# Genetic determinants of visceral adiposity in Type 2 Diabetes Mellitus

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## INTRODUCTION

Obesity is a heritable trait that arises from complex gene-environment interactions and is rapidly increasing in prevalence. It is defined by anthropometric measures such as the body mass index (BMI) and waist circumference (WC). A large number of single nucleotide variants (SNVs) have been repeatedly associated with visceral adiposity and related traits in various populations using a hypothesis-free GWAS approach. Despite the robust genomic association reported in the literature, GWAS-identified loci often show poor reproducibility and deficient phenotype associations when investigated in other populations.

Visceral obesity is a powerful driver of insulin resistance and Type 2 Diabetes Mellitus (T2DM). The Maltese population has a high prevalence for both obesity and T2DM. Propelling the upsurge in T2DM and the associated cardio-metabolic complications is the growing prevalence of overweight and obesity, which has tripled in countries adopting a Western lifestyle with decreased physical activity and overconsumption of cheap, energy dense food and the general improvement in socio-economic status in most populations.

The population of Malta, being very small with good access to high quality health services and centrally located in the Mediterranean close to both the Northern and Southern shores offers useful platform to explore the problem. The genetic origins, mobility and epidemiology are rather well documented. Contemporary Maltese are descendants of migrants from nearby Sicily and the Calabria region in Southern Italy in the first half of the prior millennium. Many of them were Siculo-Arabs possibly from Tunisia[1]. The subsequent turbulent history characterized by multiple conquests, immigration and depopulation have affected the genetic legacy of the Maltese. The origin, genetic epidemiology and structure of the Maltese have been well defined and quantified as part of the ongoing Malta Genome Project and the Malta BioBank, that aims to sequence one percent of the Maltese population for single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) (see Malta BioBank http://www.um.edu.mt/biobank).

## OBJECTIVES

The aim of this investigation was to:

1. Study the relationship between a number of genetic polymorphism having established association with BMI, waist circumference (WC) and related traits in the Maltese population, using a cohort of T2DM patients.

## METHODS

57 SNPs having GWAS-derived association with body mass index, waist circumference and related traits identified from NHGRI catalog

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Recently- described associations with visceral adiposity, and never studied in the Maltese population

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Genotyped in 187 T2DM cases of Maltese ethnicity, using single-base extension reaction with ddNTP terminators and detection on a MALDI-TOF MS platform

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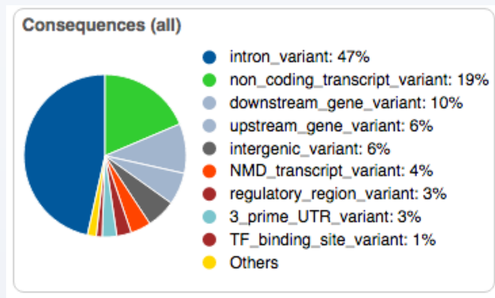
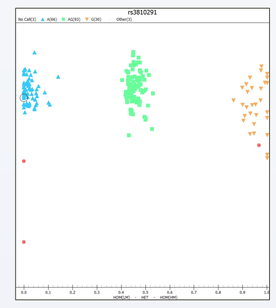
Genotype-phenotype associations were examined using an additive genetic model using linear regression. Stepwise regression modeling was used to identify the best genotype predictors of the continuous anthropometric and biochemical traits in the study cohort.

## ANNOTATION of Genotyped SNVs

56 SNVs genotyped in 187 T2DM cases, average call rate 98.75%

| | | | |
|---|---|---|---|
| rs10146997 | NRXN3 | rs11030104 | BDNF |
| rs10790162 | BUD13 | rs11142387 | KLF9 |
| rs11647936 | KLHL36 | rs11191580 | NT5C2 |
| rs12594515 | SQRDL | rs11671664 | GIPR |
| rs1260326 | GCKR | rs12229654 | MYL2 |
| rs13156607 | CCDC99 | rs12463617 | TMEM18 |
| rs1345301 | IL1RL1-IL1RL2 | rs12597579 | GP2 |
| rs1440072 | KCNE4 | rs16858082 | GNPDA2 |
| rs1555967 | PKHD1 | rs2237892 | KCNQ1 |
| rs1558902 | FTO | rs2531995 | ADCY9 |
| rs16830366 | SATB2 | rs2535633 | ITIH4 |
| rs1875517 | PTMAP8 - IGSF | rs3810291 | TMEM160 |
| rs1919128 | C2orf16 | rs4432245 | EIF2AK4 |
| rs2075064 | LHX2 | rs4776970 | MAP2K5 |
| rs2075290 | ZPR1 | rs574367 | SEC16B |
| rs2083637 | LPL | rs591166 | MC4R |
| rs2266788 | APOA5 | rs671 | ALDH2 |
| rs2373011 | ANKS1B | rs6893807 | LINC00461 |
| rs2570467 | PCSK1 | rs7138803 | BCDIN3D - RPL |
| rs3749147 | CCDC121 | rs888789 | FLJ35779 |
| rs3764261 | CETP | rs9356744 | CDKAL1 |
| rs4471028 | GDAP1 | rs9473924 | TFAP2B |
| rs4701252 | CDH12 | rs9568867 | OLFM4 |
| rs4730779 | ASZ1 | | |
| rs489693 | MC4R | | |
| rs6867983 | MAP3K1 | | |
| rs7302017 | PPM1H | | |
| rs7601155 | BRE | | |
| rs780093 | GCKR | | |
| rs7932813 | OVCH2 | | |
| rs9290936 | IL1RAP | | |
| rs9313296 | RPL21P59 - RP | | |




## The Study Cohort

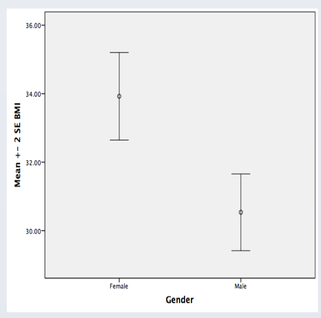
88 Female and 99 Male T2DM cases with longstanding T2DM (mean 18 years) with multiple end-organ complications.

The association of individual genotypes with anthropometric and biochemical traits was determined using GLM assuming a codominant genetic model. The genotypes were coded as (0,1,2), corresponding to the number of copies of the risk allele. Predictors included the genotypes and gender as fixed effects, and age as a covariate.

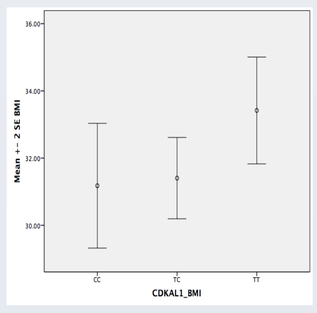
### Determinants of Body Mass Index

**Two predictors of BMI identified. These explain 14.8% of BMI variance in the T2DM cohort**

**1. Gender ($p$<0.01)** **2. *CDKAL1* rs9356744 ($p$=0.033)**




***Male T2DM patients have a BMI 3.7kg/m² [95%CI = 2.1-5.4] less than females***



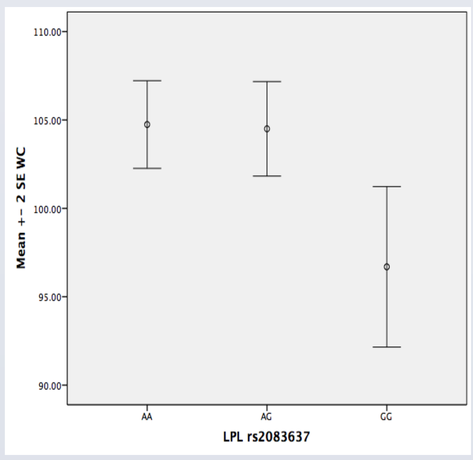

***T/T genotypes in CDKAL1 have a BMI of 1.2kg/m² [95%CI = 0.1-2.3] more than C/C homozygotes***

### Determinants of Waist Circumference

**Four genetic predictors of waist circumference identify that predict 11% of WC variance in the T2DM cohort**

***1. NRXN3* rs10146997 ($p$= 0.02)**
***2. LPL* rs2083637 ($p$=0.005)**
***3. CCDC99* rs13156607 ($p$=0.013)**
***4. CDH12* rs4701252 ($p$= 0.045)**

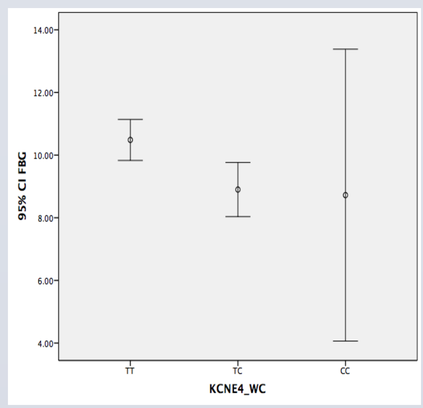
***Right: The rs2083637 variant in LPL (lipoprotein lipase) is the strongest determinant of WC, with carriers of the A allele having a WC 4cm [95%CI =1.1-6.7] than G/G homozygotes***




### Determinants of Glycaemia

***KCNE4* rs1440072 is the best genetic predictor of FBG levels ($p$ = 0.024). KCNE4 is an inhibitory component of the KCNQ1 potassium channel**

***Right: The rs1440072 variant in KCNE4 (lipoprotein lipase) is the strongest determinant of FBG , with carriers of the T allele having FBG values 1.15mmol/l [95%CI=0.15-2.1] more than carriers of the C allele.***




1. Capelli, C. et al., 2006. Population Structure in the Mediterranean Basin: A Y Chromosome Perspective. *Annals of Human Genetics*, 70(2)