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Missense mutations in the pancreatic islet beta cell inwardly rectifying K^+ channel gene (*KIR6.2/BIR*): a meta-analysis suggests a role in the polygenic basis of Type II diabetes mellitus in Caucasians

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Summary The K^+ inwardly rectifier channel (KIR) is one of the two sub-units of the pancreatic islet ATP-sensitive potassium channel complex (I_{KATP}), which has a key role in glucose-stimulated insulin secretion and thus is a potential candidate for a genetic defect in Type II (non-insulin-dependent) diabetes mellitus. We did a molecular screening of the *KIR6.2* gene by single strand conformational polymorphism (SSCP) and direct sequencing in 72 French Caucasian Type II diabetic families. We identified three nucleotide substitutions resulting in three amino acid changes (E23K, L270V and I337V), that have also been identified in other Caucasian Type II diabetic subjects. These variants were genotyped in French cohorts of 191 unrelated Type II diabetic probands and 119 normoglycaemic control subjects and association studies were done. The genotype frequencies of the L270V and I337V variants were not very different between Type II diabetic subjects and control groups. In contrast, analysis of the E23K variant showed that the KK homozygocity was more frequent in Type II diabetic than in control subjects (27 vs 14 %, $p = 0.015$). Analyses in a recessive model (KK vs EK/EE) tended to show a stronger association of the K allele with diabetes ($p = 0.0097$, corrected p-value for multiple testing < 0.02). The data for the E23K variant obtained here and those obtained from three other Caucasian groups studied so far were combined and investigated by meta-analysis. Overall, the E23K variant was found to be significantly associated with Type II diabetes ($0.001 \leq p \leq 0.0016$, corrected p-values for multiple testing $p \leq 0.01$). This study shows that *KIR6.2* polymorphisms are frequently associated with Type II diabetes in French Caucasians. Furthermore, a meta-analysis combining different Caucasian groups suggests an significant role of *KIR6.2* in the polygenic context of Type II diabetes. [Diabetologia (1998) 41: 1511–1515]

Keywords Type II (non-insulin-dependent) diabetes mellitus, gene, inwardly rectifier potassium channel, mutation.

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Abbreviations: BIR or KIR, Beta-cell inward rectifier family member; I_{KATP} pancreatic islet ATP-sensitive potassium channel complex; *KIR6.2*, K^+-inward rectifying channel encoding gene; PCR, polymerase chain reaction; PHHI, persistent hyperinsulinaemic hypoglycaemia of infancy; SSCP, single strand conformational polymorphism; SUR, sulphonylurea receptor; *SUR1*, sulphonylurea receptor encoding gene

It is widely accepted that Type II (non-insulin dependent) diabetes mellitus is a polygenic disorder characterized by chronic hyperglycaemia, with both genes and environmental factors contributing to the disease development. Recent genome scans have successfully led to the localization of major loci linked to Type II diabetes in isolates of Mexican-American and Finnish ancestry to chromosomes 2 q and 12 q, respectively [1, 2]. On the other hand, and despite intensive investigation of candidate genes of glucose metabolism, few gene mutations have been identified that have a significant role in Type II diabetes [3–5]. The genes encoding key components of insulin secretion pathways are potential candidates for a possible genetic defect

in Type II diabetes [6]. Among these proteins, the pancreatic islet ATP-sensitive potassium channel complex (I_{KATP}) has a major role in glucose-stimulated insulin secretion. The beta-pancreatic cell I_{KATP} is composed of two subunits, the sulphonylurea receptor SUR and the K^+ inwardly rectifier channel KIR, with both their respective encoding genes, the *SUR1* and *KIR6.2* (previously designated *BIR*, for beta-cell inward rectifier family member), located on human chromosome 11p15.1 [7]. It is known that molecular signals controlling insulin release are generated in the pancreatic beta cells through glucose metabolism, and act via the closure of the I_{KATP} that ultimately leads to insulin secretion [8–10]. Homozygous mutations in both *SUR1* and *KIR6.2* genes have been shown to cause familial persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI), a monogenic disorder with abnormal insulin oversecretion [11, 12]. As Type II diabetes is characterized, at least in the early stages, by hyperinsulinaemia, a pathogenic role of these genes may be possible in diabetes as well. Molecular screening of the *SUR1* gene in white Caucasian Type II diabetic patients has led to the identification of genetic variations, which have been shown to be strongly associated with diabetes in American, British, and French Type II diabetic groups of patients [13, 14]. Furthermore, a recent study showed that the *SUR1* gene variants are also associated with Type II diabetes in the Danish Caucasian population, and with impaired insulin secretion in a large cohort of young Danish healthy subjects [15]. These polymorphisms, however, seem to have no obvious functional effect on the *SUR1* gene product neither on the islet I_{KATP} activity, suggesting a possible linkage disequilibrium of the *SUR1* gene polymorphisms with a functionally relevant mutation in a nearby gene. Interestingly, *KIR6.2* gene is located 4.5 kilobases away from the *SUR1* gene [7], making it a plausible candidate for the reported allelic association and thus for possible inherited defects in human Type II diabetes. This prompted us to screen the *KIR6.2* gene for mutations in 72 late-onset Type II diabetic families of French ancestry. Moreover, to evaluate the global role of this gene in Type II diabetes, a meta-analysis with identified *KIR6.2* gene variants in different Caucasian groups of patients was carried out.

Subjects and methods

Gene screening. Seventy-two unrelated Type II diabetic subjects of French ancestry were screened for mutations in the *KIR6.2* gene. These subjects were selected from a large group of multiplex Type II diabetic families with unknown aetiology for diabetes [14, 16]. These probands, 35 men and 37 women, were aged 65.1 ± 11.2 years (means ± SD), had a body mass index of 27.5 ± 5.1 kg/m^2, and fasting plasma glucose and insulin concentrations of 9.3 ± 3.1 mmol/l and 11.9 ± 7.7 mU/l, respectively. They were treated by oral hypoglycaemic agents (71 %), insulin (18 %) or both (11 %), and had an average age at diagnosis of Type II diabetes of 41.8 ± 11.3 years. Two normoglycaemic subjects with no familial history of diabetes were selected as controls for gene screening.

Association studies. Association studies with the variants identified in *KIR6.2* were done in a cohort of 191 unrelated Type II diabetic probands (selected from the same group of patients and including the initial group of 72 Type II diabetic patients subjected to *KIR6.2* gene screening) and in 119 normoglycaemic control subjects [14, 16]. The Type II diabetic group consisted of 105 men and 86 women, and their characteristics were: age, 64.5 ± 10.5 years (means ± SD); age at diagnosis of Type II diabetes 42.3 ± 10.2 years; body mass index, 27.3 ± 4.8 kg/m^2; fasting plasma glucose and insulin concentrations, 10.2 ± 3.9 mmol/l and 12.7 ± 9.8 mU/l, respectively. 76.2 % were treated for diabetes with oral hypoglycaemic agents, 15.2 % with insulin, 4.3 % with both and 4.3 % were treated by diet only. The control group (52 men and 67 women) was composed of normoglycaemic spouses of patients from Type II diabetic families who had no familial history of diabetes and all underwent oral glucose tolerance testing. Their characteristics were: age, 57.6 ± 11.6 years; body mass index, 22.8 ± 2.4 kg/m^2; fasting plasma glucose and insulin levels, 5.1 ± 0.5 mmol/l and 11.9 ± 4.0 mU/l, respectively.

For all subjects, genomic DNA was extracted from peripheral blood leucocytes by standard procedures.

SSCP analysis. KIR6.2 gene screening in the group of 72 unrelated Type II subjects was carried out using a single strand conformational polymorphism (SSCP) protocol that we have recently developed, combining the SSCP basic principle with the use of fluorescent dyes [17, 18]. The genomic sequence of *KIR6.2* was divided into eight overlapping fragments (I to VIII) covering the entire exon with its 5′ and 3′ adjacent flanking sequences: Sense (antisense) strands, Fragment I, 5′-ctgaggctggtattaaga-3′ (agtattcctcggggatgatg); II, ccgagaggactctgcagtgaa (gccacgttgcagttgcctttc); III, ccgctttgtgtccaagaaaga (ggacatggtgaagatgagc); IV, acacattgctcatcttcacc (ccacgatgttctgcacgatg); V, tgagcctcatcgtgcagaac (tgtcacccacacgtagcatg); VI, cgcctctgcttcatgctac (gtttccaccacgccttcca); VII, gatcatcgtcatcctggaag (agtaggctgtggtcctcatc); VIII, cttgatgaggaccacagcctac (gtaacaccatggatgagcag). The first polymerase chain reaction (PCR) round was carried out on 100 ng of genomic DNA, using the primers described above with annealing temperatures of 56 °C except for fragments I (60 °C) and fragments IV and V (58 °C). Fluorescence labelling and SSCP electrophoresis procedures were done as described previously [17, 18].

Direct DNA sequencing. Samples showing abnormal SSCP patterns were directly sequenced on both strands, together with samples showing the normal pattern. Sequencing was done using an ABI PRISM Dye Terminator Cycle sequencing kit (Perkin-Elmer, Applied Biosystems, Foster City, Calif., USA) according to the manufacturer's instructions.

Genotyping of KIR6.2 gene variants. To genotype the Type II diabetic and control groups for the E23K, L270V and I337V variations PCR restriction fragment length polymorphism assays were done using *Ban*II, *Bst*NI and *Msl*I restriction enzymes, respectively. Genotyping consisted in DNA amplification of the corresponding DNA fragment, digestion with the specific enzyme and then resolution on agarose gels.

Statistical analyses. Demographic and clinical data are expressed as means ± SD. Comparisons of genotype frequencies

in the Type II diabetic and control groups were carried out using contingency table chi-square tests. The meta-analysis combined genotypic data for *KIR6.2* variants observed in Type II diabetic Caucasian groups from this and the three previous studies [19–21]. Statistical calculations used in the meta-analysis were carried out using contingency table chi-square tests, and all statistics were calculated with the JMP software (SAS Institute Inc. Cary, N. C., USA).

Results

We screened 72 unrelated Type II diabetic and 2 healthy non-diabetic subjects for genetic variations in the *KIR6.2* gene using a fluorescence-based SSCP protocol. Three *KIR6.2* gene fragments (II, VI and VII) showed abnormal SSCP migration patterns. The samples with these abnormal patterns were directly sequenced on both strands. Direct DNA sequence analysis of these samples showed three single nucleotide substitutions: a G-to-A change resulting in a glutamic acid-to-lysine substitution at codon 23 of *KIR6.2* (E23K), a C-to-G change, resulting in a leucine-to-valine substitution at codon 270 (L270V), and an A-to-G change resulting in an isoleucine-to-valine change at codon 337 (I337V). These single nucleotide variations were polymorphic and resulted in restriction site polymorphisms.

Therefore, to examine the relation between these variants and Type II diabetes, we genotyped them in a large cohort of unrelated Type II diabetic probands [$n = 191$, including the initial group of Type II diabetic patients ($n = 72$) subjected to *KIR6.2* gene screening] and in a group of unrelated normoglycaemic healthy control subjects ($n = 119$). The genotype frequencies in Type II diabetic and control subjects for each variation are shown in Table 1. In our sample, although not in complete linkage disequilibrium, the E23K and I337V variants were strongly linked: the mean concordance rate between the E allele at residue 23 and the I allele at residue 337 was 72 % ($p < 10^{-4}$, data not shown). Association analysis of the E23K variant showed that the KK homozygocity was significantly more frequent in Type II diabetic than in control subjects (27 % vs 14 %, $p = 0.015$; corrected p-value < 0.05). Analyses in a recessive model (homozygotes KK vs heterozygotes EK and homozygotes EE) showed a slightly more significant association of the K allele with diabetes ($p = 0.0097$). After correction for multiple models testing, the association between the E23K variant and Type II diabetes was still significant ($0.01 < p$-value < 0.02). The genotype frequencies of the L270V and I337V variants were not significantly different between Type II diabetic and control groups.

The three genetic variants reported here have also recently been identified in other Caucasian Type II diabetic populations: two cohorts in the UK, one in the USA and one in Denmark [19–21]. These genetic variations were slightly more prevalent, in Type II diabetic subjects compared with control subjects [19–21]. Therefore, to evaluate the global role of the *KIR6.2* gene in all these cohorts, we examined by meta-analysis the distribution of the E23K variant genotype frequencies in the combined data-sets, comprising the French cohort, the two British cohorts, and the Danish cohort [19–21]. These cohorts were designated respectively Fr, UK1, UK2 and DK, and consisted of 521 Type II diabetic and 367 non-di-

Table 1. Genotype frequencies of the *KIR6.2* missense mutations in Type II diabetic and control subjects

Mutation	Genotype	Type II diabetic subjects % *(n)*	Non diabetic control subjects % *(n)*	p-value[a]
E23K	E/E	0.28 (53)	0.40 (45)	0.015[b]
	E/K	0.45 (87)	0.46 (53)	
	K/K	0.27 (51)	0.14 (16)	
L270V	L/L	0.88 (164)	0.92 (104)	0.238
	L/V	0.12 (23)	0.08 (9)	
	V/V	0 (0)	0 (0)	
I337V	I/I	0.36 (69)	0.46 (52)	0.075
	I/V	0.50 (94)	0.36 (41)	
	V/V	0.14 (26)	0.18 (20)	

Numbers between parentheses correspond to the observed number of subjects with each genotype. [a] p-value when comparing the genotypic frequencies distributions at each amino acid variation between Type II diabetic and control subjects. [b] p-value was < 0.05, after correction for multiple testing

Table 2. *KIR6.2* codon 23 substitution meta-analysis: frequencies in the present and the previous reports

Genotype[a]	Study	Type II diabetic group ($n = 521$)	Control group ($n = 367$)
G/G E/E	UK1	72 (0.42)	38 (0.40)
	UK2	38 (0.38)	44 (0.54)
	DK	21 (0.36)	33 (0.44)
	Fr	53 (0.28)	45 (0.40)
	Combined	184 (0.353)	160 (0.436)
G/A E/K	UK1	78 (0.45)	52 (0.54)
	UK2	45 (0.45)	27 (0.33)
	DK	26 (0.45)	34 (0.45)
	Fr	87 (0.45)	53 (0.46)
	Combined	236 (0.453)	166 (0.452)
A/A K/K	UK1	22 (0.13)	6 (0.06)
	UK2	17 (0.17)	11 (0.13)
	DK	11 (0.19)	8 (0.11)
	Fr	51 (0.27)	16 (0.14)
	Combined	101 (0.194)	41 (0.112)

UK1, UK2 and DK refer to the data from the previous studies of *KIR6.2* variants among white Caucasian groups (refs. 19, 20 and 21 respectively). Fr: refer to the present study. [a] Symbols in italic and in roman indicate the genotype of *KIR6.2* codon 23 at the nucleotide and the amino acid levels, respectively. Data in parentheses correspond to the observed frequency for each genotype in the different cohorts and in the combined groups. E23K was associated with Type II diabetes in the co-dominant and recessive models, with p-values of 0.0016 and 0.001, respectively (corrected p-values were between 0.001 and 0.01)

abetic control subjects, Table 2). The cohort from the USA was not included in this meta-analysis since the control group was not in Hardy-Weinberg equilibrium for the E23K [19]. When the data from the French, UK1, UK2 and Danish studies were compared, an overall association was observed between Type II diabetes and the E23K variation (p-value = 0.0016; p-value < 0.01 after correction for multiple testing). When analysed with a dominant model, this variation showed a marginal association with Type II diabetes (E/E and E/K genotypes vs the E/E genotype) ($p = 0.0126$; corrected p-value < 0.05). In contrast, when considering a recessive model in the meta-analysis of the E23K variant, this polymorphism was found significantly more associated with diabetes (p-value = 0.001; p-value < 0.01 after correction for multiple testing).

Discussion

The *KIR6.2* gene, encoding one of the two subunits of the beta-pancreatic cell I_{KATP}, is a good candidate for genetic defects in human Type II diabetes mellitus. Linkage studies of markers near the *KIR6.2* locus have shown that this gene is unlikely to be a major diabetogene in the French Caucasian, Japanese, white U.S. and non-Hispanic white Type II diabetic populations [13, 14 and 22–24]. A minor role could not be excluded, however, in a subgroup of Type II diabetic patients or in other ethnic groups. This prompted us to screen the *KIR6.2* gene in French Caucasian Type II diabetic subjects. Here, we report the identification of three nucleotide substitutions resulting in three amino acid changes: E23K, L270V and I337V. These variants have been previously identified in other Type II diabetic populations [19–21]. Statistical analyses in the French population showed a significant association of one of these variants (E23K) with Type II diabetes. Furthermore, when combining the data from the present and the previous studies the E23K variant was further associated with diabetes. The pathophysiological mechanisms beyond this association remain unclear, as in vitro expression of the *KIR6.2* identified variants did not show any obvious alteration in the *KIR6.2* channel conductances [20]. The reported functional expression data regarding the E23K variant, however, have to be considered carefully, since the cellular system used (*Xenopus* oocytes) might not reflect exactly the channel properties of a native beta-pancreatic cell. Alternatively, it is possible that this association could reflect other unidentified defects in the *KIR6.2* gene, for example, in regulatory sequences not examined as these have not been yet characterized. Therefore, it is possible that *KIR6.2* gene variations might cause discrete changes in the channel properties, promoting the development of impaired insulin-secretion and glucose intolerance. A recent study in transgenic mice has shown that *KIR6.2* controls pancreatic beta-cells' excitability as well as their survival [25]. Transgenic mice expressing a dominant-negative form of *KIR6.2* exhibited a hyperinsulinaemic hypoglycaemia in neonates and a hyperglycaemia associated with hypoinsulinaemia along with a marked decrease in beta-cell mass in adults [25]. Similar phenotypical features (except hypoglycaemia) are also observed in human Type II diabetes since glucose-intolerant subjects are usually hyperinsulinaemic and insulin resistant before the onset of overt Type II diabetes, which is frequently associated with a secondary relative hypoinsulinaemia, possibly concomitant with an in vivo decrease of beta-cell mass [26, 27]. An important allelic association has been reported between *KIR6.2* gene variants (the combination of the homozygous K23K and V337V genotypes to the heterozygous genotype L270V) and impaired insulin sensitivity in young healthy Danish subjects [21]. Similarly, the L270V variation has been shown to associate with insulin sensitivity in British Type II diabetic subjects [20]. Therefore, it is not excluded that the *KIR6.2* gene variants could contribute to Type II diabetes by controlling subtle intermediate phenotypic traits related to insulin secretion or insulin action or both.

Another possibility is that the association between the *KIR6.2* polymorphisms and Type II diabetes could be due to other genes located in its vicinity. The most obvious candidate is *SUR1*, which is located 4.5 kilobases from the *KIR6.2* gene. In our population, however, the *KIR6.2* polymorphisms are not in linkage disequilibrium with the *SUR1* polymorphisms (data not shown). These data suggest that the observed association between *KIR6.2* polymorphisms and Type II diabetes is likely to be independent from any effect of the *SUR1* gene. Thus, other candidate genes linked to diabetes still have to be considered in the 11p15 chromosomal region such as the not yet cloned human homologue of the NIDDM1GK gene, which is the major diabetogenic locus in the GK rat [28].

In conclusion, a meta-analysis in combined groups of Caucasian patients showed that polymorphisms in the *KIR6.2* gene are associated with Type II diabetes suggesting a possible role in the polygenic context of human Type II diabetes. The molecular mechanisms associated with these observations are still to be determined.

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