Supplementary Table S1. Genetic and functional effect of the 16 non-synonymous mutations identified in *MC4R*

Mutation	rs ID	MAF*	Previously reported (ref #)	Functional effect on cAMP activity**
c.106T>A / p.S36T	NA	NA	No	Neutral
c.281G>A / p.S94N	NA	NA	Yes (1)	LOF
c.307G>A / p.V103I	rs2229616	0.0185	Yes (2)	GOF
c.335C>T / p.T112M	rs13447329	0.0007	Yes (2)	LOF
c.376G>T / p.D126Y	NA	NA	Yes (1)	LOF
c.380C>T / p.S127L	rs13447331	0.0001	Yes (2)	LOF
c.382G>T / p.V128L	NA	NA	No	Neutral
c.493C>T / p.R165W	rs13447332	NA	Yes (2)	LOF
c.523G>A / p.A175T	rs121913563	0.001	Yes (3)	LOF
c.553A>T / p.I185F	NA	NA	No	LOF
c.736A>G / p.T246A	NA	NA	No	LOF
c.751A>C / p.I251L	rs52820871	0.0116	Yes (2)	GOF
c.751A>T / p.I251F	NA	NA	No	LOF
c.896C>A / p.P299H	rs52804924	NA	Yes (2)	LOF
c.902T>C / p.I301T	NA	NA	Yes (2)	LOF
c.919C>T / p.Q307*	NA	NA	Yes (4)	LOF

*MAF in European-Americans according to the Exome Sequencing Project

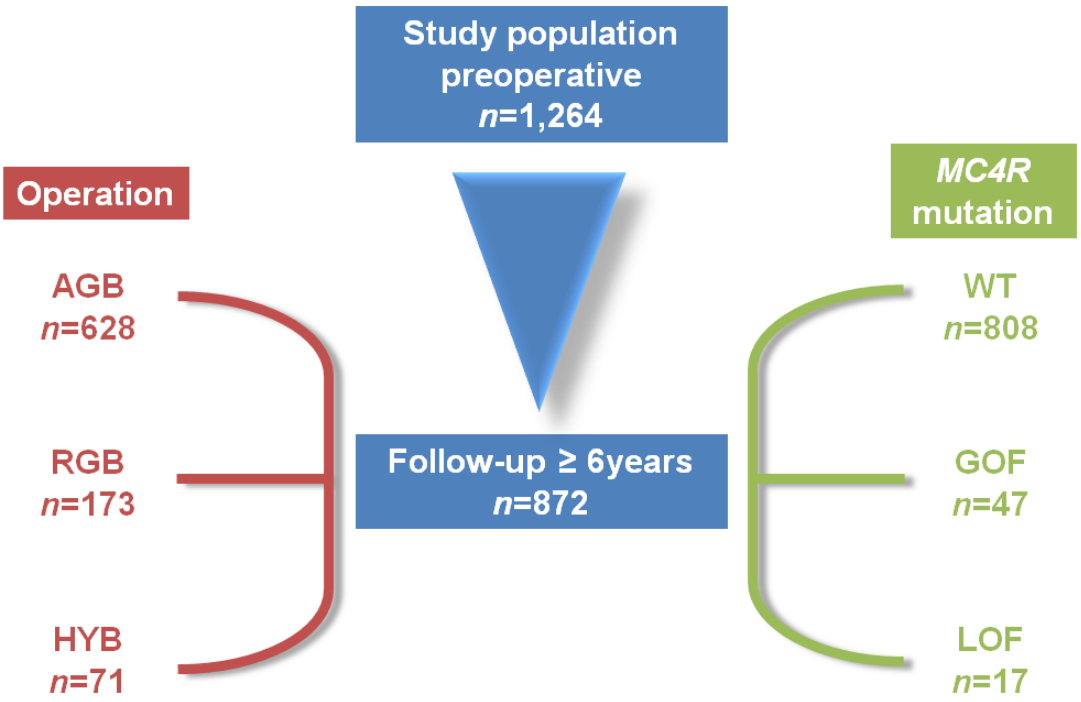
Functional effect on cAMP activity according to the present study (see **Supplementary Figure S3) or previous ones.

GOF, gain-of-function; ***LOF***, loss-of-function; ***MAF***, minor allele frequency; ***NA***, not available.

SUPPLEMENTARY DATA

Supplementary Figure S1. Design of the study

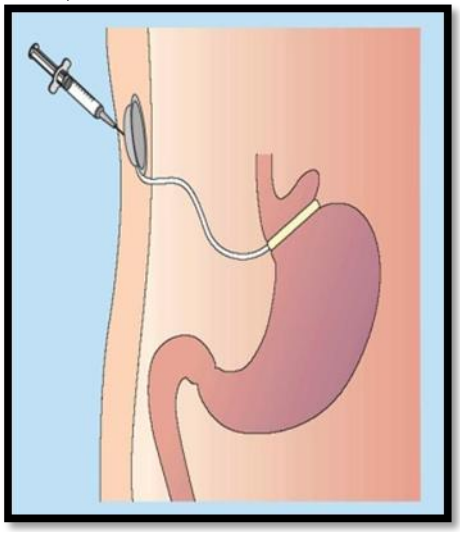
AGB, adjustable gastric banding; ***HYB***, AGB plus duodenal switch; ***GOF***, gain-of-function in *MC4R*; ***LOF***, loss-of-function in *MC4R*; ***RGB***, Roux-en Y gastric bypass; ***WT***, wild-type.



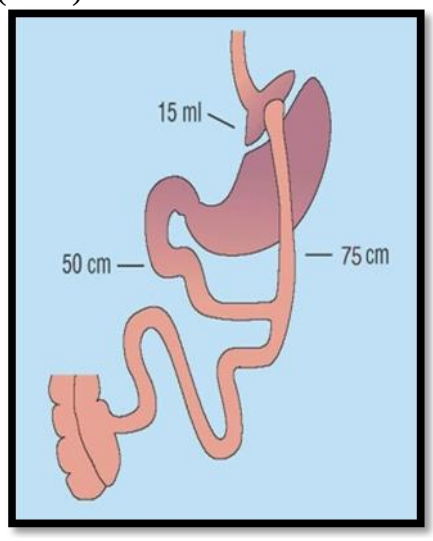
SUPPLEMENTARY DATA

Supplementary Figure S2. Gastrointestinal operations for obesity

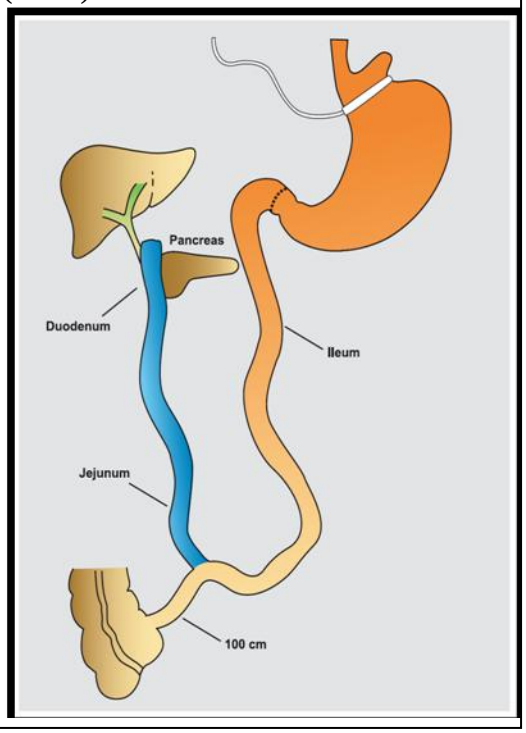
A Swedish Adjustable Gastric Band (AGB)



B Roux-en-Y gastric bypass (RGB)



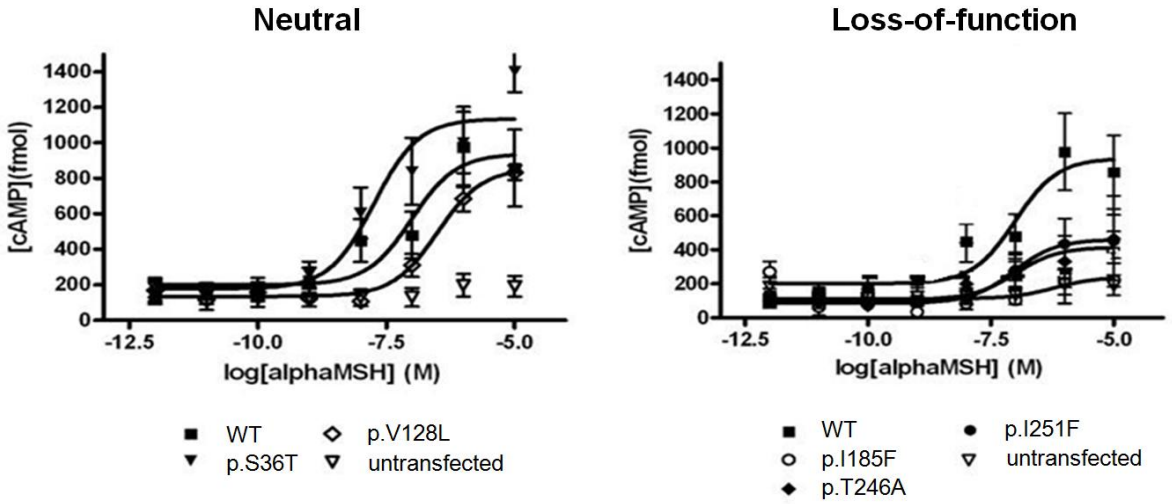
C SAGB with duodeno-jejunal bypass (HYB)



SUPPLEMENTARY DATA

Supplementary Figure S3. Functional investigation of five identified *MC4R* mutations that had not been reported previously

Curves show mean (± SE) response of wild-type (WT) and mutant receptors (p.S36T, p.V128L, p.I185F, p.T246A and p.I251F) to addition of increasing amounts of ligand (α melanocyte-stimulating hormone) on a logarithmic scale, in a cAMP-responsive enzyme immuno-assay.



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