovacs P, Lehn-Stefan A, Stumvoll M, Bogardus C, Baier LJ. Genetic variation in the human winged helix/forkhead transcription factor gene FOXC2 in Pima Indians. Diabetes 2003;52:1292–1295. [PubMed: 12716768]

23. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)

24. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D. The structure of haplotype blocks in the human genome. Science 2002;296:2225–2229. [PubMed: 12029063]

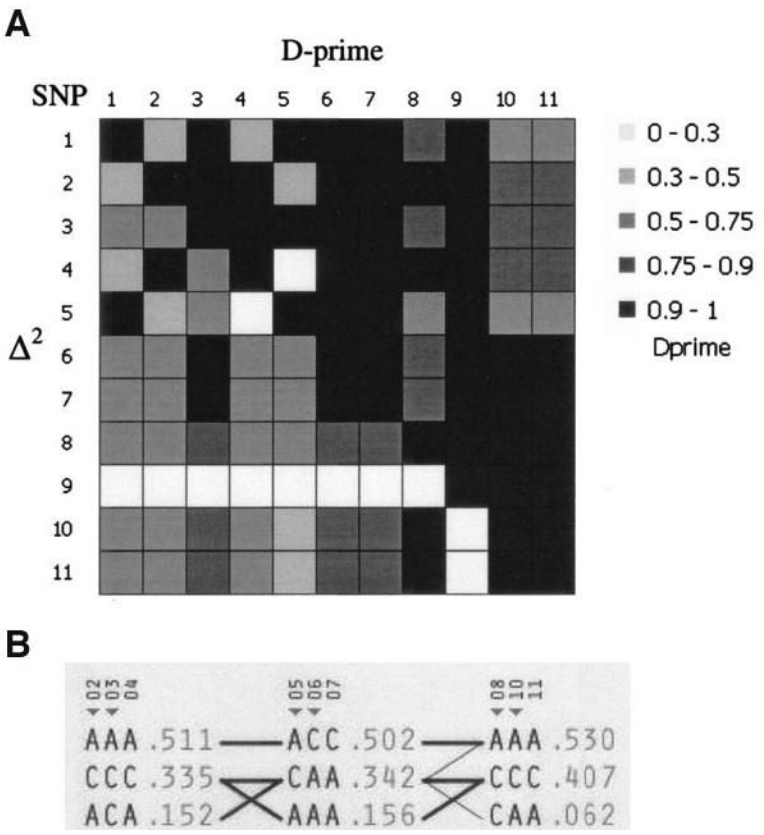

FIG 1.

A: D′ and Δ^2 matrix for 11 SNPs identified in *Y2R* gene. D′ is defined as a measure of allelic association and Δ^2 as a measure of concordance (http://www.meb.ki.se/genes-tat/tl/). *B*: Haplotype structure and diversity of *Y2R* gene. Haplotype blocks and their frequencies were estimated using an accelerated EM algorithm. A, major allele; C, minor allele. ▼, tag SNPs that designate a parsimonious haplotype for each block. Thick line, frequency ≥10%; thin line, frequency between 1 and 10%.

TABLE 1

Markers and map locations

Gene	SNP marker no.	Marker	SNP	Major allele frequency*	SNP type	Hardy-Weinberg equilibrium (*P*)			NCBI location (bp) ‡	Intermarker interval (bp)
						Case/ control combined	Case group (*n* = 362)	Control group (*n* = 127)		
PYY 17q21	1	PYY-1746	C/T	0.522/0.549†	5′ flank	0.86	0.64	0.67	42508208	93
	2	PYY-1653	G/C	0.549†	5′ flank	—	—	—	42508115	2,541
	3	rs162430	C/T	0.521	Intron 3	0.86	0.68	0.72	42505574	—
Y2R 4q31	1	rs2880414	G/T	0.714	5′ UTR	0.21	0.10	0.73	156671278	13,585
	2	rs4425326	C/T	0.663	5′ UTR	0.63	0.44	0.75	156684863	4,743
	3	rs2880412	A/C	0.509	5′ UTR	0.67	0.18	0.17	156689606	874
	4	rs10517606	A/C	0.667	5′ UTR	0.43	0.30	0.85	156690480	11,690
	5	rs2880416	C/G	0.657	5′ UTR	0.47	0.14	0.25	156702170	375
	6	rs2342675	A/G	0.504	5′ UTR	0.75	0.17	0.11	156702550	4,259
	7	rs6857715	C/T	0.501	5′ UTR	0.82	0.22	0.12	156706809	1,822
	8	rs10461257	A/G	0.529	Intron	0.66	0.23	0.27	156708631	4,601
	9	A172T	G/A (A172T)	0.985	Exon 2	0.74	0.79	0.85	156713232	71
	10	rs1047214	C/T (Ile195)	0.592	Exon 2	0.42	0.77	0.04	156713303	351
	11	rs2880415	C/T (Ile312)	0.592	Exon 2	0.42	0.77	0.04	156713654	—

*Major allele frequencies were obtained from severely obese case/control sample (*n* = 489).

†Major allele frequency obtained from 83 original extremely obese subjects for variation detection. Genotypes of PYY SNP2 assumed to be identical to PYY SNP1 based on direct sequencing of these 83 subjects.

‡NCBI builder 34.3.

TABLE 2

Characteristics of Pima subjects in severely obese and nonobese case/control groups

	Severely obesity	Nonobese control	*P* value between groups
n (M/F)	362 (100/262)	127 (67/60)	< 0.0001
Age (years)*	36.3 ± 11.0 (33.9 ± 11.1 M/37.1 ± 10.9 F)	40.4 ± 5.0 (41.4 ± 5.0 M/39.4 ± 4.9 F)	< 0.0001
Maximum BMI (kg/m^2)	51.7 ± 6.2 (51.1 ± 5.5 M/52.0 ± 6.4 F)	26.3 ± 2.7 (26.5 ± 2.4 M/26.1 ± 2.9 F)	< 0.0001

Age and BMI are expressed as means ± SD.

*Age at maximum BMI.

Diabetes. Author manuscript; available in PMC 2006 January 25.

TABLE 3

Association of *PYY* and *Y2R* gene SNPs with severe obesity under logistic regression analyses

					Logistic regression						
		Full model			Additive model			Dominant model			
Gene	**SNP marker no.**	**All**[a]	**Men**	**Women**	**All**[a]	**Men**	**Women**	**All**[a]	**Men**	**Women**	**All**[a]
PYY	1/2[*]	0.745	**0.001**	**0.038**	0.505	0.160	0.679	0.443	**0.002**[4]	0.077	0.737
	3	0.639	**0.001**	**0.020**	0.359	0.161	0.939	0.377	**0.001**[4]	0.097	0.533
Y2R	1	0.387	0.160[b]	1.00[b]	0.501	0.378	0.915	0.614	0.544[b]	1.00[b]	0.275
	2	0.356	0.181	0.540	0.174	0.261	0.418	0.530	0.842	0.298	0.154
	3	0.127	0.069	0.793	0.164	0.131	0.645	0.802	0.762	0.960	**0.046**[1]
	4	0.491	0.201	0.616	0.272	0.342	0.538	0.668	0.709	0.351	0.233
	5	0.117	0.293	0.379	0.282	0.360	0.535	0.618	0.814	0.642	0.080
	6	0.054	0.110	0.385	0.084	0.173	0.280	0.681	0.788	0.755	**0.016**[1]
	7	0.067	0.141	0.387	0.086	0.189	0.264	0.631	0.761	0.707	**0.020**[1]
	8	0.203	0.054	0.948	0.180	0.054	0.958	0.726	0.459	0.810	0.075
	9	0.942	0.637[b]	1.00[b]	0.726	0.637[b]	1.00[b]	—	—	—	0.726
	10	0.062	**0.002**	0.997	0.096	**0.019**[1]	0.979	0.813	0.714	0.981	**0.023**[1]
	11	0.062	**0.002**	0.997	0.096	**0.019**[1]	0.979	0.813	0.714	0.981	**0.023**[1]

Detailed information for OR and genotypes in case/control groups is available in online appendix Table 3. Sex-by-genotype interaction was detected and is shown in online appendix Table 4.

[*] Information derived from genotyping of SNP1 (assumed to be identical for SNP2).

[a] *P* values adjusted for sex;

[b] exact *P* values assessed by Fisher's test due to rare alleles. *P* values < 0.05 are in bold. Numbers labeled for significant *P* values refer to OR ranks as 1 (0.5 < OR < 0.67), 2 (0.4 < OR < 0.5), 3 (0.33 < OR < 0.4), and 4 (OR > 3.5).