2. Wren A, Seal L, Cohen M et al. (2001) Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 86: 5992–5995
3. Tschop M, Weyer C, Tataranni P, Devanarayan V, Ravussin E, Heiman M (2001) Circulating ghrelin levels are decreased in human obesity. Diabetes 50: 707–709
4. Ariyasu H, Takaya K, Tagami T et al. (2001) Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab 86: 4753–4758
5. Hosoda H, Kojima M, Matsuo H, Kangawa K (2000) Ghrelin and des-acyl ghrelin: two major forms of rat ghrelin peptide in gastrointestinal tissue. Biochem Biophys Res Commun 279: 909–913
6. Shiiya T, Nakazato M, Mizuta M et al. (2002) Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab 87: 240–244
7. Saad M, Bernaba B, Hwu C et al. (2002) Insulin regulates plasma ghrelin concentration. J Clin Endocrinol Metab 87: 3997–4000
8. Caixas A, Bashore C, Nash W, Pi-Sunyer F, Laferrere B (2002) Insulin, unlike food intake, does not suppress ghrelin in human subjects. J Clin Endocrinol Metab 87: 1902–1906

Corresponding author: T. Østergård, Department of Medicine M (Endocrinology and Diabetes), University Hospital of Aarhus, AKH, Nørrebrogade 42–44, 8000 Aarhus C, Denmark, E-mail: oest@dadlnet.dk

An E23K single nucleotide polymorphism in the islet ATP-sensitive potassium channel gene (Kir6.2) contributes as much to the risk of Type II diabetes in Caucasians as the PPARγ Pro12Ala variant

To the Editor: The search for the Type II (non-insulin-dependent) diabetes mellitus gene(s) has proven to be a challenge. It is still not known whether common or rare variants are involved and if these susceptibility loci will have a single allele altering risk or if combinations of these variants will affect risk. For example, the PPARγ Pro12Ala variant has consistently been shown to be associated with risk of Type II diabetes [1, 2]. We believe that the Kir6.2 E23K SNP should also be considered as a Type II diabetes risk altering polymorphism. Kir6.2 (KCNJII gene on 11p15.1) is a subunit of the inwardly rectifying ATP sensitive K+ channel, which is involved in the regulation of insulin secretion in pancreatic beta cells [3]. We have reported an association between the Kir 6.2 E23K homozygous genotype (KK) and Type II diabetes in a case-control meta-analysis [4]. Most recently, electrophysiological studies in which human isoforms of Kir6.2 in COS-1 cells were used, showed a dose-dependent reduction in ATP sensitivity of the Kir6.2 E23K variant [5]. Hence, we decided to re-evaluate the common E23K polymorphism by genotyping an additional population (Ashkenazi Jewish) and including the United Kingdom Prospective Diabetes Study (UKPDS) data [6]. We assessed the relative risk associated with the (K) allele and the homozygous E23K (KK) status.

In the original study, we analysed 521 Type II diabetic patients and 367 control subjects, where the E23K variant was more frequent in the patients than in the control subjects (0.19 vs 0.11, p=0.0016; corrected p<0.01). All subjects in our study gave their informed consent. In the Ashkenazi sample, the frequency of the KK genotype in the Type II diabetic patients (0.15) compared with the control subjects (0.10) tended in the same direction but was not significant (p=0.097). However,

DOI 10.1007/s00125-002-0947-x
Published online: 3 October 2002

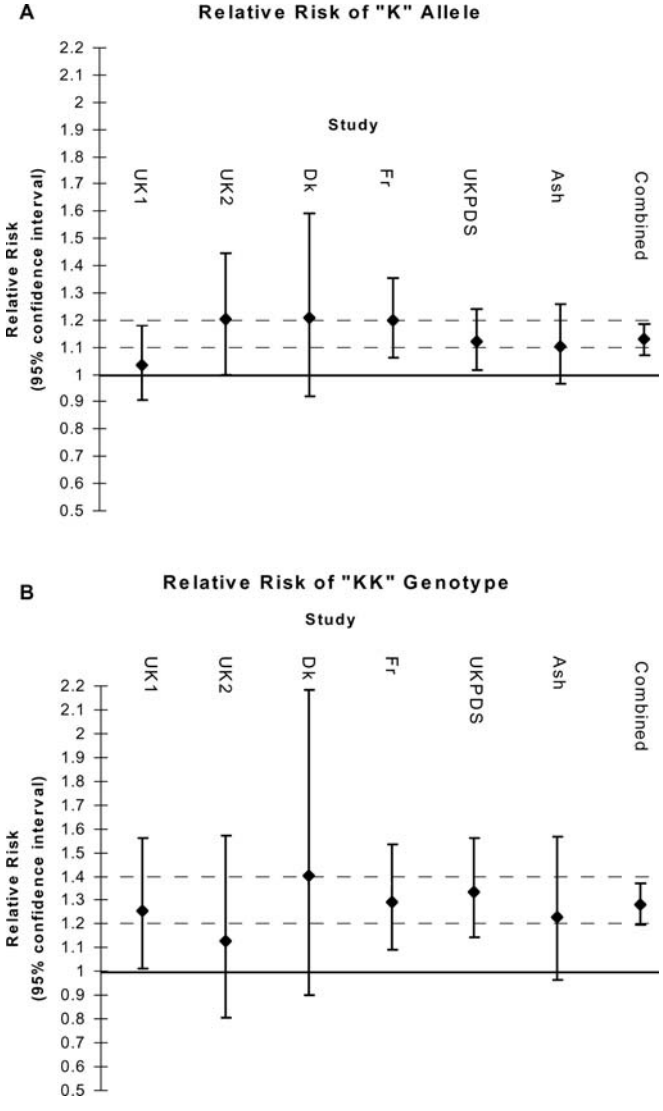

Fig. 1. A Estimated allele relative risk (95% CI) for Kir 6.2 E23K in six combined Caucasian studies. The *circle* for each study indicates the average relative risk observed for the "K" allele. The *line* represents range of the 95% CI around the estimated risk. The *dashed line* represents the 95% CI for the current combined data. **B** Estimated genotypic relative risk

analysis of all six studies continue to indicate that the Kir6.2 E23K polymorphism contributes to variation in the relative risk of developing Type II diabetes. Here we analysed 1153 Type II diabetic patients and 1076 control subjects and again observed an association between the homozygous E23K variant and Type II diabetes (0.18 in patients vs 0.11 in control subjects, corrected $p<1.0\times10^{4}$).

When the relative risks from the six studies are weighted by their sampling variance [7], meta-analysis indicates that the K allele increases risk by an average of 13% (95% CI: 1.07 to 1.18) (Fig. 1A), which translates into an average attributable risk of 11.4% for the populations surveyed in these studies. This data suggests that if this population were monomorphic for the non-risk allele (E), the prevalence of Type II diabetes would be 11.4% lower in this study group. The KK homozygote is at greatest risk (relative risk =1.28, 95% CI: 1.19 to 1.37) (Fig. 1B), confirming our original study.

Our purpose was to confirm the importance of the Kir 6.2 E23K polymorphism and estimate the risk associated with this variant to Type II diabetes. Our results indicate that E23K increases susceptibility to Type II diabetes and is comparable to the 25% population attributable risk contributed by PPARγ Pro12 Ala SNP.

L. Love-Gregory, J. Wasson, J. Lin, G. Skolnick, B. Suarez, M. A. Permutt
Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8127, Saint Louis MO 63110, USA

References

1. Altshuler D, Hirschhorn J, Klannemark M et al. (2000) The common PPARg prol12ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 26: 76–80
2. Mori H, Ikegami H, Kawaguchi Y et al. (2001) The Pro12 –>Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. Diabetes 50: 891–894
3. Koster JC, Marshall BA, Ensor N, Corbett JA, Nichols CG (2000) Targeted overactivity of beta cell K(ATP) channels induces profound neonatal diabetes. Cell 100: 645–654
4. Hani EH, Boutin P, Durand E et al. (1998) 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. Diabetologia 41: 1511–1515
5. Schwanstecher C, Meyer U, Schwanstecher M (2002) K(IR)6.2 polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic beta-cell ATP-sensitive K(+) channels. Diabetes 51: 875–879
6. Gloyn AL, Hashim Y, Ashcroft SJ, Ashfield R, Wiltshire S, Turner RC (2001) Association studies of variants in promoter and coding regions of beta-cell ATP-sensitive K-channel genes SUR1 and Kir6.2 with Type 2 diabetes mellitus (UKPDS 53). Diabet Med 18: 206–212
7. Prentice RL, Thomas DB (1987) On the epidemiology of oral contraceptives and disease. Adv Cancer Res 49: 285–401

Corresponding author: M. A. Permutt, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8127, Saint Louis MO 63110, USA, E-mail: apermutt@im.wustl.edu
Abbreviations: PPAR, Peroxisome proliferator activated receptor; Kir 6.2, potassium inwardly rectifying; ATP, sensitive channel