

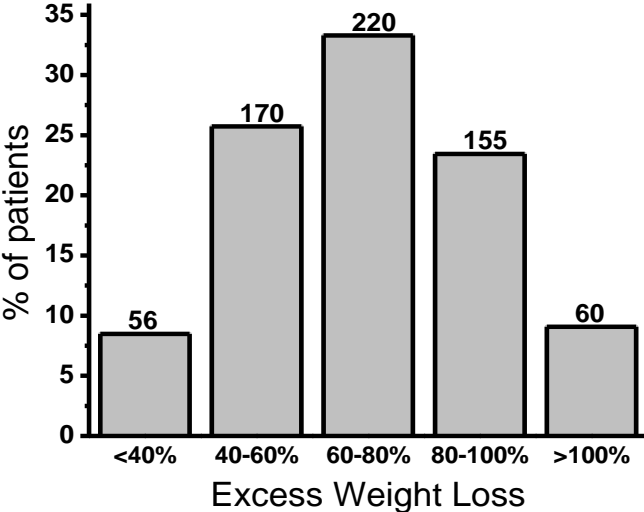
Supplemental Material

Supplemental References

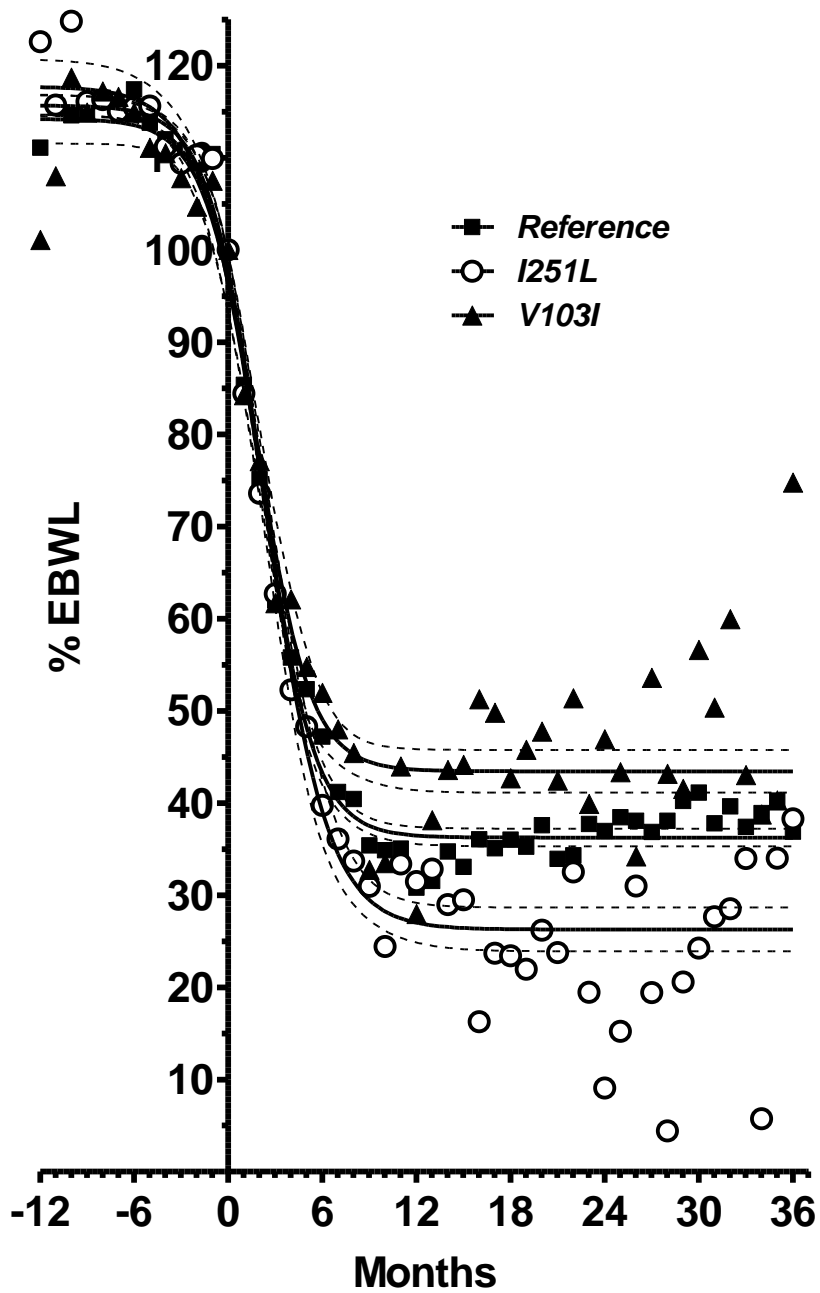
Chu X, Erdman R, Susek M, Gerst H, Derr K, Al-Agha M, Wood GC, Hartman C, Yeager S, Blosky MA, Krum W, Stewart WF, Carey D, Benotti P, Still CD, Gerhard GS (2008) Association of morbid obesity with FTO and INSIG2 allelic variants. *Arch Surg (United States)* 143:235-40

Gerhard GS, Langer RD, Carey DJ, Stewart WF (2010) Electronic medical records in genomic medicine practice and research. In: *Genomic and personalized medicine* (Ginsburg, GS and Willard HF, ed), pp142-151. Academic Press/Elsevier.

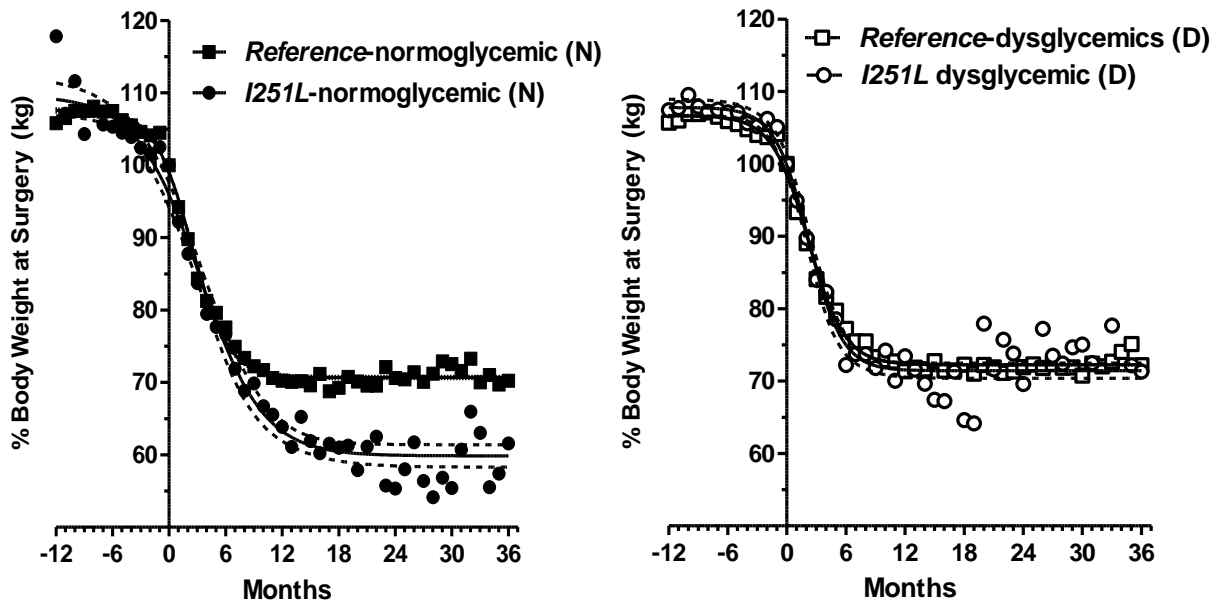
Supplemental Figures & Tables



Supplemental Figure 1. Weight loss in RYGB patients 24 ± 3 months after surgery. Number of patients in each group is indicated above the bars.



Supplemental Figure 2. Weight loss in patients undergoing RYGB stratified by *MC4R* genotype expressed as percent excess body weight loss (EBWL). Excess body weight is defined based an idealized BMI of 25 kg/m².



Supplemental Figure 3. Post-RYGB weight loss stratified by diabetic status for *Reference* and *I251L* allele carriers. Weight loss reported as %kg at surgery is shown for the two groups based on pre-surgery diabetic status.

Supplemental Table 1.Study cohorts (Means \pm SEM).

	Obese (RYGB)	Lean (Control)
Number of subjects	1433	451
Average BMI	46.6 \pm 0.001	23.1 \pm 0.001
Average age	45.8 \pm 0.002	49.5 \pm 0.02
% Female	79.9	68.5

Supplemental Table 2.

Cohort allele frequency and odd ratios (95% confidence intervals).

Genotype	Obese	Control	Odd Ratios (95% CI)
<i>V103I</i>	36/1433 (2.5%)	18/451 (4.0%)	0.62 (0.35-1.10)
<i>I251L</i>	26/1433 (1.8%)	6/451 (1.3%)	1.37 (0.56-3.35)

One of the subjects in the obese group was homozygous for V103I allele. Two-sided p values for allele frequency between the obese and control groups for V103I and I251L are 0.1 and 0.7, respectively (Fisher's exact test).

Supplemental Table 3.Obese cohort stratified by genotype (Means \pm SEM).

	Reference	I251L	V103I
Subjects (n)	1353	26	36
Female (n)	1077	23	28
Age (years)	46 \pm 0.3	47 \pm 2	46 \pm 2
BMI (kg/m²)	47 \pm 0.2	47 \pm 2	48 \pm 2
Ethnicity (n)			
White/Caucasian	1283	26	32
Black/African-American	27		1
Hispanics	12		
Other	1		
Data not collected	33		3

Supplement Table 4.

Diabetic status of study cohort

	Reference	I251L
Total (n)	1269	25
Dysglycemics [§] , n (%)	776 (62)	14 (56)

[§] Dysglycemics (Diabetics and pre-diabetics) were identified as those with Hb_{A1c} \geq 6.0 or taking therapy (biguanides, insulin, insulin-sensitizing agents, sulfonylureas) at time of surgery.

Supplemental Table 5.Additional Clinical Parameters at Time of Surgery: Mean \pm SEM (n)

		<i>Reference</i>	<i>I251L</i>	P value[¥]
ALT (units/L)	Total	31 \pm 0.7 (810)	23 \pm 2 (19) **	0.001
	Normoglycemic [§]	29 \pm 0.7 (500)	23 \pm 3 (12)	0.2
	Dysglycemic [§]	33 \pm 1 (310) ##	23 \pm 1 (7) ***	0.0001
AST (units/L)	Total	26 \pm 1 (808)	22 \pm 1 (19) ***	0.0005
	Normoglycemic	25 \pm 1 (498)	21 \pm 2 (12)	0.05
	Dysglycemic	29 \pm 1 (310) ##	22 \pm 1 (7) ***	0.0002
Alkaline Phosphatase (units/L)	Total	79 \pm 1 (809)	84 \pm 5 (19)	0.3
	Normoglycemic	78 \pm 1 (499)	85 \pm 7 (12)	0.2
	Dysglycemic	80 \pm 2 (310)	82 \pm 7 (7)	0.8
Triglyc. (mg/dL)	Total	168 \pm 3 (811)	148 \pm 12 (19)	0.2
	Normoglycemic	153 \pm 4 (499)	138 \pm 12 (12)	0.2
	Dysglycemic	191 \pm 7 (312) ###	167 \pm 29 (7)	0.6
Chol. (mg/dL)	Total	190 \pm 1 (813)	202 \pm 7 (19)	0.2
	Normoglycemic	190 \pm 2 (499)	201 \pm 9 (12)	0.3
	Dysglycemic	191 \pm 2 (314)	205 \pm 12 (7)	0.3
LDL (mg/dL)	Total	110 \pm 1 (802)	123 \pm 8 (19)	0.07
	Normoglycemic	112 \pm 1 (495)	123 \pm 10 (12)	0.2
	Dysglycemic	108 \pm 2 (307) #	124 \pm 15 (7)	0.2
HDL (mg/dL)	Total	47 \pm 0.4 (811)	49 \pm 3 (19)	0.5
	Normoglycemic	48 \pm 0.5 (499)	50 \pm 4 (12)	0.4
	Dysglycemic	47 \pm 0.7 (312)	48 \pm 5 (7)	0.7
Chol/HDL ratio	Total	4.3 \pm 0.08 (811)	4.4 \pm 0.3 (19)	0.8
	Normoglycemic	4.3 \pm 0.12 (499)	4.2 \pm 0.3 (12)	0.9
	Dysglycemic	4.3 \pm 0.07 (312)	4.5 \pm 0.4 (7)	0.6

[§] Dysglycemics (diabetics and pre-diabetics) were identified as described in Supplemental Table 4 above.

Subjects taking cholesterol absorption medicines (statins) were excluded from these calculations.

[¥] p values from unpaired t-test between genotypes using Welch's correction for unequal variances whenever necessary, *** p<0.001 vs. corresponding *Reference* genotype.

Unpaired t-test with Welch's corrections for unequal variances whenever necessary was used to compare within genotype between dysglycemic and normoglycemic groups, #p < 0.05, ### p<0.001 vs. non-diabetic group of the same genotype.