KCNJ11 E23K Affects Diabetes Risk and Is Associated With the Disposition Index

Results of two independent German cohorts

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Various cross-sectional studies suggest that a polymorphism (E23K) within the ATP-sensitive K^+ channel KCNJ11 gene is associated with type 2 diabetes (1). However, only two prospective studies have addressed the relation between KCNJ11 E23K and type 2 diabetes, and these studies were intervention trials based on individuals with impaired fasting glucose and impaired glucose tolerance (2–4). With respect to functional effects, recent studies have been inconsistent regarding demonstration of a relation of the polymorphism with markers of insulin secretion (3,5,6), although in vitro studies clearly suggested a defect in insulin secretion (7–9). One study proposed a relation to glucagon response, while insulin secretion itself was not affected (10). However, the relation between polymorphism and insulin secretion might have been masked in some of those studies by differences of insulin sensitivity, and detailed analysis might thus require consideration of insulin sensitivity of the study participants, such as that given in the disposition index (11).

We investigated the effect of KCNJ11 E23K on diabetes risk within a prospective case-cohort study (n = 2,945) of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort. We additionally tested the association with diabetes in a second independent cross-sectional study, the Metabolic Syndrome Berlin Potsdam (MeSyBePo) cohort, from the same geographical region (n = 1,891). Within this second study, the association between polymorphism and disposition index was additionally investigated.

RESEARCH DESIGN AND METHODS

— We designed a case-cohort study within the EPIC-Potsdam study, a prospective cohort involving 27,548 Caucasian volunteers, mainly aged 35–65 years, from the general population (12–14). A total of 2,263 individuals were randomly selected for a subcohort. Because the subcohort is representative of the entire cohort at baseline, 68 incident type 2 diabetes cases belonged to the subcohort and 682 incident cases were identified in the remainder of the total cohort, the latter classified as external cases (external cases/random subcohort: age 54.59/49.50 years, 283/1,394 female and 399/869 male, BMI 30.41/25.95 kg/m^2, and mean follow-up 7 years) (15). We used all incident cases (internal and external cases) in Cox regression models accounting for the case-cohort design.

For confirmation of genetic association and additional analysis of diabetes-associated subtraits, the cross-sectional MeSyBePo study, with 1,891 subjects, was investigated. Details of recruitment and phenotyping (case/control subjects: age 59.57/50.63 years, 55.5/69.1% female and 44.5/30.9% male, and BMI 32.22/28.67 kg/m^2) of study participants were also published recently (16). In all participants of MeSyBepo, a 75-g oral glucose tolerance test (OGTT) with insulin measurements was performed. Only individuals with normal glucose tolerance (n = 1,070) or confirmed type 2 diabetes (n = 324) were considered for analysis of association with type 2 diabetes. The association between the polymorphism and the disposition index was investigated only in individuals with normal glucose tolerance, impaired fasting glucose, or impaired glucose tolerance, since accepted markers of insulin sensitivity and secretion have been shown to be unreliable in patients with type 2 diabetes, especially in patients with antidiabetes treatment. A euglycemic-hyperinsulinemic clamp was performed in a subset of 56 healthy control subjects. In these participants, the insulin sensitivity index (ISI) according to Stumvoll et al. (17) (ISI calculated as follows: $0.157 - 4.576 \times 10^{-5} \times \mathrm{Ins}_{120} - 0.00519 \times \mathrm{Gluc}_{90} - 0.000299 \times \mathrm{Ins}_0$; where Ins_{120} is insulin during OGTT at 120 min, jGluc_{90} is glucose at 90 min, and Ins_0 is insulin during OGTT at 0 min) correlated best with the M value (r = 0.591; $P < 0.001$) of the clamps. Therefore, ISI was subsequently used to estimate insulin sensitivity in the total cohort. As the characteristics of our study cohort were basically comparable with those of the cohort of Stumvoll et al., the ratio of area under the curve $(\mathrm{AUC})_{\mathrm{insulin}}/\mathrm{AUC}_{\mathrm{glucose}}$, which performed best in the study of Stumvoll et al. compared with a hyperglycemic clamp, was used to estimate insulin secretion. Correspondingly, the disposition index was calculated as

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Abbreviations: AUC, area under the curve; EPIC, European Prospective Investigation into Cancer and Nutrition; ISI, insulin sensitivity index; MeSyBePo, Metabolic Syndrome Berlin Potsdam; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Relation between KCNJ11 E23K and diabetes in the prospective EPIC-Potsdam cohort and the cross-sectional MeSyBePo cohort and association with the disposition index in the cross-sectional MeSyBePo cohort*

	Genotypes		
	EE	EK	KK
EPIC-Potsdam cohort			
$n_{subcohort}/n_{case}$	913/257	1,052/326	298/99
OR (95% CI)	1 (ref.)	1.13 (0.90–1.42)	1.25 (0.91–1.71)
P	—	0.281	0.163
MeSyBePo cohort			
$n_{control}/n_{case}$	444/121	492/156	134/47
OR (95% CI)	1 (ref.)	1.32 (0.97–1.79)	1.85 (1.18–2.91)
P	—	0.080	0.007
MeSyBePo disposition index	627	730	210
Mean ± SE	3.64 ± 0.02	3.46 ± 0.02	3.38 ± 0.03

Data are adjusted for age, sex, and BMI. The subcohort of EPIC-Potsdam was representative for the entire cohort and thus included 68 incident type 2 diabetes cases. Those were considered as cases in Cox regression models accounting for the case-cohort design together with the external incident cases of the remainder cohort. *P* over all groups was 0.004 with respect to the disposition index.

the product of ISI and $AUC_{insulin}/AUC_{glucose}$ (11,17,18). Both studies have been approved by the local ethic authorities.

Genotyping was performed by Taqman technology (HT7900 System; ABI, Foster City, CA). Details of genotyping are available from the authors on request.

Data were analyzed using SPSS (version 12.0; SPSS, Chicago, IL) and SAS (version 9.1; SAS Institute, Cary, NC). General linear model was calculated to analyze the effects of the polymorphism on continuous variables after adjustment for confounders (age, sex, and BMI). Relative risks (RRs) were calculated using Cox proportional hazards regression modified according to the Barlow method in EPIC-Potsdam. Unconditional logistic regression analysis was performed to estimate odds ratios (ORs) in MeSyBePo. Multiplicative interaction terms between genotype and age, sex, or BMI were used to analyze potential interactions of these variables and disease risk. A two-tailed α error $<5\%$ was considered significant.

RESULTS — In both studies, the KCNJ11 E23K polymorphism was found in Hardy-Weinberg equilibrium. In the prospective EPIC-Potsdam cohort, the polymorphism was associated with increased RR for type 2 diabetes after adjustment for age, sex, and BMI (Table 1), although point estimates reached no statistical significance. Results were not indicative for effect modification with age or BMI. However, in sex-specific subanalyses, we found a significant association among women with KK genotype (RR 1.92 [95% CI 1.21–3.04]), while no association was observed among men with KK genotype (0.96 [0.60–1.53], *P* for interaction 0.098). The association between KCNJ11 E23K and prevalent type 2 diabetes was significant in the MeSyBePo cohort (EK genotype: 1.32 [0.97–1.79]; KK genotype: 1.85 [1.18–2.91]) (Table 1). However, in some contrast to the results in the EPIC cohort, comparable point estimates were found among KK genotype women (1.85 [1.03–3.35]) and men (1.86 [0.92–3.76]).

Interestingly, analysis of subtraits in this second cohort additionally demonstrated an effect of the polymorphism on the disposition index. Thus, individuals with the EE genotype had a higher disposition index than those with the EK or KK genotype (crude model: EE 3.66 ± 0.02, EK 3.45 ± 0.02, and KK 3.36 ± 0.03; $P = 0.003$). This relation remained significant after adjustment for age, sex, and BMI (Table 1).

CONCLUSIONS — Data from one prospective observational study and one cross-sectional study basically confirm that KCNJ11 E23K is associated with an increased risk of type 2 diabetes in Caucasian individuals, particularly among women. A potential sex-specific effect should be further investigated in subsequent studies or meta-analyses. The association with the disposition index suggested that consideration of insulin sensitivity may be required to elucidate effects of KCNJ11 E23K on insulin secretion and may partially explain controversial results of previous studies.

Some limitations of this study should be mentioned. Although other polymorphisms in KCNJ11 and ABCC8 might be relevant in the relation to type 2 diabetes, this study focused exclusively on KCNJ11 E23K for the following reasons: First, a considerable number of previous cross-sectional studies demonstrated associations between this polymorphism and type 2 diabetes. Second, in vitro data suggested a functional relevance of this polymorphism. Third, covering the KCNJ11 and the associated ABCC8 gene with haplotype tagging SNPs would have required considerably larger cohorts to avoid an underpowered study. Although we aimed to investigate a clear a priori–defined hypothesis, we cannot exclude that other polymorphisms in the genomic region of KCNJ11 might confer the relation between KCNJ11 E23K and type 2 diabetes described here. Taken together, these data further support a role of KCNJ11 E23K in the pathogenesis of type 2 diabetes in Caucasian individuals.

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