

Brief Genetics Report

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

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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/m²). Sequencing of *PYY* identified three single nucleotide polymorphisms (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. *Diabetes* 54:1598–1602, 2005

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. Periph-

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

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eral 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 hypothalamus (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, 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/m²) (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

TABLE 1
Markers and map locations

Gene	SNP marker no.	Marker	SNP	Major allele frequency*	SNP type	Hardy-Weinberg equilibrium (<i>P</i>)			NCBI location (bp)‡	Intermarker interval (bp)
						Case/control combined	Case group (<i>n</i> = 362)	Control group (<i>n</i> = 127)		
<i>PYY</i> 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	—
<i>Y2R</i> 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.

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*

TABLE 2
Characteristics of Pima subjects in severely obese and nonobese case/control groups

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

Age and BMI are expressed as means ± SD. *Age at maximum BMI.

TABLE 3
Association of PYY and Y2R gene SNPs with severe obesity under logistic regression analyses

Gene	SNP marker no.	Logistic regression												Total n
		Full model			Additive model			Dominant model			Recessive model			
		All ^a	Men	Women	All ^a	Men	Women	All ^a	Men	Women	All ^a	Men	Women	
PYY	1/2*	0.745	0.001	0.038	0.505	0.160	0.679	0.443	0.002 ⁴	0.077	0.737	0.516	0.264	489
	3	0.639	0.001	0.020	0.359	0.161	0.939	0.377	0.001 ⁴	0.097	0.533	0.501	0.120	485
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	0.135	0.903	476
	2	0.356	0.181	0.540	0.174	0.261	0.418	0.530	0.842	0.298	0.154	0.099	0.678	477
	3	0.127	0.069	0.793	0.164	0.131	0.645	0.802	0.762	0.960	0.046 ¹	0.026 ²	0.504	473
	4	0.491	0.201	0.616	0.272	0.342	0.538	0.668	0.709	0.351	0.233	0.130	0.814	473
	5	0.117	0.293	0.379	0.282	0.360	0.535	0.618	0.814	0.642	0.080	0.163	0.269	467
	6	0.054	0.110	0.385	0.084	0.173	0.280	0.681	0.788	0.755	0.016 ¹	0.043 ²	0.161	487
	7	0.067	0.141	0.387	0.086	0.189	0.264	0.631	0.761	0.707	0.020 ¹	0.055	0.161	487
	8	0.203	0.054	0.948	0.180	0.054	0.958	0.726	0.459	0.810	0.075	0.017 ²	0.889	476
	9	0.942	0.637 ^b	1.00 ^b	0.726	0.637 ^b	1.00 ^b	—	—	—	0.726	0.637 ^b	1.00 ^b	474
	10	0.062	0.002	0.997	0.096	0.019 ¹	0.979	0.813	0.714	0.981	0.023 ¹	0.001 ³	0.955	486
11	0.062	0.002	0.997	0.096	0.019 ¹	0.979	0.813	0.714	0.981	0.023 ¹	0.001 ³	0.955	486	

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). ^aP values adjusted for sex; ^bexact 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).

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 haplotype 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

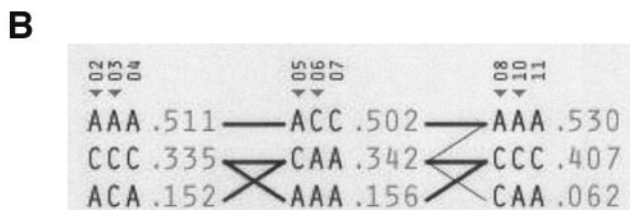
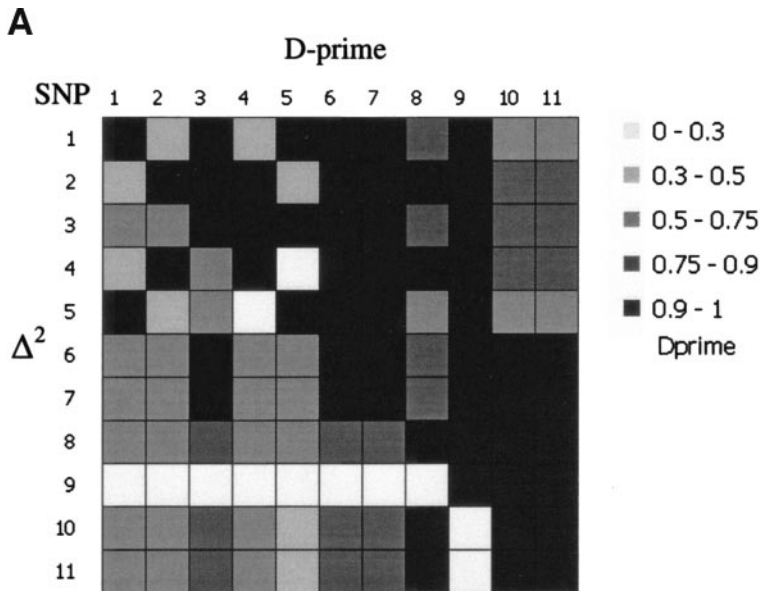


FIG 1. A: D' and Δ^2 matrix for 11 SNPs identified in Y2R gene. D' is defined as a measure of allelic association and Δ^2 as a measure of concordance (<http://www.meb.ki.se/genestat/tl/>). B: Haplotype structure and diversity of Y2R gene. Haplotype blocks and their frequencies were estimated using an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

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/m² [range 50.5–79.6 kg/m²], age 35.0 ± 9.5 years [means \pm 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/m², and 127 subjects were nonobese control subjects as defined by BMI <30 kg/m² 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 \pm 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.

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