Endocrine-Related Cancer

Type 2 diabetes-related variants influence the risk of developing multiple myeloma: results from the IMMEnSE consortium

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Abstract

Type 2 diabetes (T2D) has been suggested to be a risk factor for multiple myeloma (MM), but the relationship between the two traits is still not well understood. The aims of this study were to evaluate whether 58 genome-wide-association-studies (GWAS)-identified common variants for T2D influence the risk of developing MM and to determine whether predictive models built with these variants might help to predict the disease risk. We conducted a case–control study including 1420 MM patients and 1858 controls ascertained through the International Multiple Myeloma (IMMEnSE) consortium. Subjects carrying the KCNQ1rs2237892T allele or the CDKN2A-2Brs2383208G/G, IGF1rs35767T/T and MADDrs7944584T/T genotypes had a significantly increased risk of MM (odds ratio (OR)Z1.32–2.13) whereas those carrying the KCNJ11rs5215C, KCNJ11rs5219T and THADArs7578597C alleles or the FTOrs8050136A/A and LTArs1041981C/C genotypes showed a significantly decreased risk of developing the disease (ORZ0.76–0.85). Interestingly, a prediction model including those T2D-related variants associated with the risk of MM showed a significantly improved discriminatory ability to predict the disease when compared to a model without genetic information (area under the curve (AUC)Z0.645 vs AUCZ0.629; PZ4.05! 10K06). A gender-stratified analysis also revealed a significant gender effect modification for ADAM30rs2641348 and NOTCH2rs10923931 variants (PinteractionZ0.001 and 0.0004, respectively). Men carrying the ADAM30rs2641348C and NOTCH2rs10923931T alleles had a significantly decreased risk of MM whereas an opposite but not significant effect was observed in women (ORMZ0.71 and ORMZ0.66 vs ORWZ1.22 and ORWZ1.15, respectively). These results suggest that TD2-related variants may influence the risk of developing MM and their genotyping might help to improve MM risk prediction models.

Introduction

Multiple myeloma (MM) is a plasma-cell neoplasm of complex aetiology that may arise as a result of the interaction between adverse environmental and inherited genetic risk factors (Morgan et al. 2012). Although survival rates forMM have improved dramatically during the last two decades, likely due to the introduction of novel targeted therapies (proteasome inhibitors, immunomodulators and others), the disease outcome still remains poor with a 5-year overall survival rate not higher than 55% (Kumar et al. 2014). Age, male gender, African ancestry and monoclonal gammopathy of uncertain significance (MGUS) have been established as major risk factors for MM (Alexander et al. 2007). In addition, exposure to a wide range of toxins as well as type 2 diabetes (T2D) and obesity have been suggested as importantmediators of the complex process of myelomagenesis (Alexander et al. 2007, Lope et al. 2008, Wallin & Larsson 2011). Among these latter preventable factors, T2D has attracted significant attention since it has been consistently identified as a medical condition frequently found in MM patients (Khan et al. 2008, Richardson et al. 2009, Castillo et al. 2012) and it is thought to influence the myelomagenesis through hyperglycaemia and insulin-dependent and -independent mechanisms (Xu et al. 2014). In a recent well-poweredmeta-analysis, Castillo et al. (2012) observed that T2D was significantly associated with an increased risk of developing the disease (Castillo et al. 2012). This finding concurs with those previously reported in several epidemiological studies that showed a high incidence of T2D among MM patients ranging between 11 and 22% (Richardson et al. 2006, Badros et al. 2007). In addition, it has been reported that T2D may have a negative impact on MM prognosis (Chiu et al. 2006, Wu et al. 2014) and that the treatment with anti-diabetic drugs may effectively kill MM cells (Wu et al. 2014). Considering that T2D and MM have strong genetic components and share several biological pathways and markers (Xu et al. 2014) and that T2D-related polymorphisms may influence the risk of developing solid cancer (Folsom et al. 2008, Cheng et al. 2011, Sainz et al. 2012, Ma et al. 2014), we hypothesized that genetic risk factors for T2D may be associated with the risk of developing MM. So far there have not been studies evaluating the impact of diabetogenic variants on the risk of developing hematological cancers. Therefore, we decided to conduct a multi-centre case–control study including 1420 MM patients and 1858 controls to evaluate whether 58 variants convincingly shown to be associated with T2D contribute to the risk of developing MM. We also aimed at determining whether predictive models including T2D-related variants significantly improve the discriminatory ability to predict the risk of MM. Material and methods Study population The study population consisted of 1420 MM patients (705 women and 715 men) and 1858 controls (916 women and 942 men) ascertained through the International Multiple Myeloma (IMMEnSE) consortium (Supplementary Table 1, see section on supplementary data given at the end of this article), which has been described in detail elsewhere (Martino et al. 2012). The diagnosis of MM was assigned by physician and fulfilled the International Myeloma Working Group (IMWG) criteria (International Myeloma Working Group 2003). Controls were blood donors or hospitalized subjects with a diagnosis not related to cancer who were recruited in the same geographical area of the cases (Supplementary Table 1). Additional information concerning to the recruitment strategy of controls is shown in the Supplementary Material. The investigation was approved by the ethical committee of each participant institution, functioning according to the third edition of the Guidelines on the Practice of Ethical Committees in Medical Research issued by the Royal College of Physicians of London (www.rcplondon.ac.uk) and all participants gave their written informed consent to participate in the study. SNP selection and genotyping Fifty-eight genome-wide-association-studies (GWAS)-identified variants for T2D were selected to be genotyped in the IMMEnSE consortium population (Table 1 and Supplementary Material). The genotyping of the selected polymorphisms was carried out at GENYO (Centre for Genomics and Oncological Research: Pfizer/University of Granada/ Andalusian Regional Government, Granada, Spain) using KASPar assays (LGC Genomics,

Hoddesdon, UK) according to manufacturer's instructions. For internal quality control, 5% of samples were randomly selected and included as duplicates. Concordance between the original and the duplicate samples for the 58 SNPs was R99.0%. Call rates for all SNPs were R90.0% with the exception of the WFS1rs734312 SNP that was excluded from further analyses

Statistical analysis

The Hardy–Weinberg Equilibrium (HWE) tests were performed in the control group by a standard observedexpected c2 test. Logistic regression analyses were used to assess the effects of the genetic polymorphisms on MM risk using co-dominant, dominant, recessive and log-additive inheritance models. Overall analyses were adjusted for age at diagnosis, gender and country of origin. All analyses were conducted using the statistical software SSPS (version 20.0). Statistical power was calculated using the Quanto vs12.4 (http://biostats.usc.edu/software) assuming a logadditive model. In order to account for multiple testing, we calculated an adjusted significance level using the Meff method (Nyholt 2004), which considers the number of independent marker loci (MeffLiZ55) but also the number of models of inheritance tested (co-dominant, dominant, recessive and log-additive). Thus, the resulting threshold for the main effect analysis was 0.00022 ((0.05/55)/4) (Supplementary Material). Since a study-wide significance threshold considering all these factors is generally perceived as a 'too conservative' test, we also assessed the magnitude of observed associations between selected SNPs and risk of MM through a quantile–quantile (QQ) plot generated from the results of the IMMEnSE population. The observed association P values were ranked in order from smallest to largest on the y-axis and plotted against the expected results from a theoretical wc2 -distribution under the null hypothesis of no association on the x-axis. A deviation from the identity line would confirm that the number of corresponding associations is more than expected under the null hypothesis and therefore that these associations are likely to be true associations. Predictive models and discriminative accuracy We also examined the value of T2D-related polymorphisms for prediction of MM using stepwise logistic and Cox regression analyses. We built a prediction model including age and sex and those genetic variants that showed significant associations with MM in the single-SNP analysis (P!0.05). Then, using P values as a selection criterion, we dropped variables that have the highest P value and we stopped when all variables were significant defined by P!0.10. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve analysis was used to assess the discriminative accuracy of this particular model compared with a reference model including age and sex as covariates. A K2log likelihood ratio (LR) test was used to determine whether the predictive model including genetic information fitted significantly better the data compared to the reference model. Although the addition of genetic variables to the reference model will almost always make the model fit better, the LR test allowed us to confirm whether the difference in model fit between both models was statistically significant. Besides this suggestive analysis, we also ran a randomization test to confirm whether the improved predictive ability of the model including genetic variants significantly associated with MM was consistent after 10 000 iterations. We compared our full 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 by reassigning randomly all genotypes (null distribution; Supplementary Material). Subsequently, we calculated an empirical Piterations-value by dividing the number of times in which the 'randomized' AUC value was equal or greater than the 'original' AUC value by the number of iterations. Then, we could also calculate the Z score and PZ score-value for the original AUC using the 'randomized' AUC average of these 10 000 iterations and their S.D. All analyses were performed using R software (http://www.r-project.org/). Gender-specific association analysis We also evaluate gender-specific associations of selected SNPs with MM risk. Logistic regression analyses were corrected for age and country of origin. Of note, to evaluate whether a different gender distribution across populations within the IMMEnSE consortium could be

responsible for the gender effect modification observed for certain SNPs, we also assessed heterogeneity and index I 2 statistic using Cochran's c2 based Q statistic test (Lau et al. 1997). Heterogeneity was considered significant when P!0.1. Results Overall associations of selected SNPs with MM risk All SNPs were in HWE (PO0.001) with the exception of the COL5A1rs4240702, which was therefore excluded from the statistical analyses. Logistic regression analysis showed that carriers of the KCNQ1rs2237892T allele or the CDKN2A2Brs2383208G/G, IGF1rs35767T/T and MADDrs7944584T/T genotypes had an increased risk of MM (odds ratio (OR)Z1.32, 95% CI 1.01–1.71, PZ0.039; ORZ1.86, 95% CI 1.12–3.11, PZ0.016; ORZ2.13, 95% CI 1.35–3.37, PZ0.0012 and ORZ1.33, 95% CI 1.06–1.67, PZ0.014, respectively) whereas those harbouring the KCNJ11rs5215C, KCNJ11rs5219T and THADArs7578597C alleles or the FTOrs8050136A/A and LTArs1041981C/C genotypes showed a decreased risk for the disease (ORZ0.85, 95% CI 0.73– 0.99, PZ0.038; ORZ0.84, 95% CI 0.72–0.99, PZ0.034; ORZ0.81, 95% CI 0.68–0.98, PZ0.032; ORZ0.78, 95% CI 0.64–0.95, PZ0.013 and ORZ0.76, 95% CI 0.58–0.99, PZ0.042, respectively; Table 2). When we corrected for multiple testing (with a threshold of PZ0.00022), none of the reported associations remained statistically significant. The strongest association observed was for the IGF1rs35767 SNP with an increased risk of developing MM (ORZ2.13, 95% CI 1.35–3.37, PZ0.0012). In spite of these results, the QQ plot showed an early deviation of identity line, which suggested a high proportion of true associations for a given P value (Fig. 1). Therefore, the data suggest that the effect attributed to SNPs in T2D-related loci (FTO, MADD, CDKN2A-2B, LTA) might represent true associations. Predictive value of T2D-related variants In order to determine whether there was a joint effect of SNPs significantly associated with MM, we built a prediction model including gender and those nine SNPs showing overall significant associations with MM. After excluding the variables that did not remain significant in the model, the final model included six SNPs that increased the discriminatory ability to predict the risk of MM when compared with a reference model including age and gender as covariates (AUCZ0.645 95% CI 0.624–0.666; Table 3). The LR test showed that the model including genetic variants fitted better the data than the reference model, and that the difference in model fit between both models was statistically significant (PZ4.05!10K06). In addition, when we evaluated whether the model including genetic variants was consistent in predicting better the MM risk, we found that it showed an AUC value systematically higher than those of the 10 000 randomized models (null distribution; Z scoreZ6.42, PZ6.81!10K11; Supplementary Material), emphasizing the importance of considering genetic variants significantly associated with MM when building predictive models. Gender-specific associations with MM risk Interestingly, a gender-stratified analysis also revealed significant gender effect modifications for ADAM30rs2641348 and NOTCH2rs10923931 SNPs (Pinteraction Z0.001 and 0.0004 respectively). For ADAM30rs2641348C and NOTCH2rs10923931T alleles, a significantly reduced risk for the disease was observed in men (per-allele ORZ0.71, 95% CI 0.54–0.94, PZ0.015 and per-allele ORZ0.66, 95% CI 0.50–0.86, PZ0.0019, respectively) whereas a nonsignificant opposite effect was seen in women (per-allele ORZ1.22, 95% CI 0.93–1.60 and per-allele ORZ1.15, 95% CI 0.89–1.50 respectively). A statistically significant heterogeneity, considering P!0.05 as a threshold, was also confirmed for these two SNPs (PHETZ0.0039 and I 2 Z87.99% and PHETZ0.0024 and I 2 Z89.12%, respectively), which supports the notion suggesting a role of gender in modulating the effect of these SNPs on MM risk. Although there was not a significant interaction with gender, we observed additional genderspecific associations for WFS1rs10010131, THADArs7578597, EXT2rs1113132 and GCKrs1799884 SNPs according to dominant or recessive models of inheritance (Table 2 and Supplementary Material). When we took account of multiple testing (with a threshold of PZ0.00022), we found that the effect of the IGF1rs35767 variant was stronger in women than men with an association approaching significance with an increased risk of developing MM (ORZ3.13, 95% CI 1.46–6.71, PZ0.0026 vs ORZ1.69, 95% CI 0.94–3.02, PZ0.079 respectively). In addition, we found that the association of NOTCH2rs10923931 SNP with a decreased risk of MM in men was close to significance according to dominant and log-additive models (ORZ0.66, 95% CI 0.50–0.86, OPY ONLY PZ0.0019 and PtrendZ0.0007),

which may suggest a gender-specific allele-dosage effect for this variant to modulate the disease risk (PinteractionZ0.0004; Table 2). According to a log-additive model, we also found that the association of the ADAM30rs2641348C allele with a decreased risk of MM in men showed a slight trend to be significant considering multiple testing (ORZ0.71, 95% CI 0.55–0.92, PZ0.0072) whereas, according to a recessive model, the association of the ADAM30rs2641348C/C genotype was also close to survive multiple testing correction (ORZ4.40, 95% CI 1.44–13.40, PZ0.00059; Table 2 and Supplementary Table 2, see section on supplementary data given at the end of this article). Discussion In the present study, we report for the first time evidence of significant associations between GWAS-identified T2D genetic variants and MM risk. We found that carriers of the KCNQ1rs2237892T allele, CDKN2A-2Brs2383208G/G, IGF1rs35767T/T and MADDrs7944584T/T genotypes were at increased risk of MM, whereas those carrying the KCNJ11rs5215C, KCNJ11rs5219T and THADArs7578597C alleles or the FTOrs8050136A/A and LTArs1041981C/C genotypes showed a decreased risk for the disease. The associations for the KCNQ1, CDKN2A-2B, IGF1, MADD, KCNJ11, and THADA gene variants with the risk of MM showed an opposite direction to those previously reported in the GWAS for T2D (i.e., the risk allele was the opposite for MM and T2DM), which points towards a non-diabetogenic mechanism underlying the effect of these variants to modulate the risk of the disease. In support of this hypothesis, several studies have suggested that, besides their influence on pancreatic function and insulin secretion through a wide variety of biological mechanisms, some of these genes may also act as tumour suppressor genes (Koh et al. 1995, Kim & Sharpless 2006, Than et al. 2013) and have an impact in themodulation of cell survival (Butt et al. 1999, Ortega et al. 2002, Sharifi et al. 2013), differentiation (Pancewicz et al. 2010), proliferation (Grimberg 2003, Pancewicz et al. 2010) and apoptosis (LeRoith et al. 1995, Li et al. 2008, Pancewicz et al. 2010). Interestingly, a recent study demonstrated that T2D status was not implicated in the relationship between HNF1B and JAZF1 variants and prostate cancer risk (Stevens et al. 2010), which is in line with our hypothesis suggesting that T2Drelated variants may determine the risk of MM through non-diabetogenic mechanisms. When we took into account multiple testing correcTable 2 tions, only the association of the IGF1rs35767 promoter polymorphism with an increased risk of developing MM remained close to significance (PZ0.0012), which suggested that the IGF1 locus may play an important role in triggering cell proliferation in malignant plasma cells. In support of the hypothesis, it has been observed that IGF1 acts as a major growth factor in MM that, directly or in cooperation with other growth factors, induces MM cell growth and proliferation (Ferlin et al. 2000, Bommert et al. 2006, Sprynski et al. 2009) and can eventually lead to chemoresistance (Xu et al., 1997, Kuhn et al., 2012). Likewise, iy has been also reported that treatment with metformin, an anti-diabetic drug that inhibits IGF1 signaling pathway, significantly reduces the risk of transformation from MGUS to symptomatic MM (American Society of Clinical Oncology Annual Meeting 2014; abstract 1532) and that constant use of this treatment may induce cell apoptosis (Rattan et al. 2012) and enhance the effectiveness of chemotherapeutic regimes in blood and solid cancers (Feng et al. 2011, Pan et al. 2012, Watson 2013). Interestingly, several authors have also reported that IGF1 and its analogues are associated with an increased death in patients with progressive MM (Standal et al. 2002, Chou et al. 2012, Wu et al. 2014), whereas the administration of metformin results in the reduction of deaths in patients with progressive disease (Wu et al. 2014). In fact, Chen et al. (2013) recently demonstrated that the IGF1rs35767 SNP together with two neighbour SNPs constitutes a haplotype that efficiently regulates transcriptional activity (Chen et al. 2013). Similarly, several studies have consistently reported that carriers of the IGF1rs35767T allele showed significantly higher levels of circulating IGF1 than those harbouring the WT allele (Mannino et al. 2013, Sesti et al. 2014) and that the presence of this variant is associated with an increased risk of developing several types of cancer (Ollberding et al. 2012, Qian et al. 2014). Although it is tempting to speculate that the IGF1rs35767 SNP may be responsible for the effect attributed to diabetes on the risk of MM, we believe that rather than acting separately to modulate the risk of the disease, this

genetic variant acts along with additional variants within KCNQ1, CDKN2A-2B, MADD, KCNJ11, THADA, LTA and FTO genes to modulate the disease risk. In order to test this hypothesis, we decided to evaluate the predictive value of T2D-related polymorphisms for prediction of MM using stepwise logistic and Cox regression analyses. Interestingly, we found that adding genetic factors to a model without covariates (including only age and gender) substantially improved the prediction of disease development. A predictive model including six SNPs significantly associated with MM in the single analysis showed an adjusted concordance statistic AUC of 64.5% for MM. The consistency of this result was confirmed through a randomization test that showed that none of the 10 000 randomizedmodels showed a higher AUC value than our 'original' model including six genetic variants, age and gender. The addition of genetic variants associated with MM at P!0.10 level did not improve the discriminatory ability to predict MM, which pointed towards a joint contribution of IGF1, FTO, MADD, PRC1, KCNJ11 and KCNQ1 polymorphisms to predict the risk of the disease. Although the prediction capacity of these models could be considered relatively small when compared with a reference model, the relative absence of current diagnostic factors for MM suggest that the use of genetic variants could be a good option to improve the prediction of the disease risk. The association of the non-diabetogenic alleles or genotypes for the polymorphisms within KCNQ1, CDKN2A-2B, MADD, KCNJ11, THADA and FTO genes with the risk of MM suggests that these genes, rather than acting through an insulin-dependent mechanism, may modulate the risk of MM by acting as tumour suppressor genes (Duro et al. 1995) or through mechanisms promoting cancer cell apoptosis (Rippe et al. 2003, Turner et al. 2013). In support of this idea, it has been recently reported that most of these genes are highly expressed in tumours and that genetic polymorphisms in these loci are also associated with cancer development (Sauroja et al. 2000, Cander et al. 2014) and tumour progression (Chen et al. 2009). The association of LTArs1041981 SNP with a decreased risk of MM showed a similar direction to that observed in the GWAS for T2D (LTArs1041981A as risk allele) suggests a diabetogenic effect of this SNP to modify the risk of MM. However, we could not dismiss the idea suggesting that observed association could be due to a different distribution of diabetics between MM cases and controls. Similarly, although the direction of the association for the FTOrs8050136 SNP with the risk of MM was opposite to the one observed in the GWAS for T2D, we could not rule out the possibility that the observed effect for this obesogenic SNP (Scuteri et al., 2007) could be due to significant differences in BMI between MM cases and controls. Further studies using well-characterized cohorts are needed to confirm these latter associations. Although it was not the primary objective of this study, we also performed gender-stratified analysis to assess whether there was a gender effect modification of selected SNPs to modulate the risk of developing MM. Interestingly, we found a significant gender effect modification for ADAM30rs2641348, and NOTCH2rs10923931 SNPs, which suggested a gender-specific effect of these loci to modulate the risk of MM. We observed that, according to a logadditive model of inheritance, the association of the NOTCH2rs10923931 SNP with a decreased risk of MM in men and the association of ADAM30rs2641348C/C genotype with an increased risk of MM in women showed a marginal level of significance after correction for multiple testing. Recently, it has been demonstrated that NOTCH2 is highly expressed in MM cells and that it is a key regulator of MM pathogenesis (Colombo et al. 2013). In particular, it has been reported that the activation of the NOTCH2, which interacts with Wnt components, induces an exacerbated growth of MM cells and accelerated the course of the disease by promoting cancer stem cell self-renewal (Xu et al. 2012a) and resistance to chemotherapeutic agents (Xu et al. 2012b). Considering that NOTCH2rs10923931 and ADAM30rs2641348 are neighbour SNPs in strong linkage disequilibrium (Zeggini et al. 2008) and that they showed gender-specific associations with the risk of MM, we hypothesize that NOTCH2-ADAM30 might represent a gender-specific susceptibility region for MM. In support of this idea, it has been reported that gender-specific variants within NOTCH and WNT signalling pathways, which are involved in determining cell proliferation and differentiation, may lead to important gender-specific differences in tumour recurrence and

chemoresistance (Paez et al. 2014). Our study has both strengths and weaknesses. The major strength is the large sample size. To our knowledge, this is the first study to evaluate the overall and genderspecific associations of T2D-related variants with the risk of developing MM and to assess their predictive value for MM. Although the influence of diabetogenic variants on the risk of the disease was expected to be very modest, our study was sufficiently powered to detect such small effects. Based on the genotype frequencies observed in our study cohort, we had 80% of power (dominant model) to detect an OR of 1.29 at aZ0.00022 (multiple testing threshold) for a polymorphism with a minor allele frequency of 0.25. Although the gender-stratified analysis reduced the statistical power to detect effect of SNPs, we still had 80% of power to detect ORs of 1.43 and 1.44 for men and women respectively. It is important to realise, however, that although the present study involves data on over 3334 individuals, the retrospective and multicentre study design places inevitable limitations on clinical data availability. T2D status and BMI were not available for a substantial subset of MM cases, which did not allow us to adjust our analyses for these variables and, consequently, to rule out the possibility that some of the reported associations could arise as a result of a different distribution of diabetics and/or obese subjects between MM cases and controls. Nonetheless, considering that most of the reported associations with MM risk showed a different direction to those previously published in the GWAS for T2D and given that most of these genes are not linked to obesity, we could not expect to find false positive associations due to these confounding factors. In conclusion, our study indicate that T2D-related variants within IGF1, KCNJ11, CDKN2A-2B, MADD, THADA, LTA, FTO, ADAM30 and NOTCH2 genes may influence the risk of MM through insulin-independent mechanisms and that genotyping of specific T2D-related variants may be useful to improve the prediction of MM development. Additional work is needed to replicate our findings in independent and well-characterized populations and functional studies are also warranted to elucidate the biological mechanisms underlying the observed effects.

Funding

This work was supported by grants from the FIBAO foundation (Granada, Spain) and the CRIS foundation against cancer, from the Cancer Network of Excellence (RD12/10 Red de Ca´ncer) and from the Instituto de Salud Carlos III (Madrid, Spain; PI12/02688).

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Table 1 Selected type-2 diabetes-related SNPs

Gene name	dbSNP rs#	Nucleotide substitution	Reference allele IMMEnSE	GWAS-identified risk allele for T2D	Location/Aa substitution	References
ADAM30	rs2641348	T/C[a]	T	C	L359P	Zeggini *et al.* (2008) and Lyssenko *et al.* (2009)
ADAMTS9	rs4607103	T/C	C	C	Near gene	Mohlke *et al.* (2008), Zeggini *et al.* (2008) and Shu *et al.* (2010)
ADCY5	rs11708067	T/C	T	T	Intronic	Dupuis *et al.* (2010) and Saxena *et al.* (2010)
ADRA2A	rs10885122	G/T	G	G	Near ADRA2A	Dupuis *et al.* (2010)
ARAPI, CENTD2	rs1552224	G/T	T	A	Near gene	Voight *et al.* (2010) and Nielsen *et al.* (2011)
BCL11A	rs10490072	C/T	T	T	Near gene	Zeggini *et al.* (2008)
CDC123	rs12779790	A/G	A	G	Near gene	Mohlke *et al.* (2008), Zeggini *et al.* (2008) and Shu *et al.* (2010)
CDKAL1	rs7754840	C/G	G	C	Intronic	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Florez *et al.* (2007) and Scott *et al.* (2007)
CDKN2A-2B	rs564398	T/C	T	T	Near gene	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Scott *et al.* (2007), Mohlke *et al.* (2008), Zeggini *et al.* (2008), Takeuchi *et al.* (2009), Shu *et al.* (2010) and Yamauchi *et al.* (2010)
CDKN2A-2B	rs10811661	T/C	T	T	Near gene	
CDKN2A-2B	rs2383208	A/G[b]	A	A	Near gene	
COL5A1	rs4240702	C/T	C	NS	Intronic	Bouatia-Naji *et al.* (2009)
CRY2	rs11605924	A/C	C	A	Intronic	Dupuis *et al.* (2010)
DCD	rs1153188	A/T	A	A	Near gene	Zeggini *et al.* (2008)
EXT2	rs1113132	C/G	C	C	Intronic	Florez *et al.* (2007) and Sladek *et al.* (2007)
FADS1	rs174550	C/T	A	T	Intronic	Dupuis *et al.* (2010)
FAM148B	rs11071657	A/G	A	A	Near gene	Chambers *et al.* (2008) and Dupuis *et al.* (2010)
FLJ39370	rs17044137	A/T	T	A	Near gene	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007)
FTO	rs8050136	A/C[c]	C	A	Intronic	Wellcome Trust Case Control (2007), Zeggini *et al.* (2007) and Mohlke *et al.* (2008)
G6PC2	rs560887	G/A	G	G	Intronic	Bouatia-Naji *et al.* (2008, 2009), Chen *et al.* (2008), Prokopenko *et al.* (2009) and Dupuis *et al.* (2010)
GCK	rs1799884	G/A	G	A	Near gene	Bouatia-Naji *et al.* (2008, 2009), Chen *et al.* (2008), Prokopenko *et al.* (2009) and Dupuis *et al.* (2010)
GCKR	rs1260326	C/T	C	T	L445P	Bouatia-Naji *et al.* (2009), Dupuis *et al.* (2010) and Saxena *et al.* (2010)
HHEX	rs1111875	G/A	C	C	Near gene	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007),

Gene name	dbSNP rs#	Nucleotide substitution	Reference allele IMMEnSE	GWAS-identified risk allele for T2D	Location/Aa substitution	References
HNF1A, TCF1	rs7957197	A/T	T	T	Intronic	Voight *et al.* (2010) and Nielsen *et al.* (2011)
IGF1	rs35767	C/T[d]	C	C	Near gene	Pechlivanis *et al.* (2007) and Dupuis *et al.* (2010)
IGF2BP2	rs4402960	G/T	C	T	Intronic	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Florez *et al.* (2007), Scott *et al.* (2007), Wellcome Trust Case Control (2007), Zeggini *et al.* (2007), Mohlke *et al.* (2008) and Shu *et al.* (2010)
IL13	rs20541	C/T	C	T	R144Q	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007)
IRS1	rs2943641	C/T	C	C	Near gene	Rung *et al.* (2009), Voight *et al.* (2010) and Tang *et al.* (2013)
JAZF1	rs864745	A/G	A	T	Intronic	Zeggini *et al.* (2008) and Shu *et al.* (2010)
KCNJ11	rs5215	T/C[e]	T	C	V337I	Gloyn *et al.* (2003), Diabetes Genetics
KCNJ11	rs5219	C/T[f]	C	T	K23E	Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Scott *et al.* (2007), Wellcome Trust Case Control (2007), Zeggini *et al.* (2007), Willer *et al.* (2007) and Mohlke *et al.* (2008)
KCNQ1	rs2237897	C/T	T	C	Intronic	Unoki *et al.* (2008), Yasuda *et al.* (2008),
KCNQ1	rs2074196	G/T	G	G	Intronic	Tsai *et al.* (2010) and Yamauchi *et al.*
KCNQ1	rs2237892	C/T[g]	C	C	Intronic	(2010)
KCNQ1	rs2237895	A/C	A	C	Intronic	
KCNQ1OT1	rs231362	C/T	C	G	Intronic	Tsai *et al.* (2010), Voight *et al.* (2010) and Nielsen *et al.* (2011)
LTA	rs1041981	A/C[e]	A	A	T60N	Hamid *et al.* (2005)
MADD	rs7944584	A/T[d]	A	A	Intronic	Dupuis *et al.* (2010)
MCR4	rs12970134	A/G	G	A	Near gene	Chambers *et al.* (2008)
MTNR1B	rs1387153	C/T	C	T	Near gene	Bouatia-Naji *et al.* (2009), Prokopenko *et al.* (2009) and Voight *et al.* (2010)
NOTCH2	rs10923931	G/T[h]	G	T	Intronic	Mohlke *et al.* (2008) and Zeggini *et al.* (2008)
PKN2	rs6698181	C/T	C	T	Intergenic	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007)
PPARG	rs1801282	C/G	C	C	P12A	Altshuler *et al.* (2000), Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Scott *et al.* (2007), Wellcome Trust Case Control (2007), Willer *et al.* (2007), Zeggini *et al.* (2007, 2008) and Mohlke *et al.* (2008)
PRC1	rs8042680	A/C	C	A	Intronic	Voight *et al.* (2010) and Nielsen *et al.* (2011)
PROX1	rs340874	A/G	A	G	Promoter	Dupuis *et al.* (2010)
RBMS1	rs7593730	C/T	C	T	Intronic	Qi *et al.* (2010)
SLC2A2	rs11920090	A/T	A	T	Intronic	Dupuis *et al.* (2010)

Gene name	dbSNP rs#	Nucleotide substitution	Reference allele IMMEnSE	GWAS-identified risk allele for T2D	Location/Aa substitution	References
SLC30A8	rs13266634	C/T	C	C	R325W	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Florez *et al.* (2007), Scott *et al.* (2007), Sladek *et al.* (2007), Steinthorsdottir *et al.* (2007), Wellcome Trust Case Control (2007), Zeggini *et al.* (2007), Mohlke *et al.* (2008), Dupuis *et al.* (2010) and Shu *et al.* (2010)
TCF2	rs7501939	C/T	C	C	Intronic	Gudmundsson *et al.* (2007) and Sandhu *et al.* (2007)
TCF7L2	rs7903146	C/T	C	T	Intronic	Grant *et al.* (2006), Scott *et al.* (2006),
TCF7L2	rs12255372	G/T	G	T	Intronic	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research *et al.* (2007), Florez *et al.* (2007), Scott *et al.* (2007), Sladek *et al.* (2007), Steinthorsdottir *et al.* (2007), Wellcome Trust Case Control (2007), Zeggini *et al.* (2007), Mohlke *et al.* (2008), Dupuis *et al.* (2010) and Saxena *et al.* (2010)
THADA	rs7578597	T/C[e]	T	T	T1187A	Zeggini *et al.* (2008)
TP53INP1	rs896854	A/G	G	G	Intronic	Voight *et al.* (2010) and Nielsen *et al.* (2011)
TSPAN8	rs7961581	C/T	T	C	Near gene	Grarup *et al.* (2008)
VEGFA	rs9472138	C/T	C	T	Near gene	Zeggini *et al.* (2008)
WFS1	rs734312	A/G	A	NS	H611R	Sandhu *et al.* (2007)
WFS1	rs10010131	A/G	G	G	Intronic	Sandhu *et al.* (2007)

NS, not specified; Aa, aminoacid; GWAS, genome-wide association studies. Effect allele in bold and underlined.
[a]C allele was associated with a decreased risk of MM in men whereas an opposite effect was detected in women.
[b]G allele was associated with an increased risk of developing MM.
[c]A/A genotype was associated with a decreased risk of MM (recessive model).
[d]T/T genotype was associated with a decreased risk of MM (recessive model).
[e]C allele was associated with a decreased risk of MM.
[f]T allele was associated with an decreased risk of MM.
[g]T allele was associated with an increased risk of MM.
[h]T allele was associated with a decreased risk of MM in men whereas an opposite effect was detected in women.

Variant_dbSNP	Gene	Overall (n = 3278)		Men (n = 1657)		Women (n = 1621)		
		OR (95% CI)[a]	*P* value	OR (95% CI)[b]	*P* value	OR (95% CI)[b]	*P* value	$P_{interaction}$
rs2641348[cd]	*ADAM30*	0.94 (0.78–1.14)	0.53	**0.71 (0.54–0.94)**	**0.015**	1.22 (0.93–1.60)	0.15	**0.001**
rs4607103	*ADAMTS9*	1.00 (0.86–1.16)	1.00	0.97 (0.79–1.20)	0.80	1.05 (0.84–1.30)	0.69	0.803
rs11708067	*ADCY5*	1.02 (0.88–1.20)	0.77	1.05 (0.85–1.31)	0.64	0.97 (0.77–1.22)	0.79	0.425
rs10885122	*ADRA2A*	1.08 (0.91–1.28)	0.40	1.16 (0.92–1.47)	0.21	0.99 (0.77–1.28)	0.96	0.494
rs1552224[e]	*ARAPI, CENTD2*	1.16 (0.72–1.88)	0.54	1.78 (0.96–3.29)	0.066	0.58 (0.25–1.37)	0.20	0.090
rs10490072	*BCL11A*	1.01 (0.87–1.17)	0.92	1.01 (0.82–1.25)	0.91	1.01 (0.81–1.25)	0.94	0.691
rs12779790	*CDC123, CAMK1D*	0.87 (0.74–1.02)	0.075	0.82 (0.66–1.03)	0.083	0.90 (0.71–1.13)	0.35	0.758
rs7754840	*CDKAL1*	0.98 (0.85–1.14)	0.84	1.05 (0.86–1.29)	0.63	0.91 (0.74–1.13)	0.40	0.376
rs564398	*CDKN2A-2B*	0.94 (0.80–1.10)	0.42	0.90 (0.72–1.11)	0.33	0.97 (0.78–1.22)	0.80	0.893
rs10811661	*CDKN2A-2B*	1.02 (0.87–1.20)	0.79	1.11 (0.89–1.38)	0.35	0.93 (0.74–1.17)	0.52	0.358
rs2383208[e]	*CDKN2A-2B*	**1.86 (1.12–3.11)**	**0.016**	**1.92 (1.03–3.58)**	**0.039**	1.68 (0.69–4.10)	0.25	0.585
rs11605924	*CRY2*	0.93 (0.79–1.10)	0.40	0.95 (0.75–1.19)	0.64	0.92 (0.72–1.17)	0.49	0.747
rs1153188	*DCD*	0.91 (0.79–1.06)	0.24	0.83 (0.67–1.02)	0.082	1.05 (0.84–1.30)	0.69	0.072
rs1113132[e]	*EXT2*	0.92 (0.68–1.24)	0.57	1.24 (0.83–1.87)	0.30	0.64 (0.41–1.00)	**0.046**	0.067
rs174550	*FADS1*	1.11 (0.95–1.28)	0.18	1.13 (0.92–1.38)	0.25	1.08 (0.87–1.34)	0.48	0.359
rs11071657	*FAM148B*	1.03 (0.88–1.20)	0.73	0.95 (0.77–1.17)	0.62	1.16 (0.93–1.46)	0.18	0.275
rs17044137	*FLJ39370*	0.91 (0.78–1.05)	0.19	1.05 (0.85–1.29)	0.65	0.89 (0.72–1.11)	0.30	0.357
rs8050136[e]	*FTO*	**0.78 (0.64–0.95)**	**0.013**	**0.70 (0.53–0.93)**	**0.013**	0.88 (0.66–1.17)	0.37	0.420
rs560887[e]	*G6PC2*	1.16 (0.88–1.52)	0.30	0.98 (0.67–1.44)	0.93	1.46 (0.98–2.18)	0.065	0.386
rs1799884[c]	*GCK*	1.10 (0.93–1.30)	0.29	**1.27 (1.01–1.61)**	**0.044**	0.92 (0.72–1.18)	0.51	0.254
rs1260326	*GCKR*	0.92 (0.78–1.08)	0.32	0.93 (0.74–1.17)	0.53	0.90 (0.71–1.13)	0.36	0.926
rs1111875	*HHEX*	1.14 (0.98–1.33)	0.093	1.09 (0.88–1.36)	0.41	1.21 (0.97–1.52)	0.095	0.452
rs35767[e]	*IGF1*	**2.13 (1.35–3.37)**	**0.0012**	1.69 (0.94–3.02)	0.079	**3.13 (1.46–6.71)**	**0.0026**	0.538
rs4402960	*IGF2BP2*	1.05 (0.91–1.22)	0.52	0.95 (0.77–1.16)	0.60	1.16 (0.93–1.44)	0.18	0.304
rs20541	*IL13*	1.01 (0.86–1.18)	0.91	1.14 (0.92–1.42)	0.22	0.88 (0.70–1.10)	0.26	0.147
rs2943641	*IRS1*	1.08 (0.93–1.26)	0.31	1.16 (0.94–1.43)	0.17	1.00 (0.80–1.24)	0.99	0.492
rs864745[e]	*JAZF1*	0.88 (0.74–1.04)	0.14	0.98 (0.77–1.25)	0.85	0.79 (0.61–1.01)	0.060	0.225
rs5215	*KCNJ11*	**0.85 (0.73–0.99)**	**0.038**	0.89 (0.72–1.10)	0.28	0.82 (0.66–1.02)	0.074	0.795
rs5219	*KCNJ11*	**0.84 (0.72–0.99)**	**0.034**	0.92 (0.74–1.14)	0.43	**0.78 (0.62–0.98)**	**0.033**	0.587
rs2237897[c]	*KCNQ1*	1.25 (0.97–1.61)	0.081	1.08 (0.74–1.56)	0.69	1.42 (1.00–2.01)	0.052	0.580
rs2074196	*KCNQ1*	1.01 (0.75–1.37)	0.93	0.80 (0.50–1.27)	0.33	1.21 (0.81–1.81)	0.35	0.456
rs2237892	*KCNQ1*	**1.32 (1.01–1.71)**	**0.039**	1.15 (0.78–1.69)	0.48	**1.47 (1.03–2.10)**	**0.036**	0.741
rs2237895	*KCNQ1*	0.91 (0.77–1.08)	0.28	0.94 (0.75–1.18)	0.59	0.91 (0.71–1.16)	0.44	0.878
rs231362	*KCNQ1OT1*	1.03 (0.87–1.22)	0.71	1.07 (0.85–1.34)	0.59	1.01 (0.80–1.29)	0.92	0.873
rs1041981[e]	*LTA*	**0.76 (0.58–0.99)**	**0.042**	0.85 (0.59–1.21)	0.36	0.68 (0.45–1.01)	**0.050**	0.453
rs7944584[e]	*MADD*	**1.33 (1.06–1.67)**	**0.014**	**1.47 (1.08–2.00)**	**0.015**	1.16 (0.83–1.62)	0.39	0.245
rs12970134	*MCR4*	0.96 (0.82–1.11)	0.58	1.01 (0.82–1.25)	0.89	0.92 (0.72–1.18)	0.51	0.643
rs1387153	*MTNR1B*	1.03 (0.89–1.19)	0.73	1.01 (0.82–1.24)	0.91	1.05 (0.85–1.30)	0.67	0.761
rs10923931[c]	*NOTCH2*	0.88 (0.73–1.06)	0.16	**0.66 (0.50–0.86)**	**0.0019**	1.15 (0.89–1.50)	0.29	**0.0004**
rs7957197[e]	*HNF1A, OASL*	1.33 (0.93–1.92)	0.12	1.60 (0.98–2.60)	0.059	1.04 (0.60–1.81)	0.88	0.388
rs6698181	*PKN2*	1.00 (0.85–1.17)	0.99	1.10 (0.88–1.36)	0.41	0.90 (0.72–1.12)	0.34	0.450
rs1801282	*PPARG*	1.06 (0.89–1.26)	0.52	1.02 (0.80–1.30)	0.88	1.11 (0.86–1.43)	0.43	0.655
rs8042680[e]	*PRC1*	1.24 (0.99–1.55)	0.056	1.21 (0.89–1.64)	0.24	1.37 (0.99–1.89)	0.055	0.777
rs340874	*PROX1*	0.95 (0.80–1.13)	0.55	0.90 (0.71–1.14)	0.37	1.02 (0.79–1.30)	0.89	0.387
rs7593730	*RBMS1*	1.10 (0.95–1.29)	0.20	1.18 (0.95–1.46)	0.13	1.06 (0.85–1.33)	0.58	0.852
rs1531343	*RPSAP52, HMGA2*	0.96 (0.81–1.15)	0.69	1.07 (0.84–1.37)	0.57	0.86 (0.66–1.11)	0.24	0.288
rs11920090	*SLC2A2*	1.02 (0.86–1.20)	0.84	1.17 (0.93–1.47)	0.18	0.88 (0.68–1.12)	0.29	0.257

T able2AssociationofT2D-relatedvariantsandriskofdevelopingMM

Variant_dbSNP	Gene	Overall ($n=3278$)		Men ($n=1657$)		Women ($n=1621$)		$P_{interaction}$
		OR (95% CI)[a]	*P* value	OR (95% CI)[b]	*P* value	OR (95% CI)[b]	*P* value	
rs13266634	*SLC30A8*	0.91 (0.78–1.05)	0.19	0.95 (0.78–1.17)	0.64	0.86 (0.69–1.07)	0.17	0.727
rs7501939	*TCF2*	1.06 (0.91–1.24)	0.43	1.06 (0.85–1.33)	0.58	1.11 (0.89–1.38)	0.37	0.440
rs7903146	*TCF7L2*	0.99 (0.85–1.15)	0.90	1.10 (0.89–1.36)	0.37	0.88 (0.71–1.10)	0.26	0.487
rs12255372	*TCF7L2*	0.94 (0.81–1.09)	0.43	1.06 (0.86–1.30)	0.60	0.83 (0.67–1.03)	0.088	0.452
rs7578597[c]	*THADA*	**0.81 (0.68–0.98)**	**0.032**	0.91 (0.70–1.18)	0.47	**0.73 (0.56–0.96)**	**0.025**	0.125
rs896854[c]	*TP53INP1*	1.17 (0.99–1.39)	0.072	1.22 (0.96–1.55)	0.01	1.13 (0.88–1.45)	0.33	0.269
rs7961581	*TSPAN8, LGR5*	1.03 (0.89–1.19)	0.71	1.03 (0.84–1.27)	0.78	1.04 (0.84–1.29)	0.71	0.973
rs9472138	*VEGFA*	1.13 (0.97–1.31)	0.11	1.19 (0.97–1.46)	0.10	1.09 (0.88–1.35)	0.43	0.737
rs734312	*WFS1*	0.98 (0.83–1.16)	0.84	1.05 (0.83–1.33)	0.67	0.90 (0.71–1.15)	0.39	0.593
rs10010131	*WFS1*	0.94 (0.80–1.10)	0.42	1.11 (0.89–1.38)	0.34	**0.77 (0.62–0.96)**	**0.022**	0.056

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; NS, not specified. Estimates were adjusted for age, sex, country of origin. $P<0.05$ in bold.
[a]Estimates calculated according to a dominant model of inheritance and adjusted for age, gender and region.
[b]Estimates calculated according to a dominant model of inheritance and adjusted for age and region.
[c]$ADAM30_{rs2641348}$ (per-allele $OR_{MEN}=0.71$, 95% CI 0.55–0.92; $P_{trend}=0.0072$ vs per-allele $OR_{WOMEN}=1.29$, 95% CI 1.00–1.65; $P_{trend}=0.046$). $GCK_{rs1799884}$ (per-allele $OR_{MEN}=1.24$, 95% CI 1.00–1.54; $P_{trend}=0.050$ vs per-allele $OR_{WOMEN}=0.94$, 95% CI 0.75–1.18; $P_{trend}=0.58$). $KCNQ1_{rs2237897}$ (per-allele $OR_{MEN}=1.09$, 95% CI 0.77–1.54; $P_{trend}=0.63$ vs per-allele $OR_{WOMEN}=1.41$, 95% CI 1.02–1.97; $P_{trend}=0.041$). $KCNQ1_{rs2237892}$ (per-allele $OR_{MEN}=1.13$, 95% CI 0.77–1.66; $P_{trend}=0.52$ vs per-allele $OR_{WOMEN}=1.47$, 95% CI 1.04–2.08; $P_{trend}=0.030$). $NOTCH2_{rs10923931}$ (per-allele $OR_{MEN}=0.66$, 95% CI 0.52–0.84; $P_{trend}=0.0007$ vs per-allele $OR_{WOMEN}=1.22$, 95% CI 0.96–1.56; $P_{trend}=0.010$). $THADA_{rs7578597}$ (per-allele $OR_{MEN}=0.96$, 95% CI 0.75–1.22; $P_{trend}=0.73$ vs per-allele $OR_{WOMEN}=0.75$, 95% CI 0.58–0.96; $P_{trend}=0.021$). $TP53INP1_{rs896854}$ (per-allele $OR_{MEN}=1.17$, 95% CI 1.01–1.35; $P_{trend}=0.04$ vs per-allele $OR_{WOMEN}=1.03$, 95% CI 0.89–1.20; $P_{trend}=0.68$).
[d]$ADAM30_{rs2641348}$ ($OR_{RECESSIVE\text{-}MEN}=0.36$, 95% CI 0.12–1.13; $P=0.060$ vs $OR_{RECESSIVE\text{-}WOMEN}=4.40$, 95% CI 1.44–13.40; $P=0.0059$).
[e]Estimates calculated according to a recessive model of inheritance.

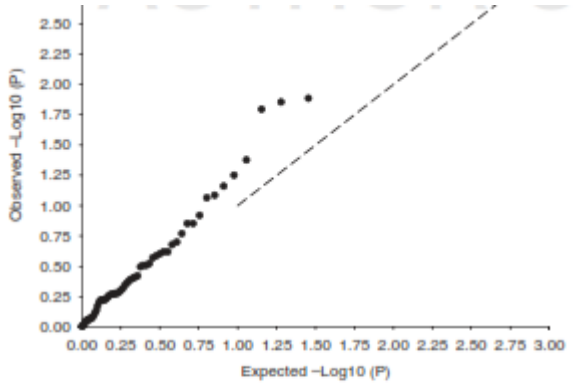

Figure 1
QQ plot used to evaluate the magnitude of observed associations of T2D-related variants with risk of MM. QQ plot was calculated assuming a recessive model of inheritance. Deviation from the expected distribution is observed above an expected X^2 of 0.75. The x-axis is -log10 of the expected *P* values (under a null hypothesis of no effects) whereas the y-axis is -log10 values of the actual *P* values.

Table 3 Discriminative value AUC for models including T2D-related variants

SNPs	*P* value	OR 95% CI	AUC 95% CI[a,b]
Reference model[c]			
Gender	0.731	0.972 (0.828–1.141)	
Age	$<2.00\times10^{-16}$	1.036 (1.030–1.042)	0.629 (0.607–0.650)[e]
Predictive model built with six significant SNPs[d]			
IGF1$_{rs35767}$	0.004	2.076 (1.258–3.426)	
FTO$_{rs8050136}$	0.002	0.723 (0.586–0.892)	
MADD$_{rs7944584}$	0.094	1.218 (0.967–1.535)	
PRC1$_{rs8042680}$	0.061	1.261 (0.989–1.607)	
KCNJ11$_{rs5215}$	0.027	0.832 (0.706–0.980)	
KCNQ1$_{rs2237892}$	0.008	1.468 (1.106–1.950)	
Gender	0.776	1.024 (0.871–1.204)	
Age	$<2.00\times10^{-16}$	1.037 (1.031–1.043)	0.645 (0.624–0.666)[ef]

[a]Including age and gender as variables never dropped from models.
[b]Compared with a baseline model with AUC = 0.5.
[c]Including age and gender as covariates.
[d]SNPs showing a significant association with MM ($P<0.05$). After removing missing values, 2460 subjects were available for prediction capacity analysis.
[e]A LR test showed that the model including genetic variants fitted the data better than the reference model and that the difference in model fit between both models was statistically significant (−2log likelihood ratio test, df = 6, $P=4.05\times10^{-06}$). residual deviance (reference model): 3380.4. residual deviance (significant SNPs model): 3345.2.
[f]A sort analysis revealed that this model showed an AUC value systematically higher than those observed in 10 000 randomized models (null distribution; *Z* score = 6.42, $P=6.81\times10^{-11}$; Supplementary Material).