failure. The limited number of trios included in our study did not allow us to do further stratification analyses (e.g. by cause of kidney disease). However, allele transmission did not differ from random after stratification by gender (data not shown).

In summary, Rippin et al. observed no association between the *eNOS* *a/b* polymorphism and the presence of overt nephropathy in Type 1 diabetic patients in a case-control study. We now present data from a family-based study showing no association between this marker and the development of chronic renal failure in patients with various causes of chronic renal disease. According to our observation, the hypothesis that the *eNOS* polymorphism represents a molecular mechanism leading to chronic renal failure, independent of causes, is highly unlikely. On the other hand, a minor role of this marker in particular subsets of renal patients with different causes of kidney disease cannot be excluded on the basis of our observations.

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–to: Poa NR, Cooper GJS, Edgar PF: Amylin gene promoter mutations predispose to Type 2 diabetes in New Zealand Maori. *Diabetologia* 46: 574–578

Keywords Amylin mutations, IAPP mutations, Type 2 diabetes, ethnic background.

To the Editor: Poa et al. [1] screened for amylin gene mutations in New Zealand Maori and identified two different mutations in the promoter region of the amylin gene (–215 T/G and –132 G/A) and a missense mutation in exon 3 (Q10R), with a prevalence of 5.4%, 0.76% and 0.76%, respectively, in Type 2 diabetic Maori patients. The authors suggest that amylin is likely to be a susceptibility gene for Type 2 diabetes in this population, which has a high prevalence of diabetes.

We agree with the authors on the potential role of the amylin gene in the development of Type 2 diabetes. However, because the authors omitted any reference to the –132 G/A muta-

tion in their article, we would also like to remark the importance of this mutation. The presence of this mutation in Spanish subjects was described by our group [2] and corroborated by another group in a British cohort [3] of Caucasian origin. The aim of our study was to investigate the presence of the amylin gene mutations in a group of 186 Spanish Type 2 diabetic patients and 130 non-diabetic subjects. We detected a single heterozygous mutation consisting of a G/A substitution at position –132 bp in 18 patients with Type 2 diabetes and in two (2) control subjects. The frequency of the G/A genotype was higher in diabetic patients, than in controls (9.7% vs 1.5%, $p < 0.005$, odds ratio: 6.85, 95% CI: 1.56–30.08). Furthermore, studies of a family cohort (14 first-degree relatives belonging to eight families) detected the presence of the mutation in nine relatives, two of which were identified to be homozygous and having disturbed glucose metabolism.

A similar screening approach was carried out on British subjects, where the –132 G/A mutation was detected in 5.3% of the diabetic patients, compared to 3.2% of the non-diabetic control group [3]. The same mutation has been reported in 4.1% of a Type 2 diabetic Danish cohort, compared with 7.1% non-diabetic controls [4]. Unlike our findings, no difference in the frequency of the –132 G/A variant was detected between these two groups, probably due to differences in the genetic background of the British and Danish cohorts.

Due to the high prevalence of this mutation in our study group (this mutation is located in the enhancer domain close to transcription-factor DNA-binding motifs), we hypothesised that this polymorphism confers increased IAPP promoter activity and could result in an increased expression and peptide se-

Table 1. Polymorphisms and mutations identified in the IAPP gene*

Location Promoter	Population	Prevalence		p value
		Type-2	Controls	
–259 C/T	Japanese	One case	–	–
–229 C/A	Japanese	One case	–	–
–230 A/C	Maori	26%	24%	NS
	Japanese	60%	57%	NS
–215 T/G	Maori	5.4%	0.76%	=0.008
–132 G/A	Spanish	9.7%	1.5%	<0.005
	British	4.5%	3.2%	NS
	Finnish	0%	0%	NS
	Danish	4.1%	7.1%	NS
	Maori	0.76%	0%	NS
Intron 2				
+79 C/A	Spanish	6.8%	7.7%	NS
+75 A/G	Danish	0.81%	0%	NS
539 (deletion)	Japanese	One case	–	–
Exon 3				
Q/10/R	Maori	0.7%	0%	NS
S/20/G	Japanese	4.1%	0%	–
	Japanese	2.6%	0.8%	=0.0007
	Japanese	4.7%	1.6%	NS
	Chinese	2.8%	0.5%	=0.05
	Chinese	2.6%	0%	=0.05
	South Korean	1.92%	1.99%	NS
	Taiwanese	1.6%	4.4%	–

* All the data in the table are from studies published in international journals

cretion. In preliminary in vitro studies, done by our group, it was shown that the transcriptional regulation of the –132 G/A plasmid construct showed a two-fold increase in activity, compared to the wild-type construct [5].

The mutation in the IAPP coding sequence, at position 20 of exon 3 (S20G), was first reported in 4.1% of a Japanese study group with Type 2 diabetes [6], and the same mutation was described in a Chinese group [7]. The S20G mutation appears to be restricted to the Asian populations, as we were unable to detect it in Spain or in other European countries, such as the UK and Finland.

In overall amylin gene screening [8] we detected a new polymorphism, located at +79 C/A in intron 2, with a high prevalence in all studied groups (6.8% in Type 2 diabetic patients, 7.7% in the non-diabetic control group, 11.2% in gestational diabetes (GDM) and 9.2% in gestational control women). The allele distribution in diabetic patients was not different from the control subjects with normal glucose tolerance, suggesting that this polymorphism is not associated to the genetic predisposition to Type 2 diabetes or GDM. It is of interest to mention that the +79 bp amylin gene polymorphism was asso-

ciated with a specific phenotype. Both non-diabetic and Type 2 diabetic subjects bearing the CA genotype had lower levels of LDL cholesterol, ($p<0.001$) (multivariate logistic regression analysis) than subjects with wild genotype.

Some other polymorphisms and mutations have been identified in the amylin gene, with different prevalences depending on the ethnic variant (Table 1). In conclusion, we consider the amylin gene could play an important role in the complex heterogeneity of Type 2 diabetes, which also is highly related to the ethnic background.

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