Supplementary Material

Control population: Recruitment information
Different region-specific subpopulations of un-matched controls were enrolled in the study. Controls were selected among the general population (Italian), blood donors (Spanish, Polish, Portuguese and French) or among hospitalized subjects with different diagnoses excluding cancer (Hungarian). Danish controls were healthy individuals collected in the context of the European Prospective Investigation into Cancer and Nutrition (EPIC). A total of 1,858 controls were selected for this study. All control subjects used in this study were of Caucasian origin. Supplementary table 1 displays the details of the case-control population by region.

Meff method for correction of multiple testing: SNPSpDlite software
SNPSpDlite calculates a multiple testing correction for SNPs that in LD with one another, by calculating the LD correlation matrix for given SNPs, then estimating the number of independent tests within the sample. The estimation of independency was performed with our data set in MERLIN/GOLD format (family ID, ID, father and mother ID, sex and genotypes). After uploading our data and according to the format proposed by Li and Ji (2005), the analysis estimated that there were 55 independent variants, resulting in a corrected significance level of \( \alpha = 0.00090 \). After considering the number of inheritance models tested (co-dominant, dominant, recessive and log-additive), we came up with a final study-wide significance threshold of 0.00022. Detailed information about this user-friendly interface for performing this correction is available online [http://neurogenetics.qimrberghofer.edu.au/SNPSpDlite](http://neurogenetics.qimrberghofer.edu.au/SNPSpDlite).
**Randomization test method**

We compared the predictive model including significant SNPs, age and gender ("original" model) with 10,000 "randomized" models in which the effect of SNPs on MM risk was neutralized. The neutralization of procedure was as follows: 1) we randomly reassigned genotypes for according the genotype frequencies observed in controls and kept unchanged affected status (case/control), sex and age for each particular subject in the data set; 2) we adjust the model with reassigned genotypes including original affected status, sex and age as covariates and; 3) we calculate the AUC for this randomized model. Then, we repeated this three-step process 10,000 times giving rise to 10,000 "randomized" models (null distribution) with an average AUC that was subsequently used to calculate Z score and $P_{Z\text{-score}}$-value.

AUC original model: 0.645

$P_{10,000\text{ iter}} < 0.0001$

Average AUC of null distribution (10,000 models)=0.6321

Standard deviation of the AUC=0.00204

Z score=6.32

$P_{Z\text{-score}}$-value=6.81E-11

**Potentially interesting gender-specific associations.**

Although there was not a significant gender effect modification, we observed that women harbouring the $WFS1_{rs10010131A}$ and $THADA_{rs7578597C}$ alleles had significantly reduced risk of MM (OR=0.77, 95%CI 0.62-0.97 and OR=0.73, 95%CI 0.55-0.95) whereas no effect was detected in men (OR=1.12, 95%CI 0.90-1.39 and OR=0.91, 95%CI 0.70-1.18, $P_{interaction}=0.056$ and 0.125, respectively). Similarly, we found that, according to a recessive model, women bearing the $EXT2_{rs1113132G/G}$ genotype showed a trend to be associated with a decreased risk of the disease (OR$_{G/G}$=0.64, 95%CI 0.41-1.00) while an opposite but not significant effect was observed in men (OR$_{G/G}$=1.25, 95%CI 0.83-1.88; $P_{interaction}=0.067$). In men, we also found that those patients bearing the $GCK_{rs1799884A}$ allele had a significantly increased risk of MM...
(OR=1.28, 95%CI 1.01-1.61,) whereas those harbouring the \textit{ARAPI/CENTD2} rs1552224G/G genotype also tended to be associated with an increased risk for the disease (OR\textsubscript{G/G}=1.78, 95%CI 0.96-3.30). These genetic variants did not have any effect on the risk of MM in women (OR=0.92, 95%CI 0.72-1.18 and OR\textsubscript{G/G}=0.59, 95%CI 0.25-1.37, \textit{P}_{\text{interaction}}=0.254 and 0.090, respectively).
HETEROGENEITY TEST FOR ADAM30<sub>rs2641348</sub> and NOTCH2<sub>rs10923931</sub> SNPs

<table>
<thead>
<tr>
<th>Fixed effects (Mantel-Haenszel) meta-analysis</th>
<th>ADAM30&lt;sub&gt;rs2641348&lt;/sub&gt;</th>
<th>NOTCH2&lt;sub&gt;rs10923931&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic model: Dominant (CC+CT vs. TT)</td>
<td>ADAM30&lt;sub&gt;rs2641348&lt;/sub&gt;</td>
<td>NOTCH2&lt;sub&gt;rs10923931&lt;/sub&gt;</td>
</tr>
<tr>
<td>Population</td>
<td>MM</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>(CT+CC vs. TT)</td>
<td>(CT+CC vs. TT)</td>
</tr>
<tr>
<td>Men</td>
<td>103/560</td>
<td>185/734</td>
</tr>
<tr>
<td>Women</td>
<td>138/512</td>
<td>156/726</td>
</tr>
</tbody>
</table>

Test for heterogeneity:
(1) Cochran Q test: $Q = 8.33$, df = 1, P-value = 0.0039
(2) Woolf's test: $X^2 = 8.33$, df = 1, P-value = 0.0039
(3) $I^2$ statistic: $I^2 [95\% CI] = 87.99\% [53.74\% - 96.88\%]$

<table>
<thead>
<tr>
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<th>NOTCH2&lt;sub&gt;rs10923931&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>Genetic model: Dominant (CC+CT vs. TT)</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>MM</td>
</tr>
<tr>
<td></td>
<td>(GT+TT vs. GG)</td>
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<tr>
<td>Men</td>
<td>106/570</td>
</tr>
<tr>
<td>Women</td>
<td>143/525</td>
</tr>
</tbody>
</table>

Test for heterogeneity:
(1) Cochran Q test: $Q = 9.19$, df = 1, P-value = 0.0024
(2) Woolf's test: $X^2 = 9.19$, df = 1, P-value = 0.0024
(3) $I^2$ statistic: $I^2 [95\% CI] = 89.12\% [59.16\% - 97.1\%]$
REFERENCES (TABLE 1)

1. **Lyssenko V, Nagorny CL, Erdos MR, et al.** 2009 Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nature genetics 41:82-88


17. Wellcome Trust Case Control C 2007 Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447:661-678


26. **Gloyn AL, Weedon MN, Owen KR, et al.** 2003 Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 52:568-572


