

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

Rafael Ríos^{1,2,*}, Carmen Belén Lupiáñez^{1,2,*}, Daniele Campa^{3,4}, Alessandro Martino³, Joaquin Martínez-López⁵, Manuel Martínez-Bueno⁶, Judit Varkonyi⁷, Ramón García-Sanz⁸, Krzysztof Jamrozak⁹, Charles Dumontet¹⁰, Andrés Jerez Cayuela¹¹, Marzena Wętek¹², Stephano Landi⁴, Anna Maria Rossi⁴, Fabienne Lesueur¹³, Rui Manuel Reis^{14,15,16}, Victor Moreno¹⁷, Herlander Marques^{14,15}, Artur Jurczyszyn¹⁸, Vibeke Andersen^{19,20}, Ulla Vogel²⁰, Gabriele Buda²¹, Enrico Orciuolo²¹, Svend E H Jacobsen²², Mario Petrini²¹, Annette J Vangsted²³, Federica Gemignani⁴, Federico Canzian³, Manuel Jurado^{1,2} and Juan Sainz^{1,2}

¹Genomic Oncology Area, GENYO, Centre for Genomics and Oncological Research: Pfizer/ University of Granada/Andalusian Regional Government, PTS, Granada, 18016 Granada, Spain

²Hematology Department, Virgen de las Nieves University Hospital, Granada, Spain

³Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany

⁴Department of Biology, University of Pisa, Pisa, Italy

⁵Department of Hematology, Hospital Universitario Doce de Octubre, Madrid, Spain

⁶Area of Genomic Medicine, GENYO, Centre for Genomics and Oncological Research: Pfizer/ University of Granada/Andalusian Regional Government, PTS Granada, Granada, Spain

⁷Semmelweis University, Budapest, Hungary

⁸Haematology Department, University Hospital of Salamanca and IBSAL, Salamanca, Spain

⁹Medical University of Lodz, Lodz, Poland

¹⁰INSERM UMR 1052/CNRS 5286, Université Claude Bernard Lyon I, Lyon, France

¹¹Morales Meseguer General University Hospital, Murcia, Spain

¹²Haematology Clinic, Holly Cross Cancer Center, Kielce, Poland

¹³INSERM, U900, Genetic Epidemiology of Cancers team, Institut Curie, Mines ParisTech, Paris, France

¹⁴Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal

¹⁵ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal

¹⁶Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil

¹⁷IDIBELL – Catalan Institute of Oncology, University of Barcelona, Barcelona 08907, Spain

¹⁸Department of Hematology, Cracow University Hospital, Cracow, Poland

¹⁹Organ Center, Hospital of Southern Jutland, DK-6200 Aabenraa, Denmark

²⁰Faculty of Health Sciences, Institute of Regional Health Research, University of Southern Denmark, DK-5000 Odense C, Denmark

²¹UO Hematology, Department of Internal and Experimental Medicine, University of Pisa, Pisa, Italy

²²Clinic of Biochemistry and Immunology, Laboratory Center, Hospital of Southern Jutland, Aabenraa, Denmark

²³Department of Haematology, Rigshospitalet and Roskilde Hospital, Copenhagen University, Copenhagen, Denmark

* (R Ríos and C B Lupiáñez contributed equally to this work)

Correspondence should be addressed to J Sainz
Email
 juan.sainz@genyo.es

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 *KCNQ1*_{rs2237892T} allele or the *CDKN2A-2B*_{rs2383208G/G}, *IGF1*_{rs35767T/T} and *MADD*_{rs7944584T/T} genotypes had a significantly increased risk of MM (odds ratio (OR) = 1.32–2.13) whereas those carrying the *KCNJ11*_{rs5215C}, *KCNJ11*_{rs5219T} and *THADA*_{rs7578597C} alleles or the *FTO*_{rs8050136A/A} and *LTA*_{rs1041981C/C} genotypes showed a significantly decreased risk of developing the disease (OR = 0.76–0.85). 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) = 0.645 vs AUC = 0.629; $P = 4.05 \times 10^{-06}$). A gender-stratified analysis also revealed a significant gender effect modification for *ADAM30*_{rs2641348} and *NOTCH2*_{rs10923931} variants ($P_{\text{interaction}} = 0.001$ and 0.0004, respectively). Men carrying the *ADAM30*_{rs2641348C} and *NOTCH2*_{rs10923931T} alleles had a significantly decreased risk of MM whereas an opposite but not significant effect was observed in women ($OR_M = 0.71$ and $OR_M = 0.66$ vs $OR_W = 1.22$ and $OR_W = 1.15$, respectively). These results suggest that T2D-related variants may influence the risk of developing MM and their genotyping might help to improve MM risk prediction models.

Key Words

- ▶ multiple myeloma
- ▶ diabetes
- ▶ genetic variants
- ▶ susceptibility

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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 for MM 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 important mediators 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-powered meta-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 $\geq 99.0\%$. Call rates for all SNPs were $\geq 90.0\%$ with the exception of the *WFS1*_{rs734312} SNP that was excluded from further analyses.

Statistical analysis

The Hardy–Weinberg Equilibrium (HWE) tests were performed in the control group by a standard observed–expected χ^2 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 log-additive model.

In order to account for multiple testing, we calculated an adjusted significance level using the M_{eff} method (Nyholt 2004), which considers the number of independent marker loci ($M_{\text{eff},i}=55$) 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 $\sim\chi^2$ -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 $-2\log$ likelihood ratio (LR) test

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), Florez et al. (2007), Scott et al. (2007), Sladek et al. (2007), Wellcome Trust Case Control (2007), Zeggini et al. (2007) and Mohlke et al. (2008) |
| HMGA2 | rs1531343 | C/G | G | C | Near gene | Voight et al. (2010) and Nielsen et al. (2011) |

Table 1 Continued

| Gene name | dbSNP rs# | Nucleotide substitution | Reference allele IMMENSE | GWAS-identified risk allele for T2D | Location/Aa substitution | References |
|--------------------|------------|-------------------------|--------------------------|-------------------------------------|--------------------------|---|
| <i>HNF1A, TCF1</i> | rs7957197 | A/T | T | T | Intronic | Voight et al. (2010) and Nielsen et al. (2011) |
| <i>IGF1</i> | rs35767 | C/T ^d | C | C | Near gene | Pechlivanis et al. (2007) and Dupuis et al. (2010) |
| <i>IGF2BP2</i> | 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) |
| <i>IL13</i> | 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) |
| <i>IRS1</i> | rs2943641 | C/T | C | C | Near gene | Rung et al. (2009), Voight et al. (2010) and Tang et al. (2013) |
| <i>JAZF1</i> | rs864745 | A/G | A | T | Intronic | Zeggini et al. (2008) and Shu et al. (2010) |
| <i>KCNJ11</i> | rs5215 | T/C ^e | T | C | V337I | Gloyn et al. (2003), 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), Zeggini et al. (2007), Willer et al. (2007) and Mohlke et al. (2008) |
| <i>KCNJ11</i> | rs5219 | C/T ^f | C | T | K23E | |
| <i>KCNQ1</i> | rs2237897 | C/T | T | C | Intronic | Unoki et al. (2008), Yasuda et al. (2008), Tsai et al. (2010) and Yamauchi et al. (2010) |
| <i>KCNQ1</i> | rs2074196 | G/T | G | G | Intronic | |
| <i>KCNQ1</i> | rs2237892 | C/T ^g | C | C | Intronic | |
| <i>KCNQ1</i> | rs2237895 | A/C | A | C | Intronic | |
| <i>KCNQ1OT1</i> | rs231362 | C/T | C | G | Intronic | Tsai et al. (2010), Voight et al. (2010) and Nielsen et al. (2011) |
| <i>LTA</i> | rs1041981 | A/C ^e | A | A | T60N | Hamid et al. (2005) |
| <i>MADD</i> | rs7944584 | A/T ^d | A | A | Intronic | Dupuis et al. (2010) |
| <i>MCR4</i> | rs12970134 | A/G | G | A | Near gene | Chambers et al. (2008) |
| <i>MTNR1B</i> | rs1387153 | C/T | C | T | Near gene | Bouatia-Naji et al. (2009), Prokopenko et al. (2009) and Voight et al. (2010) |
| <i>NOTCH2</i> | rs10923931 | G/T ^h | G | T | Intronic | Mohlke et al. (2008) and Zeggini et al. (2008) |
| <i>PKN2</i> | 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) |
| <i>PPARG</i> | 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) |
| <i>PRC1</i> | rs8042680 | A/C | C | A | Intronic | Voight et al. (2010) and Nielsen et al. (2011) |
| <i>PROX1</i> | rs340874 | A/G | A | G | Promoter | Dupuis et al. (2010) |
| <i>RBMS1</i> | rs7593730 | C/T | C | T | Intronic | Qi et al. (2010) |
| <i>SLC2A2</i> | rs11920090 | A/T | A | T | Intronic | Dupuis et al. (2010) |

Table 1 Continued

| Gene name | dbSNP rs# | Nucleotide substitution | Reference allele IMMENSE | GWAS-identified risk allele for T2D | Location/Aa substitution | References |
|-----------------|------------|-------------------------|-----------------------------|-------------------------------------|--------------------------|--|
| <i>SLC30A8</i> | 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) |
| <i>TCF2</i> | rs7501939 | C/T | C | C | Intronic | Gudmundsson et al. (2007) and Sandhu et al. (2007) |
| <i>TCF7L2</i> | rs7903146 | C/T | C | T | Intronic | Grant et al. (2006), Scott et al. (2006), 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) |
| <i>TCF7L2</i> | rs12255372 | G/T | G | T | Intronic | |
| <i>THADA</i> | rs7578597 | T/C ^e | T | T | T1187A | Zeggini et al. (2008) |
| <i>TP53INP1</i> | rs896854 | A/G | G | G | Intronic | Voight et al. (2010) and Nielsen et al. (2011) |
| <i>TSPAN8</i> | rs7961581 | C/T | T | C | Near gene | Grarup et al. (2008) |
| <i>VEGFA</i> | rs9472138 | C/T | C | T | Near gene | Zeggini et al. (2008) |
| <i>WFS1</i> | rs734312 | A/G | A | NS | H611R | Sandhu et al. (2007) |
| <i>WFS1</i> | 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.

^aC allele was associated with a decreased risk of MM in men whereas an opposite effect was detected in women.

^bG allele was associated with an increased risk of developing MM.

^cA/A genotype was associated with a decreased risk of MM (recessive model).

^dT/T genotype was associated with a decreased risk of MM (recessive model).

^eC allele was associated with a decreased risk of MM.

^fT allele was associated with an increased risk of MM.

^gT allele was associated with an increased risk of MM.

^hT allele was associated with a decreased risk of MM in men whereas an opposite effect was detected in women.

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 $P_{\text{iterations}}$ -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 $P_{Z \text{ score}}$ -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 χ^2 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 ($P > 0.001$) with the exception of the *COLSA1*_{rs4240702}, which was therefore excluded from the statistical analyses. Logistic regression analysis showed that carriers of the *KCNQ1*_{rs2237892T} allele or the *CDKN2A-2B*_{rs2383208G/G}, *IGF1*_{rs35767T/T} and *MADD*_{rs7944584T/T} genotypes had an increased risk of MM (odds ratio (OR) = 1.32, 95% CI 1.01–1.71, $P = 0.039$; OR = 1.86, 95% CI 1.12–3.11, $P = 0.016$; OR = 2.13, 95% CI 1.35–3.37, $P = 0.0012$ and OR = 1.33, 95% CI 1.06–1.67, $P = 0.014$, respectively) whereas those harbouring the *KCNJ11*_{rs5215C}, *KCNJ11*_{rs5219T} and *THADA*_{rs7578597C} alleles or the *FTO*_{rs8050136A/A} and *LTA*_{rs1041981C/C} genotypes showed a decreased risk for the disease (OR = 0.85, 95% CI 0.73–0.99, $P = 0.038$; OR = 0.84, 95% CI 0.72–0.99, $P = 0.034$; OR = 0.81, 95% CI 0.68–0.98, $P = 0.032$; OR = 0.78, 95% CI 0.64–0.95, $P = 0.013$ and OR = 0.76, 95% CI 0.58–0.99, $P = 0.042$, respectively; Table 2). When we corrected for multiple testing (with a threshold of $P = 0.00022$), none of the reported associations remained statistically significant. The strongest association observed was for the *IGF1*_{rs35767} SNP with an increased risk of developing MM (OR = 2.13, 95% CI 1.35–3.37, $P = 0.0012$). 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 (AUC = 0.645 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 ($P = 4.05 \times 10^{-06}$). 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 score = 6.42, $P = 6.81 \times 10^{-11}$; 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 *ADAM30*_{rs2641348} and *NOTCH2*_{rs10923931} SNPs ($P_{\text{interaction}} = 0.001$ and 0.0004 respectively). For *ADAM30*_{rs2641348C} and *NOTCH2*_{rs10923931T} alleles, a significantly reduced risk for the disease was observed in men (per-allele OR = 0.71, 95% CI 0.54–0.94, $P = 0.015$ and per-allele OR = 0.66, 95% CI 0.50–0.86, $P = 0.0019$, respectively) whereas a non-significant opposite effect was seen in women (per-allele OR = 1.22, 95% CI 0.93–1.60 and per-allele OR = 1.15, 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 ($P_{\text{HET}} = 0.0039$ and $I^2 = 87.99\%$ and $P_{\text{HET}} = 0.0024$ and $I^2 = 89.12\%$, 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 gender-specific associations for *WFS1*_{rs10010131}, *THADA*_{rs7578597}, *EXT2*_{rs1113132} and *GCK*_{rs1799884} 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 $P = 0.00022$), we found that the effect of the *IGF1*_{rs35767} variant was stronger in women than men with an association approaching significance with an increased risk of developing MM (OR = 3.13, 95% CI 1.46–6.71, $P = 0.0026$ vs OR = 1.69, 95% CI 0.94–3.02, $P = 0.079$ respectively). In addition, we found that the association of *NOTCH2*_{rs10923931} SNP with a decreased risk of MM in men was close to significance according to dominant and log-additive models (OR = 0.66, 95% CI 0.50–0.86,

Table 2 Association of T2D-related variants and risk of developing MM

| 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 | |
| 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 | CDK123, 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 | CDCAL1 | 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 | HNFA1, 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 | RPSAP5, 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 |

Table 2 Continued

| 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 |
| 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 |
| 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 |
| 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 |
| rs1225372 | 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |

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.

^aEstimates calculated according to a dominant model of inheritance and adjusted for age, gender and region.

^bEstimates calculated according to a dominant model of inheritance and adjusted for age and region.

^cADAM30_{rs2641348} (per-allele OR_{MEN} = 0.71, 95% CI 0.55–0.92; $P_{\text{trend}} = 0.0072$ vs per-allele OR_{WOMEN} = 1.29, 95% CI 1.00–1.65; $P_{\text{trend}} = 0.046$). GCK_{rs1799884} (per-allele OR_{MEN} = 1.24, 95% CI 1.00–1.54; $P_{\text{trend}} = 0.050$ vs per-allele OR_{WOMEN} = 0.94, 95% CI 0.75–1.18; $P_{\text{trend}} = 0.58$). KCNQ1_{rs2237897} (per-allele OR_{MEN} = 1.09, 95% CI 0.77–1.54; $P_{\text{trend}} = 0.63$ vs per-allele OR_{WOMEN} = 1.41, 95% CI 1.02–1.97; $P_{\text{trend}} = 0.041$). KCNQ1_{rs2237892} (per-allele OR_{MEN} = 1.13, 95% CI 0.77–1.66; $P_{\text{trend}} = 0.52$ vs per-allele OR_{WOMEN} = 1.47, 95% CI 1.04–2.08; $P_{\text{trend}} = 0.030$). NOTCH2_{rs10923831} (per-allele OR_{MEN} = 0.66, 95% CI 0.52–0.84; $P_{\text{trend}} = 0.0007$ vs per-allele OR_{WOMEN} = 1.22, 95% CI 0.96–1.56; $P_{\text{trend}} = 0.010$). THADA_{rs7578597} (per-allele OR_{MEN} = 0.96, 95% CI 0.75–1.22; $P_{\text{trend}} = 0.73$ vs per-allele OR_{WOMEN} = 0.75, 95% CI 0.58–0.96; $P_{\text{trend}} = 0.021$). TP53INP1_{rs896854} (per-allele OR_{MEN} = 1.17, 95% CI 1.01–1.35; $P_{\text{trend}} = 0.04$ vs per-allele OR_{WOMEN} = 1.03, 95% CI 0.89–1.20; $P_{\text{trend}} = 0.68$).

^dADAM30_{rs2641348} (OR_{RECESSIVE-MEN} = 0.36, 95% CI 0.12–1.13; $P = 0.060$ vs OR_{RECESSIVE-WOMEN} = 4.40, 95% CI 1.44–13.40; $P = 0.0059$).

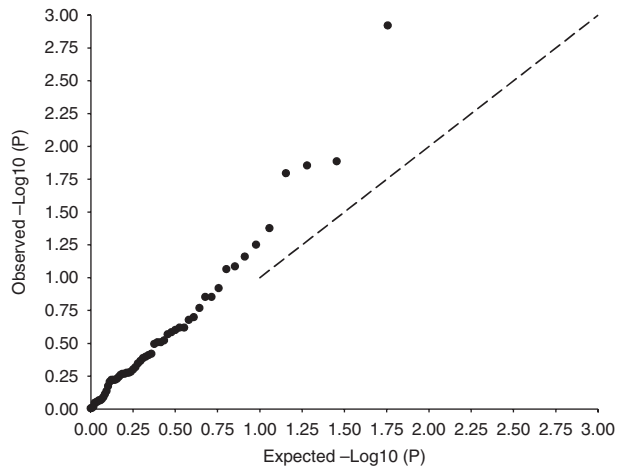
^eEstimates calculated according to a recessive model of inheritance.

$P = 0.0019$ and $P_{\text{trend}} = 0.0007$), which may suggest a gender-specific allele-dosage effect for this variant to modulate the disease risk ($P_{\text{interaction}} = 0.0004$; Table 2). According to a log-additive model, we also found that the association of the ADAM30_{rs2641348C} allele with a decreased risk of MM in men showed a slight trend to be significant considering multiple testing (OR = 0.71, 95% CI 0.55–0.92, $P = 0.0072$) whereas, according to a recessive model, the association of the ADAM30_{rs2641348C/C} genotype was also close to survive multiple testing correction (OR = 4.40, 95% CI 1.44–13.40, $P = 0.00059$; 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 KCNQ1_{rs2237892T} allele, CDKN2A-2B_{rs2383208G/G}, IGF1_{rs35767T/T} and MADD_{rs7944584T/T} genotypes were at increased risk of MM, whereas those carrying the KCNJ11_{rs5215C}, KCNJ11_{rs5219T} and THADA_{rs7578597C} alleles or the FTO_{rs8050136A/A} and LTA_{rs1041981C/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 the modulation 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 T2D-related variants may determine the risk of MM through non-diabetogenic mechanisms.

When we took into account multiple testing corrections, only the association of the IGF1_{rs35767} promoter

**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 χ^2 of 0.75. The x-axis is $-\log_{10}$ of the expected P values (under a null hypothesis of no effects) whereas the y-axis is $-\log_{10}$ values of the actual P values.

polymorphism with an increased risk of developing MM remained close to significance ($P=0.0012$), 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, it 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 *IGF1*_{rs35767} 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 *IGF1*_{rs35767T} 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 *IGF1*_{rs35767} SNP may be responsible for the effect attributed to diabetes on the risk of MM, we believe that rather than

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

| SNPs | <i>P</i> value | OR 95% CI | AUC 95% CI ^{ab} |
|---|-------------------------|---------------------|-----------------------------------|
| Reference model ^c | | | |
| Gender | 0.731 | 0.972 (0.828–1.141) | |
| Age | $<2.00 \times 10^{-16}$ | 1.036 (1.030–1.042) | 0.629 (0.607–0.650) ^e |
| Predictive model built with six significant SNPs ^d | | | |
| <i>IGF1</i> _{rs35767} | 0.004 | 2.076 (1.258–3.426) | |
| <i>FTO</i> _{rs8050136} | 0.002 | 0.723 (0.586–0.892) | |
| <i>MADD</i> _{rs7944584} | 0.094 | 1.218 (0.967–1.535) | |
| <i>PRC1</i> _{rs8042680} | 0.061 | 1.261 (0.989–1.607) | |
| <i>KCNJ11</i> _{rs5215} | 0.027 | 0.832 (0.706–0.980) | |
| <i>KCNQ1</i> _{rs2237892} | 0.008 | 1.468 (1.106–1.950) | |
| Gender | 0.776 | 1.024 (0.871–1.204) | |
| Age | $<2.00 \times 10^{-16}$ | 1.037 (1.031–1.043) | 0.645 (0.624–0.666) ^{ef} |

^aIncluding age and gender as variables never dropped from models.

^bCompared with a baseline model with AUC=0.5.

^cIncluding age and gender as covariates.

^dSNPs showing a significant association with MM ($P<0.05$). After removing missing values, 2460 subjects were available for prediction capacity analysis.

^eA 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 ($-2\log$ likelihood ratio test, $df=6$, $P=4.05 \times 10^{-06}$). residual deviance (reference model): 3380.4. residual deviance (significant SNPs model): 3345.2.

^fA 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, $P=6.81 \times 10^{-11}$; Supplementary Material).

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 randomized models 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 *LTA*_{rs1041981} SNP with a decreased risk of MM showed a similar direction to that observed in the GWAS for T2D (*LTA*_{rs1041981A} 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 *FTO*_{rs8050136} 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 *ADAM30*_{rs2641348}, and *NOTCH2*_{rs10923931} SNPs, which suggested a gender-specific effect of these loci to modulate the risk of MM. We observed that, according to a log-additive model of inheritance, the association of the *NOTCH2*_{rs10923931} SNP with a decreased risk of MM in men and the association of *ADAM30*_{rs2641348C/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 *NOTCH2*_{rs10923931} and *ADAM30*_{rs2641348} 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 gender-specific 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 $\alpha = 0.00022$ (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.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/ERC-15-0029>.

Declaration of interest

V Andersen is receiving compensation as a consultant for MSD (Merck) and Janssen. The rest of the authors have nothing to disclose.

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