Brief Genetics Report

Large-Scale Association Studies of Variants in Genes Encoding the Pancreatic β-Cell K_{ATP} Channel Subunits Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) Confirm That the *KCNJ11* E23K Variant Is Associated With Type 2 Diabetes

Anna L. Gloyn,[1] Michael N. Weedon,[1] Katharine R. Owen,[1] Martina J. Turner,[1] Bridget A. Knight,[1] Graham Hitman,[2] Mark Walker,[3] Jonathan C. Levy,[4] Mike Sampson,[5] Stephanie Halford,[6] Mark I. McCarthy,[6,7] Andrew T. Hattersley,[1] and Timothy M. Frayling[1]

The genes *ABCC8* and *KCNJ11*, which encode the subunits sulfonylurea receptor 1 (SUR1) and inwardly rectifying potassium channel (Kir6.2) of the β-cell ATP-sensitive potassium (K_{ATP}) channel, control insulin secretion. Common polymorphisms in these genes (*ABCC8* exon 16–3t/c, exon 18 T/C, *KCNJ11* E23K) have been variably associated with type 2 diabetes, but no large (~2,000 subjects) case-control studies have been performed. We evaluated the role of these three variants by studying 2,486 U.K. subjects: 854 with type 2 diabetes, 1,182 population control subjects, and 150 parent-offspring type 2 diabetic trios. The E23K allele was associated with diabetes in the case-control study (odds ratio [OR] 1.18 [95% CI 1.04–1.34], $P = 0.01$) but did not show familial association with diabetes. Neither the exon 16 nor the exon 18 *ABCC8* variants were associated with diabetes (1.04 [0.91–1.18], $P = 0.57$; 0.93 [0.71–1.23], $P = 0.63$, respectively). Meta-analysis of all case-control data showed that the E23K allele was associated with type 2 diabetes (K allele OR 1.23 [1.12–1.36], $P = 0.000015$; KK genotype 1.65 [1.34–2.02], $P = 0.000002$); but the *ABCC8* variants were not associated. Our results confirm that E23K increases risk of type 2 diabetes and show that large-scale association studies are important for the identification of diabetes susceptibility alleles. *Diabetes* 52:568–572, 2003

Type 2 diabetes is a polygenic disorder (1). Progress in defining the underlying molecular genetics has been limited. In pancreatic β-cells, ATP-sensitive potassium (K_{ATP}) channels control insulin secretion by coupling metabolism to membrane electrical activity. The K_{ATP} channel is a complex of two types of essential subunits, the sulfonylurea receptor (SUR1) and the inwardly rectifying potassium channel (Kir6.2) (2).

Mutations in both genes (SUR1, *ABCC8*; Kir6.2, *KCNJ11*) cause familial hyperinsulinemia of infancy (HI) (3). Polymorphisms in the genes (*ABCC8*, exon 16–3t/c, exon 18 C/T, *KCNJ11* E23K) have been reported to be associated with type 2 diabetes in several populations, although the data are inconsistent (4–15). Even though there are no data to support a functional role of either of the two *ABCC8* variants, a recent study has provided evidence that E23K alters function by inducing spontaneous over-activity of pancreatic β-cells, thus increasing the threshold ATP concentration for insulin release (16).

Genetic association studies can be problematic and have been beset by poor reproducibility due to inadequate statistical power, multiple hypothesis testing, population stratification, publication bias, and phenotypic heterogeneity. Meta-analysis, particularly of small and moderate studies, may overestimate the risk; thus, large association studies are needed to assess possible associations (4). In type 2 diabetes, a large association study of 3,000 subjects, which was supported by a meta-analysis of all the previous published studies, established association of the Pro12Ala peroxisome proliferator–activated receptor gene-γ (*PPARγ*) with type 2 diabetes (4). Very few association studies of a similar sample size to the *PPARγ* study have been performed. The aim of this study was to assess the

From the [1]Centre for Molecular Genetics, Peninsula Medical School, Exeter, U.K.; the [2]Department of Diabetes and Metabolic Medicine, Barts and the London, Queen Mary School of Medicine and Dentistry, University of London, London, U.K.; the [3]Department of Medicine, School of Medicine, Newcastle upon Tyne, U.K.; [4]The Diabetes Research Laboratories, Radcliffe Infirmary, University of Oxford, Oxford, U.K.; the [5]Elsie Bertram Diabetes Centre, Norfolk and Norwich, University Hospital, Norwich, U.K.; [6]Imperial College Genetics and Genomics Research Institute and Division of Medicine, Imperial College, London, U.K.; and the [7]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, U.K.

Address correspondence and reprint requests to Professor Andrew T Hattersley, Diabetes and Vascular Medicine, Peninsula Medical School, Barrack Rd., Exeter, EX2 5AX. E-mail: a.t.hattersley@exeter.ac.uk.

Received for publication 20 September 2002 and accepted in revised form 5 November 2002.

A.L.G. and M.N.W. contributed equally to this work.

ECACC, European Collection of Cell Cultures; EFS, Exeter Family Study; exon16, exon 16 −3t/c; exon18, exon 18 C/T; HI, hyperinsulinemia of infancy; HWE, Hardy-Weinberg equilibrium; K_{ATP} channel, ATP-sensitive potassium channel; Kir6.2 channel, inwardly rectifying potassium channel; LD, linkage disequilibrium; OR, odds ratio; SUR1, sulfonylurea receptor 1; TDT, transmission disequilibrium test.

TABLE 1
Clinical details of subjects studied

	Case subjects			Control subjects	
	Warren 2 sib-pair probands	Young-onset type 2 diabetes	Warren 2 trios probands	Population control 1 (EFS)	Population control 2 (ECACC)
n	622	232	150	855	327
Male (%)	53	54.7	62	50	NA
Age of diagnosis (years)*	56 (50–61)	40.4 (36–44)	40 (30–45)	31 (28–35)	NA
BMI	28.1 (25.3–31.4)	30.9 (27.0–34.9)	30.7 (26.9–36.4)	26.6 (24.4–29.7)	NA
Treatment D/OHA/I (%)	18/67/15	9/38/53	21/64/15	†	NA
WHR male	0.95 (0.91–1.00)	0.96 (0.94–1.01)	0.96 (0.94–1.00)	0.88 (0.83–0.92)	NA
WHR female	0.86 (0.83–0.91)	0.88 (0.83–0.93)	0.90 (0.85–0.96)	‡	NA

Continuous data are given as median (interquartile range). *Age at diagnosis for case subjects, age at study for control subjects; †control subjects were not on treatment; ‡there are no data for waist-to-hip ratio (WHR) for females in the EFS because females were pregnant at the time of the study. No clinical details were available for the ECACC population control samples. D/OHA/I, diet/oral hypoglycemic agents/insulin.

reported associations with type 2 diabetes of the *KCNJ11* E23K variant and the exon 16 −3t/c (exon16), exon 18 C/T (exon18) variants in *ABCC8* in a large U.K. cohort.

We performed both family-based and case-control association studies using collaborative U.K. resources of 854 cases, 1,182 population control subjects, and 150 parent-offspring trios. Details of the cohorts studied are given in Table 1. Table 2 gives genotype and allele frequencies for the E23K, exon 16, and exon 18 variants. All genotypes were in Hardy-Weinberg equilibrium (HWE), apart from a slight deviation from equilibrium ($P = 0.02$) in the young-onset type 2 diabetic cohort for the exon 16 variant. No error was found on retyping this cohort and we have no hypothesis to explain this slight deviation; therefore, we have combined the two case cohorts.

In the case-control study, the K allele of the E23K variant was associated with type 2 diabetes, (OR 1.18 [95% CI 1.04–1.34], $P = 0.01$ [two tailed]) (Table 2). In the 150 trios the heterozygous parents were more likely to transmit the E allele than the K allele to their affected offspring, but this was not significantly different from the expected 50:50 transmission rate (E = 79, K = 64, $P = 0.21$). The combined case-control and transmission disequilibrium test (TDT) OR for the K allele is 1.15 (1.02–1.30), $P = 0.026$ (two tailed). There was no difference (at $P < 0.05$) between the phenotypic characteristics (age of diagnosis, BMI, treatment, and waist-to-hip ratio) studied in any of the cohorts according to E23K genotype (data not shown).

We found no association of either of the two *ABCC8* variants with diabetes ($P = 0.57$ and $P = 0.63$ for exon 16 and exon 18, respectively) (Table 3). There was no significant deviation in the 150 parent-offspring trios from the expected 50:50 transmission rate from heterozygous parents for either the exon 16 or exon 18 variants (exon 16: c = 65, t = 73, $P = 0.50$; exon 18: c = 11, t = 14, $P = 0.55$). The combined case-control and TDT results are the exon 18 allele t OR 0.93 (0.71–1.22), $P = 0.62$, and exon 16 allele c OR 1.04 (0.92–1.18), $P = 0.52$.

To determine the extent of linkage disequilibrium (LD) between the three variants at the *ABCC8/KCNJ11* locus, we calculated D′ and r^2 from the frequencies of the haplotypes created by the three variants in the Exeter Family Study (EFS) trios (Table 4). There was modest LD across the locus (E23K, K/exon 16 c) (D′ −0.017, $r^2 = 0.0053$, $P = 0.025$). Strong LD was detected between the *ABCC8* exon 16 c and exon 18 T variants (D′ = 0.906, $r^2 = 0.031$, $P < 0.001$). Given the significant LD between the exon 16 and exon 18 variants, we tested the three two-locus haplotypes with a frequency of >5% for association with type 2 diabetes. There was no association of any of the haplotypes with type 2 diabetes at $P < 0.05$ (data not shown).

We carried out a meta-analysis of all published case-control data for the three variants (Fig. 1). For the E23K allele, all studies are consistent with the modest effect that we have described in our case-control study. Combining

TABLE 2
Association studies of the *KCNJ11* E23K variants in all cohorts

	Case subjects			Control subjects		
Genotype/alleles	W2S	YT2D	Case total	EFS	ECACC	Control total
n	622	232	854	855	327	1182
E23K						
E/E	219 (0.35)	89 (0.38)	308 (0.36)	358 (0.42)	133 (0.41)	491 (0.42)
E/K	303 (0.49)	109 (0.47)	412 (0.48)	382 (0.45)	152 (0.46)	534 (0.45)
K/K	100 (0.16)	34 (0.15)	134 (0.16)	115 (0.13)	42 (0.13)	157 (0.13)
P						0.03
E	741 (0.60)	287 (0.62)	1228 (0.60)	1098 (0.64)	418 (0.64)	1516 (0.64)
K	503 (0.40)	177 (0.38)	680 (0.40)	612 (0.36)	236 (0.36)	848 (0.36)
OR (95% CI)						1.18 (1.04–1.34)
P (two tailed)						0.01

Values in parenthesis represent genotype or allelic genotype frequency. Genotype distributions in type 2 diabetic subjects and population control subjects are shown for each individual cohort. W2S, Warren 2 sib-pair probands; YT2D, young-onset type 2 diabetes.

TABLE 3.
Association studies of the *ABCC8* exon16 and exon18 variants in all cohorts

Genotype/alleles	Case subjects			Control subjects		
	W2S	YT2D	Case total	EFS	ECACC	Control total
n	622	232	854	855	327	1182
Exon 18						
C/C	558 (0.90)	209 (0.90)	767 (0.90)	772 (0.90)	285 (0.87)	1057 (0.89)
C/T	64 (0.10)	22 (0.10)	86 (0.10)	79 (0.09)	41 (0.12)	120 (0.10)
T/T	0 (0.00)	1 (0.00)	1 (0.00)	4 (0.01)	1 (0.00)	5 (0.01)
P						*0.77
C	1180 (0.95)	440 (0.95)	1620 (0.95)	1623 (0.95)	611 (0.93)	2234 (0.95)
T	64 (0.05)	24 (0.05)	88 (0.05)	87 (0.05)	43 (0.07)	130 (0.05)
OR (95% CI)						0.93 (0.71–1.23)
P (two tailed)						0.63
Exon 16						
−3c/c	202 (0.33)	64 (0.28)	266 (0.31)	301 (0.35)	103 (0.32)	404 (0.34)
−3c/t	306 (0.49)	138 (0.60)	444 (0.52)	397 (0.46)	167 (0.51)	564 (0.48)
−3t/t	114 (0.18)	30 (0.13)	144 (0.17)	157 (0.18)	57 (0.18)	214 (0.18)
P						0.161
−3t	710 (0.57)	266 (0.57)	976 (0.57)	999 (0.58)	373 (0.57)	1372 (0.58)
−3c	534 (0.43)	198 (0.43)	732 (0.43)	711 (0.42)	281 (0.43)	992 (0.42)
OR (95% CI)						1.04 (0.91–1.18)
P (two tailed)						0.57

Values in parentheses represent genotype or allelic genotype frequency. Genotype distributions in type 2 diabetic subjects and population control subjects are shown for each individual cohort. *For exon 18 CT + TT versus CC. W2S, Warren 2 sib-pair probands; YT2D, young-onset type 2 diabetes.

all previously published case-control studies (5,6,9,10,12) gives an estimated OR for the K allele of 1.30 (95% CI 1.13–1.49), $P = 0.0003$. If we include our study, the estimated OR is 1.23 (1.12–1.36), $P = 0.000015$. For the exon 16 allele c, combining all previous published data (5,7,8,11,13,15) does not show significant association (1.07 [0.97–1.17], $P = 0.19$). Inclusion of our current study results in an estimated OR of 1.03 (0.95–1.11), $P = 0.48$. Finally, a meta-analysis of all published (4,5,7,8,11,13) data for the exon 18 allele t was significantly associated (1.26 [1.01–1.57], $P = 0.039$). However, when our current study was included in this analysis, the odds ratio is 1.12 (0.95–1.33), $P = 0.18$.

Our study includes 2,036 subjects and is the largest case-control study performed on these three variants to date. In large studies, it is more likely that true susceptibility genetic variants will show association and less likely that stochastic variation will result in false positive and false negative results (17). Our study is only the third individual study that has shown significant association for the E23K allele (see Fig. 1). Our finding, that E23K has a similar moderate association to a meta-analysis, is strong support for this being a genuine type 2 diabetes variant. For the exon 16 and exon 18 variants in *ABCC8*, our study and the combined meta-analysis provide no evidence of association with type 2 diabetes. It is noteworthy that the previous two largest published studies of the *ABCC8* variants like ours found no association of either variant with type 2 diabetes (5,14). We cannot exclude that the exon 16 and exon 18 variants are in LD with another unidentified predisposing polymorphism in some populations studied, but the meta-analysis would suggest this is not widespread.

TABLE 4
Magnitude of linkage disequilibrium (D′ and r^2) across the *ABCC8/KCNJ11* locus calculated from the rare allele at each locus in 436 nondiabetic families

Haplotype	D′	r^2	*P*
KCNJ11 E23K (K)/*ABCC8* ex 16 (−3c)	−0.017	0.0053	0.025
KCNJ11 E23K (K)/*ABCC8* ex18 (T)	−0.114	0.00038	0.88
ABCC8 ex 16 (−3c)/*ABCC8* ex18 (T)	0.906	0.031	<0.001

Despite the large numbers of individuals, it is not possible in our study to conclude whether the association is driven by the KK genotype or the K allele (KK versus EE: OR 1.36 [95% CI 1.04–1.78], $P = 0.026$; EK versus EE: 1.23 [1.02–1.49], $P = 0.034$). Previous results have suggested that the association could be driven by KK homozygosity (6), and our results are compatible with this. A meta-analysis of all studies was strongly suggestive that KK confers greater risk than EK (KK versus EE: 1.65 [1.34–2.02], $P = 0.000002$; EK versus EE: 1.13 [0.98–1.30], $P = 0.09$. Functional studies also support the KK genotype being required to markedly reduce glucose-induced insulin release from the β-cell (16).

In our study, the OR for both the E23K allele and the KK genotype were lower than the meta-analysis of previous results. As our result was within the 95% confidence limit of all previous studies, this could merely represent stochastic variation. Publication bias could have meant a meta-analysis of previous small studies artificially inflated the OR as has been seen for the ACE gene (18). The selection of cases could have altered the OR; our subjects, when compared with the subjects of previous studies, were of a younger onset and more likely to have a diabetic first-degree relative, but this should result in greater genetic predisposition and hence a higher OR. Finally, our control subjects were relatively young and so might develop diabetes when older, which could result in a lower

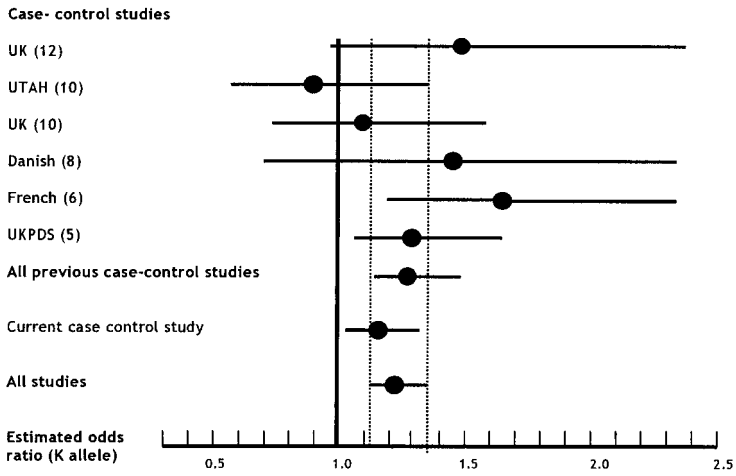

FIG. 1. OR (95% CI) for *KCNJ11* E23K. For each study, the ● represents the estimated OR for the K allele and the line indicates the 95% CI around this estimate. The dashed lines indicate the 95% CI for the current case-control study. For clarity, the two studies testing for familial association (4, and this study) were excluded. Inclusion of these studies in the meta-analysis results in an OR of 1.16 (95% CI 1.06–1.27), $P = 0.0012$.

OR compared with using older control subjects with normal glucose tolerance, who have been used in most other studies.

Despite good evidence for association in our large case-control study, we did not find any evidence for familial association in our cohort of 150 trios in whom the E allele was transmitted, nonsignificantly, more than the K allele. The only other familial association study (4) showed a similar nonsignificant trend. The trios used by Altshuler et al. (4) have been criticized (16), but our cohort all had type 2 diabetes and had a similar age of diagnosis to the young-onset cases in our study who showed association. The most likely explanation for this lack of familial association is insufficient power—as this study only had 21% power to detect an OR of 1.21. Until adequate-sized familial association studies are performed, the possibility that population stratification results in the association seen with E23K cannot be excluded. However, the functional studies (16) and association in many different populations strongly argue against this explanation.

In conclusion, we have confirmed the previously reported association between the E23K variant and susceptibility to type 2 diabetes in a large cohort. Like the *PPARγ* Pro12Ala (4) variant, E23K has a modest impact on type 2 diabetes risk, but due to its high allele frequency, it is likely to have a large effect on population attributable risk. To assess the true population attributable risk of this variant, cohorts of random type 2 diabetes populations will be needed rather than the cohorts used in this study that are enriched for familiality.

RESEARCH DESIGN AND METHODS

Subjects. Table 1 gives details of the subjects genotyped. Informed consent was obtained from all subjects. Type 2 diabetic subjects were unrelated, Caucasian, and had diabetes defined either by World Health Organization criteria (19) or by being treated with medication for diabetes. Known genetic subtypes were excluded by clinical criteria and/or genetic testing. Patients were excluded if they had a first-degree relative with type 1 diabetes, an elevated titer of GAD antibodies, or became insulin dependent. The type 2 diabetic subjects were recruited from three Diabetes U.K. Warren 2 Repository sources: *1*) parent-offspring trios with type 2 diabetes (20); *2*) type 2 diabetic subjects with at least one affected sibling (21); and *3*) an additional collection of young-onset (≥18 and ≤45 years at age of diagnosis) type 2 diabetic subjects (22). All patients were therefore selected for either early-onset or familial diabetes. Population control subjects were U.K., Caucasian, and recruited from two sources: *1*) parents from a consecutive birth cohort, the Exeter Family Study (EFS), with normal (<6.0 mmol/l) fasting glucose and/or normal HbA_{1c} levels (22); and *2*) from a nationally recruited population control sample of blood donors without known diabetes from the European Collection of Cell Cultures (ECACC). DNA from offspring of the parents from the EFS was available and genotyped for LD analysis.

Genotyping. PCR-restriction fragment–length polymorphism analysis was performed as previously described (9,10) with the following modification: for exon 18, the restriction enzyme *BSIE*1 was used for 15% of samples. We regenotyped the *ABCC8* exon 16 variant in 115 subjects from the young-onset type 2 diabetic cohort using a second method, four primer ARMS (amplification refractory mutation system) (23), and no discrepancies were found.

Statistical methods. Statistical power was calculated using EpiInfo (version 1.1.2). Based on control allele frequencies obtained in our study, we had 80% power to detect ORs of 1.20, 1.47, and 1.21 (exon 16, exon 18, and E23K, respectively) at $P < 0.05$. The family-based association study had 21% power (at $P < 0.05$) to detect these ORs.

The magnitude (D′ and r^2) (24) of LD across the *ABCC8/KCNJ11* locus was calculated using the haplotype proportions from TRANSMIT (25) from the EFS parent offspring cohorts (26). The significance of LD was calculated using a χ^2 test of the number of expected haplotypes versus observed haplotypes.

TDT in parent off-spring trios for individual variants was performed using TRANSMIT (25).

The significance of allele and genotype frequency differences were calculated using χ^2 analysis, with overall allele numbers used to calculate ORs and 95% CIs using 2 × 2 contingency tables. The meta-analysis ORs for the combined studies were calculated by the Mantel-Haenszel test.

ACKNOWLEDGMENTS

The sib-pair and sib-trio collections were supported by Diabetes U.K. through the Warren bequest and the Medical Research Council. The control subjects were funded by the South and West National Health Service Research Directorate. The laboratory work was funded by Diabetes U.K. BDA:RD01/002252. A.L.G. is supported by the European Grant Genomic Integrated Force for Diabetes (GIFT QLG2-1999-00). K.R.O. is supported by a Diabetes U.K. Clinical Training Fellowship.

We thank Dr. Moria Murphy and Simon Howell for their considerable contribution to establishing the Diabetes U.K. Warren 2 trios collection and sib-pair collections; Diane Jarvis for the DNA extraction; and the many research nurses, diabetes physicians, general practitioners, patients, and family members who contributed to both the Diabetes U.K. (formerly the British Diabetic Association) Warren 2 trios collection and Diabetes U.K. Warren 2 Repository sib-pairs collection. We thank Dr. Sian Ellard for laboratory organization. T.M.F. is a career scientist of the South and West National Health Service Research Directorate.

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