

# Genetic Risk Reclassification for Type 2 Diabetes by Age Below or Above 50 Years Using 40 Type 2 Diabetes Risk Single Nucleotide Polymorphisms

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preventive strategies could delay diabetes onset (11).

## RESEARCH DESIGN AND METHODS

— We have previously described the methods (1). We pooled data of the Framingham Offspring Study (12) into four time periods (exams 1 and 2, 2 to 4, 4 to 6, and 6 to 8) (3), extending follow-up 6 years beyond our previous report (1). We generated 11,358 person-observations for 3,471 subjects with available genetic data. We excluded prevalent diabetes at the baseline of each period. Diabetes was defined as fasting plasma glucose >7.0 mmol/l (>125 mg/dl) or use of antidiabetic therapy.

We genotyped or imputed 40 autosomal diabetes-SNPs reported in European-origin populations (4–10), thus adding 23 new SNPs and excluding *INS* from our previous 18-SNP analysis (1). Genotypes were obtained from Affymetrix array data available in the Framingham Heart Study SNP Health Associate Resource dataset (13) or from de novo genotyping on the iPLEX (Sequenom) platform. Minimum call rates were 97% for Affymetrix and 96.9% for iPLEX SNPs. All SNPs were in Hardy-Weinberg equilibrium. Median variance ratio for the imputed SNPs was 0.94; only for rs725210 at *HNF1B*, the variance ratio was <0.3 (namely, 0.2).

We modeled the 40 SNPs by constructing a 40-SNP weighted genetic risk score based on the published  $\beta$  coefficients (8,10) (see footnote, Table 1) and alternatively by entering one term per SNP in an additive model using the expected or observed number of minor alleles plus terms for sex or clinical variables. A general nonadditive genetic model was also fit for each SNP, but inclusion of a nonadditive term did not improve the fit ( $P > 0.043$  for all SNPs). We also performed bootstrap resampling with replacement to assess the degree of statistical overestimation.

Association tests were done after age-stratification (<50 and  $\geq$ 50 years) and in the sample overall. We compared the mean genetic risk score for persons who

**OBJECTIVE** — To test if knowledge of type 2 diabetes genetic variants improves disease prediction.

**RESEARCH DESIGN AND METHODS** — We tested 40 single nucleotide polymorphisms (SNPs) associated with diabetes in 3,471 Framingham Offspring Study subjects followed over 34 years using pooled logistic regression models stratified by age (<50 years, diabetes cases = 144; or  $\geq$ 50 years, diabetes cases = 302). Models included clinical risk factors and a 40-SNP weighted genetic risk score.

**RESULTS** — In people <50 years of age, the clinical risk factors model C-statistic was 0.908; the 40-SNP score increased it to 0.911 ( $P = 0.3$ ; net reclassification improvement (NRI): 10.2%,  $P = 0.001$ ). In people  $\geq$ 50 years of age, the C-statistics without and with the score were 0.883 and 0.884 ( $P = 0.2$ ; NRI: 0.4%). The risk per risk allele was higher in people <50 than  $\geq$ 50 years of age (24 vs. 11%;  $P$  value for age interaction = 0.02).

**CONCLUSIONS** — Knowledge of common genetic variation appropriately reclassifies younger people for type 2 diabetes risk beyond clinical risk factors but not older people.

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A genetic risk score built with 18 type 2 diabetes genetic loci predicted new diabetes cases (1), though it did not add to common diabetes clinical risk factors that usually appear during adulthood (1–3). In recent years, the number of genetic loci convincingly associated with diabetes has doubled (4–10).

Here, we test two hypotheses: an updated genetic risk score incorporating a larger number of common diabetes-associated single nucleotide polymorphisms (SNPs) improves  $\sim$ 8-year risk prediction of diabetes beyond common clinical diabetes risk factors; and the predictive ability is better in younger subjects in whom early

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**Table 1—Odds ratios (ORs) and risk for incident type 2 diabetes associated with 40 individual SNPs, a weighted 40-SNP genetic risk score, and a weighted 17-SNP genetic risk score in the Framingham Offspring Study, stratified by age (<50 years and ≥50 years old), in the simple clinical variables—adjusted model†**

	Subjects <50 years old (n = 144 diabetes cases)			
	Model without genetic information	Model using 40 individual SNPs	Model using 40-SNP weighted risk score	Model using prior 17-SNP weighted risk score
Men (vs. women)	0.45 (0.30–0.68)	0.43 (0.28–0.67)	0.46 (0.30–0.70)	0.46 (0.30–0.70)
Family history of diabetes vs. not	2.26 (1.55–3.30)	2.22 (1.49–3.29)	2.20 (1.50–3.22)	2.18 (1.49–3.19)
BMI (kg/m <sup>2</sup> )	1.10 (1.06–1.14)	1.11 (1.07–1.15)	1.11 (1.07–1.15)	1.11 (1.08–1.15)
Fasting plasma glucose (mg/dl)	1.14 (1.11–1.16)	1.13 (1.11–1.16)	1.13 (1.11–1.16)	1.13 (1.11–1.16)
Systolic blood pressure (mmHg)	1.02 (1.01–1.03)	1.03 (1.01–1.04)	1.02 (1.01–1.03)	1.02 (1.01–1.03)
HDL cholesterol (mg/dl)	0.96 (0.95–0.98)	0.96 (0.95–0.98)	0.96 (0.95–0.98)	0.96 (0.95–0.98)
Fasting triglycerides (mg/dl)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.02)	1.00 (1.00–1.00)
Genetic risk score	—	—	1.24 (1.13–1.36)	1.39 (1.22–1.59)
C-statistic (95% CI)	0.908 (0.884–0.932)	0.920 (0.898–0.941)	0.911 (0.887–0.935)	0.909 (0.884–0.933)
P value for difference in C-statistic		<b>0.02</b>	0.3	0.89
Calibration $\chi^2$ (P value)		4.37 (0.8)	6.60 (0.6)	9.78 (0.28)
NRI (%)		11.4	10.2	7.5
P value		<b>0.002</b>	<b>0.001</b>	<b>0.01</b>
	Subjects ≥50 years old (n = 302 diabetes cases)			
	Model without genetic information	Model using 40 individual SNPs	Model using 40-SNP weighted risk score	Model using prior 17-SNP weighted risk score
Men (vs. women)	1.03 (0.76–1.38)	1.04 (0.76–1.41)	1.05 (0.78–1.41)	1.05 (0.78–1.41)
Family history of diabetes vs. not	2.09 (1.54–2.85)	2.18 (1.58–3.00)	2.11 (1.55–2.88)	2.12 (1.56–2.88)
BMI (kg/m <sup>2</sup> )	1.08 (1.05–1.11)	1.09 (1.06–1.12)	1.09 (1.06–1.12)	1.09 (1.06–1.12)
Fasting plasma glucose (mg/dl)	1.14 (1.13–1.16)	1.14 (1.12–1.16)	1.14 (1.12–1.16)	1.14 (1.12–1.16)
Systolic blood pressure (mmHg)	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (1.01–1.02)	1.01 (1.01–1.02)
HDL cholesterol (mg/dl)	0.98 (0.97–0.99)	0.98 (0.97–0.99)	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Fasting triglycerides (mg/dl)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Genetic risk score	—	—	1.11 (1.03–1.19)	1.13 (1.02–1.25)
C-statistic (95% CI)	0.883 (0.863–0.903)	0.888 (0.869–0.908)	0.884 (0.865–0.904)	0.884 (0.865–0.904)
P value for difference in C-statistic		<b>0.02</b>	0.2	0.18
Calibration $\chi^2$ (P value)		10.97 (0.2)	15.01 (0.06)	8.46 (0.39)
NRI (%)		5.7	0.4	0.02%
P value		<b>0.001</b>	0.7	0.98

Data are OR (95% CI) unless otherwise indicated. Data in bold represent statistical significance. †The simple clinical variables—adjusted model included sex, family history of diabetes (self-report that one or both parents had diabetes), BMI, fasting glucose level, systolic blood pressure, HDL cholesterol, and fasting triglycerides levels (3). No age adjustment was done in the age-stratified models.

To evaluate the individual contribution of each SNP, we entered one term per SNP (total 40 terms plus terms for sex or clinical variables) in the logistic regression models.

We constructed a weighted genetic risk score using 40 SNPs currently associated with type 2 diabetes and a weighted genetic risk score using 17 SNPs that we used in our previous report (1). rs689 at *INS* on chromosome 11, previously included in our 18-SNP genetic risk score (1), was not replicated in posterior meta-analyses and is therefore not included in the current 17-SNP or 40-SNP analyses. Moreover, rs5945326 at *DUSP9* on chromosome X (10) is not included in the analysis because there are no available genotyping or imputation data for this SNP in the Framingham Offspring Study.

For the construction of the weighted risk scores, we counted risk alleles (0, 1, 2) for each genotyped SNP—or its dosage when imputed—(actual distribution ranging from 28 to 53) and multiplied each SNP genotype by its published  $\beta$  coefficient for diabetes risk (10). We added up the product of that multiplication at each SNP, divided the sum by twice the sum of the  $\beta$  coefficients, and multiplied the result by the number of SNPs.

ORs, 95% CIs, and C-statistics for the 144 cases of diabetes in 6,763 person-observations in subjects <50 years old and for the 302 cases of diabetes in 4,595 person-observations in subjects ≥50 years old were calculated using pooled logistic regression with generalized estimating equations. Mean age at diabetes onset was 49.30 years for subjects <50 years old at baseline and 66.07 years for subjects ≥50 years old at baseline. We took 50 years as the age cutoff point because of the low incidence rate of diabetes in younger subjects when lower values were chosen. Sensitivity analyses using a cutoff age of 45 years (84 cases in 5,095 person-observations) showed a lower NRI in younger subjects (3.59%;  $P = 0.2$ ), though this result should be taken with caution because of the low number of cases.

For NRI evaluation, we established three risk categories (low, intermediate, and high). The percentages of low, medium, and high risk of diabetes are based on the distribution of the cumulative incidence of diabetes across our population, in which cumulative incidence was low for a predicted risk <2%, intermediate for predicted risks ≥2% and ≤8%, and high when predicted risk was >8% (this assumption is an a priori requirement for the NRI calculation) (15). NRI is better if more people who develop diabetes are reclassified as higher risk when the genotype score is added to the model, and more people who remain free of diabetes are classified as lower risk when the score is added. The NRI is penalized for misclassification; for instance, if many people who develop diabetes are classified as lower risk by adding the genetic risk score to the model.

Data for the sex-adjusted model in age-stratified analyses are shown in supplementary Table A3. Complete data for the population overall are shown in supplementary Table A4.

did develop diabetes with those who did not using mixed-effects linear models to account for family relatedness. Likewise, we used generalized estimating equations in pooled logistic-regression models (14) to test associations of the genetic risk scores with diabetes onset in sex- and simple clinical diabetes risk factors–adjusted models, which included sex, family history of diabetes (self-report that any parent had diabetes), BMI, fasting glucose and triglyceride levels, systolic blood pressure, and HDL cholesterol (3).

We evaluated model discrimination using C-statistics and net reclassification improvement (NRI) (15) (see footnote, Table 1). A two-tailed *P* value <0.05 indicated statistical significance. The institutional review board at Boston University approved the study, and all participants gave written informed consent.

**RESULTS**— Mean age was  $36 \pm 9$  years at the first exam; nearly half the subjects were men, and BMI increased over follow-up (supplementary Table A1 in the online appendix available at <http://care.diabetesjournals.org/cgi/content/full/dc10-1265/DC1>). Over 11,358 person-observations we diagnosed 446 cases of diabetes. Few individual SNPs were significantly associated with diabetes in our sample, but for most SNPs the effects were in the same direction as in the original reports and of expected effect sizes (1.05–1.3) (supplementary Table A2). Individuals who developed diabetes had higher genetic risk scores than those who did not (20.4 vs. 19.7;  $P = 1.7 \times 10^{-10}$ ).

The 40-SNP genetic risk score significantly reclassified subjects <50 years of age in the simple clinical variables model (NRI: 10.2%;  $P = 0.001$ ), although it did not improve model discrimination ( $P = 0.3$ ) (Table 1). In subjects  $\geq 50$  years, the 40-SNP score neither improved model discrimination ( $P = 0.2$ ) nor risk reclassification (NRI: 0.4%;  $P = 0.7$ ). The relative risk per risk allele was higher in subjects <50 years of age (24%) than in those  $\geq 50$  years of age (11%) ( $P = 0.02$  for age-interaction effect). Results for the sex-adjusted model are shown in supplementary Table A3.

We also tested a weighted genetic risk score constructed with the originally modeled 17 SNPs (1), whereby fewer subjects were appropriately reclassified for diabetes risk (Table 1).

In the population overall, the 40-SNP genetic risk score marginally improved

risk prediction (C-statistics: 0.903 and 0.906, without and with the score;  $P = 0.04$ ), whereas the 17-SNP score did not ( $P = 0.11$ ) (supplementary Table A4). In the whole population, NRI with the score was lower than in subjects <50 years of age (at most, 1.8%).

The individual incorporation of 40 SNPs improved model discrimination beyond the 40-SNP score (C-statistics: 0.908 and 0.920 without and with individual SNPs;  $P = 0.02$ ), but after bootstrap resampling, median C-statistic values dropped to 0.905 and 0.907, respectively, thus lowering optimism about the effect of modeling individual SNPs.

**CONCLUSIONS**— We found that 40 SNPs selected based on the latest genetic association data improved diabetes risk reclassification after accounting for common diabetes clinical risk predictive factors.

The 40 SNPs contributing individually had the highest discrimination ability, but this model was probably overfit. The increased prediction performance of 40 as opposed to 17 SNPs appeared to be due to additional, more comprehensively modeled genetic information rather than to longer follow-up or greater number of diabetes cases as compared to our earlier report.

Limitations include that the Framingham Offspring Study subjects are mostly white and of European ancestry. Although we did not find sufficient evidence for departure from an additive model, we cannot definitely rule out that other nonadditive models are operating. We only analyzed common genetic variants; eventual incorporation of rare variants might enhance prediction. Lastly, criticism has been raised on the somewhat arbitrary assumptions needed to estimate NRI.

In summary, diabetes risk prediction improved with 40 diabetes-associated SNPs, especially in people <50 years of age. More subjects were appropriately reclassified for diabetes risk. Genetic prediction could be useful in younger people. Nonetheless, the clinical usefulness of common genetic variants for diabetes risk prediction should be further confirmed in other samples and in randomized controlled trials.

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J.M.D.M.Y. researched data and wrote the manuscript. P.S. researched data and contributed to discussion. M.J.P., J.D., R.B.D., and L.A.C. researched data, contributed to discussion, and reviewed the manuscript. C.S.F. and A.K.M. researched data and reviewed the manuscript. R.W.G. and J.C.F. contributed to discussion and reviewed the manuscript. J.B.M. contributed to discussion and wrote the manuscript.

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## References

- Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008;359:2208–2219
- Lyssenko V, Jonsson A, Almgren P, Puzlizi N, Isomaa B, Tuomi T, Berglund G, Altshuler D, Nilsson P, Groop L. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* 2008;359:2220–2232
- Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med* 2007;167:1068–1074
- Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Sperlotes EK, Taskiran MR, Tuomi T, Guiducci C, Berglund A, Carlsson J, Gianniny L, Hackett R, Hall L,

- Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tevhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007;316:1331–1336
5. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jørgensen T, Kong A, Kubalanza K, Kuruville FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lysenko V, Marvele AF, Meisinger C, Midhjelld K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Petersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjögren M, Steinthorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ, Wellcome Trust Case Control Consortium, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M, Altshuler D. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* 2008;40:638–645
  6. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadawaki T, Kasuga M. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 2008;40:1092–1097
  7. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, Jonasdottir A, Sigurdsson A, Kristinsson KT, Jonasdottir A, Frigge ML, Gylfason A, Olason PI, Gudjonsson SA, Sverrisson S, Stacey SN, Sigurgeirsson B, Benediktsdottir KR, Sigurdsson H, Jonsson T, Benediktsson R, Olafsson JH, Johannsson OT, Hreidarsson AB, Sigurdsson G, DIAGRAM Consortium, Ferguson-Smith AC, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Parental origin of sequence variants associated with complex diseases. *Nature* 2009;462:868–874
  8. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Mägi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparsø T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proença C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccascella RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Böttcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllenstein U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jørgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimäki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Lysenko V, Mahley R, Mangino M, Manning AK, Martínez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orrù M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadaneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvänen AC, Tanaka T, Thorand B, Tichet J, Tönjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, Vogelzang N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, DIAGRAM Consortium, GIANT Consortium, Global BPgen Consortium, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP, Wichmann HE, Illig T, Rudan I, Wright AF, Stumvoll M, Campbell H, Wilson JF, Anders Hamsten on behalf of Procardis Consortium, MAGIC investigators, Bergman RN, Buchanan TA, Collins FS, Mohlke KL, Tuomilehto J, Valle TT, Altshuler D, Rotter JI, Siscovick DS, Penninx BW, Boomsma DI, Deloukas P, Spector TD, Frayling TM, Ferrucci L, Kong A, Thorsteinsdottir U, Stefansson K, van Duijn CM, Aulchenko YS, Cao A, Scuteri A, Schlessinger D, Uda M, Ruokonen A, Jarvelin MR, Waterworth DM, Vollenweider P, Peltonen L, Mooser V, Abecasis GR, Wareham NJ, Sladek R, Froguel P, Watanabe RM, Meigs JB, Groop L, Boehnke M, McCarthy MI, Florez JC, Barroso I. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 2010;42:105–116
  9. Qi L, Cornelis MC, Kraft P, Stanya KJ, Linda Kao WH, Pankow JS, Dupuis J, Florez JC, Fox CS, Paré G, Sun Q, Girman CJ, Laurie CC, Mirel DB, Manolio TA, Chasman DI, Boerwinkle E, Ridker PM, Hunter DJ, Meigs JB, Lee CH, Hu FB, van Dam RM, Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC), Diabetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium. Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. *Hum Mol Genet* 2010;19:2706–2715
  10. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Langenberg C, Hofmann OM, Dupuis J, Qi L, Segrè AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bengtsson Boström K, Bravenboer B, Bumpstead S, Burtt NP, Charpentier G, Chines PS, Cornelis M, Couper DJ, Crawford G, Doney AS, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves CJ,

- Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PR, Jørgensen T, Kao WH, Klopp N, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Perry JR, Petersen AK, Platou C, Proença C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shradler P, Sigurdsson G, Sparso T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haften TW, van Herpt T, van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllenstein U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Mohlke KL, Morris AD, Palmer CN, Pramstaller PP, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Wareham NJ, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Hu FB, Meigs JB, Pankow JS, Pedersen O, Wichmann HE, Barroso I, Florez JC, Frayling TM, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI, MAGIC investigators, GIANT Consortium. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 2010;42:579–589
11. Grant RW, Moore AF, Florez JC. Genetic architecture of type 2 diabetes: recent progress and clinical implications. *Diabetes Care* 2009;32:1107–1114
  12. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol* 1979;110:281–290
  13. Framingham SNP Health Association Resource [Internet]. National Center for Biotechnology Information. Available from [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000007.v9.p4](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v9.p4). Accessed 8 May 2010
  14. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med* 1990;9:1501–1515
  15. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–172