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ARTICLE

Variations in the *HHEX* gene are associated with increased risk of type 2 diabetes in the Japanese population

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Abstract
Aims/hypothesis Recently, several groups have carried out whole-genome association studies in European and European-origin populations and found novel type 2 diabetes-susceptibility genes, fat mass and obesity associated (*FTO*), solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*), haematopoietically expressed homeobox (*HHEX*), exostoses (multiple) 2 (*EXT2*), CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4) (*CDKN2B*) and insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*), which had not been in the list of functional candidates. The aim of this study was to determine the association between single nucleotide polymorphisms (SNPs) in these genes and type 2 diabetes in participants from the Japanese population.
Methods Sixteen previously reported SNPs were genotyped in 864 Japanese type 2 diabetes individuals (535 men and 329 women; age 63.1±9.5 years (mean±SD), BMI 24.3±3.9 kg/m^2) and 864 Japanese control individuals (386 men and 478 women; age 69.5±6.8 years, BMI 23.8±3.7 kg/m^2).
Results The SNPs rs5015480 [odds ratio (OR)=1.46 (95% CI 1.20–1.77), $p=2.0\times10^{-4}$], rs7923837 [OR=1.40 (95% CI 1.17–1.68), $p=2.0\times10^{-4}$] and rs1111875 [OR=1.30 (95% CI 1.11–1.52), $p=0.0013$] in *HHEX* were significantly associated with type 2 diabetes with the same direction as previously reported. SNP rs8050136 in *FTO* was nominally associated with type 2 diabetes [OR=1.22 (95% CI 1.03–1.46), $p=0.025$]. SNPs in other genes such as rs7756992 in *CDKAL1*, rs10811661 in *CDKN2B* and rs13266634 in *SLC30A8* showed nominal association with type 2 diabetes. rs7756992 in *CDKAL1* and rs10811661 in *CDKN2B* were correlated with impaired pancreatic beta cell function as estimated by the homeostasis model assessment beta index ($p=0.023$, $p=0.0083$, respectively).
Conclusions/interpretation HHEX is a common type 2 diabetes-susceptibility gene across different ethnic groups.

Keywords Japanese population · Single nucleotide polymorphism · Susceptibility gene · Type 2 diabetes

M. Horikoshi and K. Hara contributed equally to this study.

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Abbreviations

HOMA-beta	homeostasis model assessment of beta cell function
HOMA-IR	homeostasis model assessment of insulin resistance
LD	linkage disequilibrium
MAF	minor allele frequency
OR	odds ratio
SNP	single nucleotide polymorphism

Introduction

Type 2 diabetes is a complex disease; multiple genes are involved in its onset and development. To date, a number of genes have been reported to be associated with type 2 diabetes. Most of the genes are investigated because they are presumed to be relevant to the pathogenesis of type 2 diabetes based on the function of the gene. However, because the whole picture of the pathogenesis of type 2 diabetes is still to be clarified, this 'candidate-gene approach' is limited in power to detect novel disease-susceptibility genes.

Due to the recent development of single nucleotide polymorphism (SNP) typing technology and accumulation of the information on the linkage disequilibrium (LD) of the human genome, whole-genome association studies have now become a feasible way of searching for a novel disease-susceptibility gene across the whole genome without prior information as to the function of the gene. Indeed, since the original discovery of the powerful type 2 diabetes gene, transcription factor 7-like 2 (T cell specific, HMG-box) (*TCF7L2*), by a joint group from Iceland, the USA and Denmark [1], many groups have confirmed the significant association between type 2 diabetes and this gene in several populations [2–4]. Following the detection of *TCF7L2*, a number of groups, including French-Canadian [5], Icelandic [6], UK [7, 8], Finnish [9] and Finnish–Swedish [10], have described new type 2 diabetes-susceptibility genes obtained by whole-genome association study. These genes are solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*), haematopoietically expressed homeobox (*HHEX*), exostoses (multiple) 2 (*EXT2*), CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), fat mass and obesity associated (*FTO*), cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) (*CDKN2A*), cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4) (*CDNK2B*) and insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*), which have not been well-documented and thus not thought to be good candidates for type 2 diabetes genes.

It is well known that frequencies of genetic variations are different among ethnic groups, leading to differences in the effect and importance of the same susceptibility gene according to the different ethnic groups. It is especially important to investigate this in populations in Eastern Asia, including Japan and China, where the number of individuals with type 2 diabetes is increasing rapidly. Therefore, we have investigated whether the confirmed type 2 diabetes variants in these genes in Europid populations are also associated with type 2 diabetes in participants from the Japanese population.

Methods

Participants We performed an association study in 864 Japanese type 2 diabetes individuals and 864 Japanese non-diabetic individuals. The clinical characteristics are described in Electronic supplementary material (ESM) Table 1. The diabetic patients were randomly recruited from among those attending the outpatient clinic of the Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo (Tokyo, Japan), and the non-diabetic individuals from among those undergoing annual health check-ups at the Hiroshima Atomic Bomb Casualty Council Health Management Center (Hiroshima, Japan) [3]. Details of the inclusion and exclusion criteria of our case–control samples are described in the ESM. In order to evaluate the possibilities of population stratification in our case–control samples, we chose 50 SNPs from the database of International HapMap project that are not in LD with each other and genotyped them in 382 Tokyo cases and 382 Hiroshima controls. Then, we investigated whether there was inflation of the number of SNPs with $p<0.05$ for association between the 50 SNPs and type 2 diabetes. As described in ESM Table 2, there was no evidence of inflation of the number of SNPs with $p<0.05$. The number of SNPs with $p<0.05$ was 2, whereas the expected number of SNPs with $p<0.05$ was 2.35 (47×0.05, three SNPs were not variants in the Japanese population). All the participants gave informed consent, and the Ethics Committee of the University of Tokyo approved this study.

Selection of SNPs genotyped in this study We selected all the SNPs in genes that were repeatedly confirmed as type 2 diabetes-susceptibility variants in the recent six association studies [5–10]. SNPs that reside in a gene which were reported only in a single study were not included in this study, e.g. SNPs in *LOC387761,* chromosome 4 open reading frame 32 (*FLJ39370*, also known as *C4orf32*) and protein kinase N2 (*PKN2*). SNPs that we had previously reported were also excluded, e.g. SNP rs7903146 in *TCF7L2* and rs1801282 in peroxisome proliferator-activated receptor gamma (*PPARG*). As for *CDKAL1*, SNP rs7754840 was not included as it was only 216 bp downstream of rs10946398, and these were in LD with each other. SNP

rs5219 of potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*) was also excluded because it was within 1 kb of rs5215. All together, 16 SNPs were investigated in this study.

Genotyping SNPs Among the 16 SNPs, *FTO* rs9939609 was genotyped by direct sequencing, performed with a BigDye Terminator (Applied Biosystems, Foster City, CA, USA) and resolved using an ABI 3700 automated DNA sequencer (Applied Biosystems). The rest of the SNPs were genotyped using Taqman SNP genotyping assays by means of an ABI 7900HT (Applied Biosystems) according to the manufacturer's protocol. Genotyping success rates ranged between 97.7% (rs4402960) and 100% (rs9939609). Concordance rate, based on duplicate comparisons in 192 control participants and 192 type 2 diabetes patients, was 100%. Samples with ambiguous base calling were genotyped twice. All the SNPs were in accord with Hardy–Weinberg equilibrium in type 2 diabetes participants ($p>0.09$) and control participants ($p>0.17$).

Evaluating LD The r^2 values between SNPs were estimated using a software package based on the expectation-maximisation algorithm, SNPAlyze version 3.5.0 (Dynacom, Tokyo, Japan). The LD structure was plotted using GOLD software (http://www.sph.umich.edu/csg/abecasis/GOLD/).

Biological measurements Insulin resistance and pancreatic beta cell function were quantified using homeostasis model assessment (HOMA-IR and HOMA-beta, respectively); HOMA-IR=fasting insulin (pmol/l)×glucose (mmol/l)/22.5×6 (correction for μU/l in original formula) and HOMA-beta=fasting insulin (pmol/l)×20/glucose (mmol/l) −3.5×6 (correction for μU/l in original formula) as widely used [11]. Data were expressed as means±SD. Details for the methods of other biological measurements are described in the ESM.

Statistical analysis The proportions of genotypes or alleles were compared between type 2 diabetic and non-diabetic participants using a multiple logistic regression analysis adjusted for age and sex. Differences in HOMA index according to genotypes were determined by analysis of covariates in non-diabetic participants, after adjustment for age and sex. The statistical analyses were performed using JMP for Windows version 6.00 software (SAS Institute, Cary, NC, USA). Values of p were corrected by Bonferroni adjustment and $p<0.0031$ (0.05 divided by 16, the total number of SNPs studied), was considered significant. The allele-specific odds ratio (OR) was assessed by counting the number of risk alleles for each individual, and we used the number of risk alleles to predict case/control status using logistic regression.

Results

The association results of the type 2 diabetes-susceptibility variants in the present study are shown in Table 1. Among the 16 SNPs from eight genes, all three SNPs, rs5015480 [OR=1.46 (95% CI 1.20–1.77), $p=2.0\times10^{-4}$], rs7923837 [OR=1.40 (95% CI 1.17–1.68), $p=2.0\times10^{-4}$] and rs1111875 [OR=1.30 (95% CI 1.11–1.52), $p=0.0013$] in *HHEX* were significantly associated with type 2 diabetes in the Japanese population after adjustment for multiple testing. The OR for SNP rs5015480 was the highest in the present study. The risk alleles were all minor alleles and the associations were in the same direction as the previous studies [5, 8–10]. We determined the LD pattern in this region and found that this region was separated into two LD blocks in our samples; one containing insulin degrading enzyme (*IDE*) and kinesin family member 11 (*KIF11*), and the other containing *HHEX* (ESM Fig. 1). All three SNPs showed nominal association with BMI (rs5015480 TT vs TC vs CC, 24.0±0.15 vs 23.3±0.24 vs 22.1±0.92, $p=0.011$; rs7923837 AA vs AG vs GG, 24.0±0.16 vs 23.3±0.23 vs 23.9±0.70, $p=0.037$; rs1111875 TT vs TC vs CC, 24.1±0.17 vs 23.4±0.20 vs 23.3±0.49, $p=0.042$). When we stratified the participants into obese (BMI≥25 kg/m^2) and non-obese (BMI <25 kg/m^2) participants, each SNP showed a higher OR in the obese participants [OR=1.91 (95% CI 1.34–2.75), $p=5.0\times10^{-4}$; OR=1.58 (95% CI 1.15–2.17), $p=0.0049$; OR=1.51 (95% CI 1.16–1.98), $p=0.0025$, respectively] (ESM Table 3) than in non-obese participants. The associations were negative or only nominally significant in participants with BMI <25 kg/m^2 ($p=0.029$, $p=0.011$ and $p=0.080$, respectively).

Among the two SNPs in the *FTO* gene, only rs8050136 showed a nominal significance in terms of the association with type 2 diabetes [OR=1.22 (95% CI 1.03–1.46), $p=0.025$]. rs8050136 was not associated with BMI (CC 23.8±0.16 vs CA 23.7±0.23 vs AA 23.8±0.49, $p=0.99$), and the nominal association between rs8050136 and type 2 diabetes was not strengthened after correction for BMI [OR=1.22 (95% CI 1.03–1.46), $p=0.025$ adjusted for age, sex and BMI]. The other SNP in the *FTO* gene, rs9939609, was identified as a type 2 diabetes-susceptibility variant that predisposes to diabetes through an effect on BMI in the UK population [7]. However, we could not detect any significant association between rs9939609 and type 2 diabetes or with BMI (TT 24.1±0.17 vs TA 24.6±0.22 vs AA 24.3±0.62, $p=0.17$). No other clinical parameters related to type 2 diabetes such as HbA_{1c}, fasting glucose, fasting insulin, HOMA-IR, and HOMA-beta were associated with rs9939609.

SNPs in *CDKAL1, CDKN2B* and *SLC30A8* genes showed nominally significant association with type 2 diabetes. As for *EXT2*, *IGF2BP2* and *KCNJ11*, we could not detect any SNPs that were significantly associated with type 2 diabetes,

Table 1 Association results for confirmed type 2 diabetes-susceptibility variants in the Japanese population

SNP	Chr	Region	Major allele (A)	Minor allele (a)	Type 2 diabetes		Control		Genotype-specific *p* value	OR (95% CI)	Allele-specific *p* value	Reference
					MAF	AA/Aa/aa	MAF	AA/Aa/aa				
rs1111875	10	*HHEX*	T	C[a]	0.326	394/371/95	0.265	461/342/57	0.0053	1.30 (1.11–1.52)	0.0013	[5, 8–10]
rs7923837	10	*HHEX*	A	G[a]	0.237	496/317/45	0.187	564/264/28	0.0010	1.40 (1.17–1.68)	2.0×10^{-4}	[5]
rs5015480	10	*HHEX*	T	C[a]	0.197	549/279/29	0.146	626/219/16	8.0×10^{-4}	1.46 (1.20–1.77)	2.0×10^{-4}	[8]
rs8050136	16	*FTO*	C	A[a]	0.238	486/334/37	0.200	554/269/38	0.022	1.22 (1.03–1.46)	0.025	[8, 9]
rs9939609	16	*FTO*	T	A[a]	0.220	528/298/38	0.190	573/251/40	0.27	1.10 (0.92–1.32)	0.27	[7]
rs7756992	6	*CDKAL1*	A	G[a]	0.514	238/426/188	0.471	191/450/216	0.027	1.20 (1.03–1.39)	0.017	[6]
rs10946398	6	*CDKAL1*	A	C[a]	0.465	239/434/179	0.429	280/423/158	0.16	1.16 (1.00–1.34)	0.55	[8]
rs10811661	9	*CDKN2B*	T[a]	C	0.387	324/408/129	0.434	290/398/176	0.018	1.22 (1.05–1.41)	0.0076	[8–10]
rs564398	9	*CDKN2B*	T	C[a]	0.164	609/221/31	0.150	623/207/25	0.70	1.08 (0.89–1.32)	0.41	[8]
rs1113132	11	*EXT2*	C[a]	G	0.355	360/390/110	0.381	326/411/122	0.21	1.12 (0.96–1.30)	0.14	[5]
rs11037909	11	*EXT2*	T[a]	C	0.349	366/393/105	0.376	330/417/116	0.21	1.13 (0.97–1.31)	0.12	[5]
rs3740878	11	*EXT2*	A[a]	G	0.357	352/403/106	0.388	318/418/125	0.23	1.14 (0.98–1.33)	0.089	[5]
rs1470579	3	*IGF2BP2*	A	C[a]	0.372	324/432/104	0.345	372/378/107	0.039	1.12 (0.96–1.30)	0.16	[10]
rs4402960	3	*IGF2BP2*	G	T[a]	0.323	384/380/84	0.309	407/348/86	0.65	1.05 (0.90–1.23)	0.55	[8–10]
rs13266634	8	*SLC30A8*	C[a]	T	0.396	328/383/149	0.430	293/394/172	0.055	1.19 (1.03–1.37)	0.016	[5, 6, 8–10]
rs5215	11	KCNJ11	T	C[a]	0.382	334/393/131	0.373	332/417/113	0.56	1.03 (0.89–1.20)	0.68	[8]

The SNPs are shown with the risk allele and MAF and the exact count of each genotype in type 2 diabetes and controls. Genotype-specific *p* values are adjusted for age and sex. Risk allele-specific ORs and *p* values are calculated using an additive genetic model that in logistic regression is multiplicative on the OR scale. The OR for each SNP was adjusted simultaneously for age and sex.
Chr chromosome
[a] Risk allele

but the associations were in the same direction as the previous reports in the European populations.

When we tested the SNPs for quantitative trait association in non-diabetic participants, we found several SNPs to be nominally associated with pancreatic beta cell function as estimated by HOMA-beta. Participants with the risk allele of rs7756992 in *CDKAL1* ($p=0.023$), rs10811661 in *CDKN2B* ($p=0.0083$), rs11037909 ($p=0.0353$) and rs3740878 ($p=0.022$) in *EXT2*, and rs1470579 ($p=0.0446$) and rs4402960 ($p=0.0096$) in *IGF2BP2* had lower HOMA-beta values (Fig. 1). However, when taking the multiple comparisons into account, none of the SNPs reached significance. As for HOMA-IR, none of the SNPs was associated with HOMA-IR.

Discussion

Recent reports have revealed novel type 2 diabetes-susceptibility genes, such as *SLC30A8*, *CDKAL1*, *CDKN2A/2B*, *IGF2BP2*, *EXT2*, *HHEX* and *FTO*, in the European population [5–10]. In this study, we confirmed the significant association of *HHEX* with type 2 diabetes in the Japanese population. The OR values of the three SNPs genotyped in *HHEX* (1.20–1.46) were higher than those of the European population (1.20). However, there was a noticeable difference in the frequencies of the risk alleles; 0.24–0.33 in the Japanese populations and 0.65 in Europids, which was also observed for the *TCF7L2* gene variants in our previous report [3]. We observed a nominal inverse

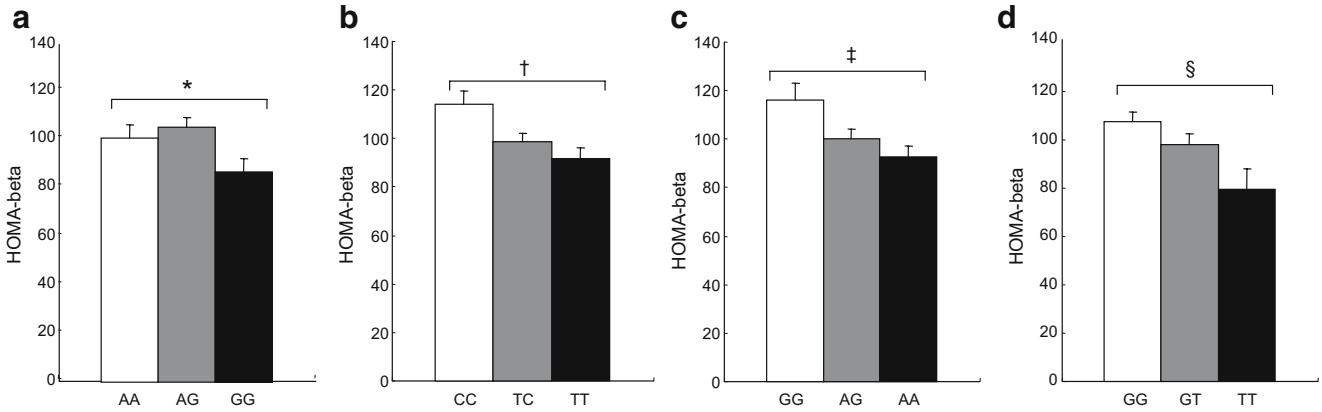

Fig. 1 Association between variants in *CDKAL1* rs7756992 (*p=0.023) (**a**), *CDKN2B* rs10811661 ($^{\dagger}p$=0.0083) (**b**), *EXT2* rs3740878 ($^{\ddagger}p$=0.022) (**c**), and *IGF2BP2* rs4402960 ($^{\S}p$=0.0096) (**d**) with pancreatic beta cell function as estimated by HOMA-beta index. Associations between SNPs representing the four genes and the indices of pancreatic beta cell function are shown. Associations were assessed in non-diabetic participants

association between the SNPs in *HHEX* and BMI in the control participants (p=0.011–0.042). Adjustment for BMI did not strengthen the association between SNPs in *HHEX* and type 2 diabetes. Haplotype analysis of the *HHEX* gene did not strengthen the association, either (p=0.0013). However, when we performed a stratified association study, the ORs grew higher in the group of obese participants. This may indicate that the risk alleles of *HHEX* do not predispose to diabetes through an effect on BMI, but it may predispose to diabetes under obesity-inducing circumstances. Sladek et al. [5] reported that multiple SNPs within an extended region containing *IDE*, *KIF11* and *HHEX* were associated with type 2 diabetes due to preserved LD in this region. In our samples, LD in this region was not relatively preserved and *HHEX* represents one block of strong LD (ESM Fig. 1), suggesting that an SNP in *HHEX* is the functional SNP conferring type 2 diabetes susceptibility. *HHEX* has been reported to be essential for beta cell function and development and is a target of the wingless-type MMTV integration site family (*WNT*) signalling pathway, as is *TCF7L2* [5].

FTO, *CDKAL1*, *CDKN2B* and *SLC30A8* showed nominal association with type 2 diabetes. *FTO* was identified as a type 2 diabetes-susceptibility variant that predisposes to diabetes through an effect on BMI in the UK population [7]. As to possible reasons for not detecting association between BMI and *FTO* SNPs in the Japanese population, this may be due to the fact that our samples were from a less obese Japanese population compared with Europids. Indeed, mean BMI of participants with the risk genotype in UK non-diabetic controls is 25.4–27.1 kg/m^2, whereas that of Japanese non-diabetic controls is 24.3 kg/m^2. The Japanese population has similar prevalence of type 2 diabetes to Europids, whereas the prevalence of obesity in the Japanese population is much lower, indicating that the Japanese population has a predisposition to type 2 diabetes under a lower burden of obesity compared with the Europid. Therefore, it is possible that the present study could not detect the effect of the *FTO* gene on BMI in the Japanese population, a less obese population than the Europid.

SNP rs7756992 in *CDKAL1* is the SNP that is reportedly associated with type 2 diabetes in Han Chinese individuals from Hong Kong [6]. The minor allele frequency (MAF) of rs7756992 in the Han Chinese was higher than that in the European-origin population and the MAF in the Japanese was very similar to that of the Han Chinese. We detected a nominally significant association between this SNP and Japanese type 2 diabetes [OR=1.20 (95% CI 1.03–1.39), p=0.017]. Given that *CDKAL1* and *CDKN2B* showed nominal association with impaired pancreatic beta cell function as estimated by HOMA-beta index in the present study, and that they may well have some role in transduction of glucose toxicity or regenerative capacity of pancreatic beta cells [6], they could be good candidate genes for Japanese type 2 diabetes. *EXT2* and *IGF2BP2* also showed nominal association with impaired pancreatic beta cell function, but we could not detect any significant association with type 2 diabetes.

The absence of significant association is often attributed to lack of power. The present study had 80% power to detect an OR of 1.20, when the frequency of a risk allele was 30%. However, the power to detect an OR of 1.12, the smallest OR in the whole-genome association studies [8–10], was 50%. Also, the characterisation of the control sample lacks OGTT data. These facts should be regarded as limitations of the present study.

It has been reported that life-style alteration can reduce the risk of type 2 diabetes, even in individuals carrying the type 2 diabetes-susceptibility variant of *TCF7L2* [2]. Frequencies of risk alleles of three SNPs in *HHEX* were lower in our samples than in European populations but

effects of those SNPs on susceptibility to diabetes were stronger. Therefore, genotyping SNPs of *HHEX* in an individual may be effective for a personalised preventive medicine in Asian populations.

In conclusion, this is the first report to describe a significant association between type 2 diabetes and *HHEX* in the Asian population. Further replication of these studies in Eastern Asian populations who share a quite similar genetic background are awaited.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Grant SF, Thorleifsson G, Reynisdottir I et al (2006) Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. Nat Genet 38:320–323
2. Florez JC, Jablonski KA, Bayley N et al (2007) *TCF7L2* polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 355:241–250
3. Horikoshi M, Hara K, Ito C et al (2007) A genetic variation of the transcription factor 7-like 2 gene is associated with risk of type 2 diabetes in the Japanese population. Diabetologia 50:747–751
4. Cauchi S, El Achhab Y, Choquet H et al (2007) *TCF7L2* is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. J Mol Med 85:777–782
5. Sladek R, Rocheleau G, Rung J et al (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 445:881–885
6. Steinthorsdottir V, Thorleifsson G, Reynisdottir I et al (2007) A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes. Nat Genet 39:770–775
7. Frayling TM, Timpson NJ, Weedon MN et al (2007) A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316:889–894
8. Zeggini E, Weedon MN, Lindgren CM et al (2007) Replication of genome-wide association signals in UK. Samples reveals risk loci for type 2 diabetes. Science 316:1336–1341
9. Scott LJ, Mohlke KL, Bonnycastle LL et al (2007) A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 316:1341–1345
10. Saxena R, Voight BF, Lyssenko V et al (2007) Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 316:1331–1336
11. Matthew DR, Hosker JP, Rudenski AS et al (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419