

**PREVALENCE OF THE MUTATION (-132/GA)
IN THE AMYLIN PROMOTER GENE OF TYPE 2
DIABETIC PATIENTS AND CLINICAL
FEATURES OF THE CARRIERS**

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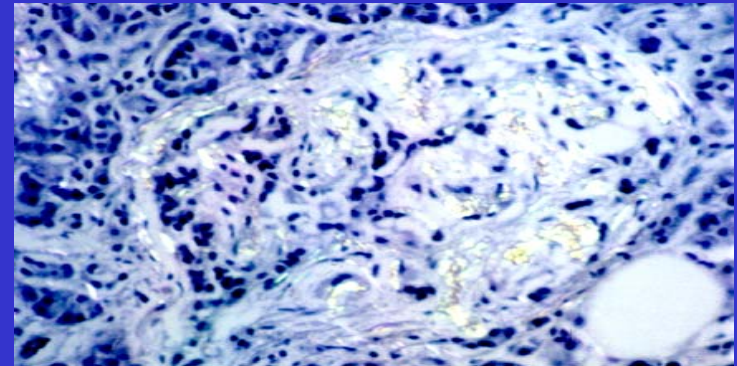


BACKGROUND OF IAPP (AMYLIN)

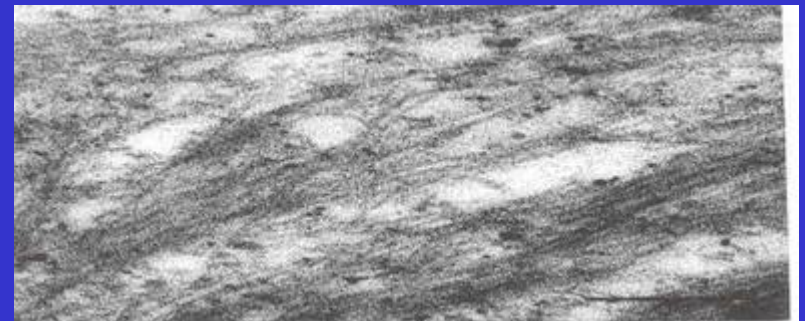
Islet amyloid polypeptide (IAPP also called amylin) is the main constituent peptide of islet amyloid deposits which are localized in the pancreas of type 2 diabetic patients.

Amylin is co-localized and co-secreted with Insulin in beta cell.

The mechanisms for the conversion of amylin to insoluble fibrils, a characteristic feature of amyloidogenesis are unknown.

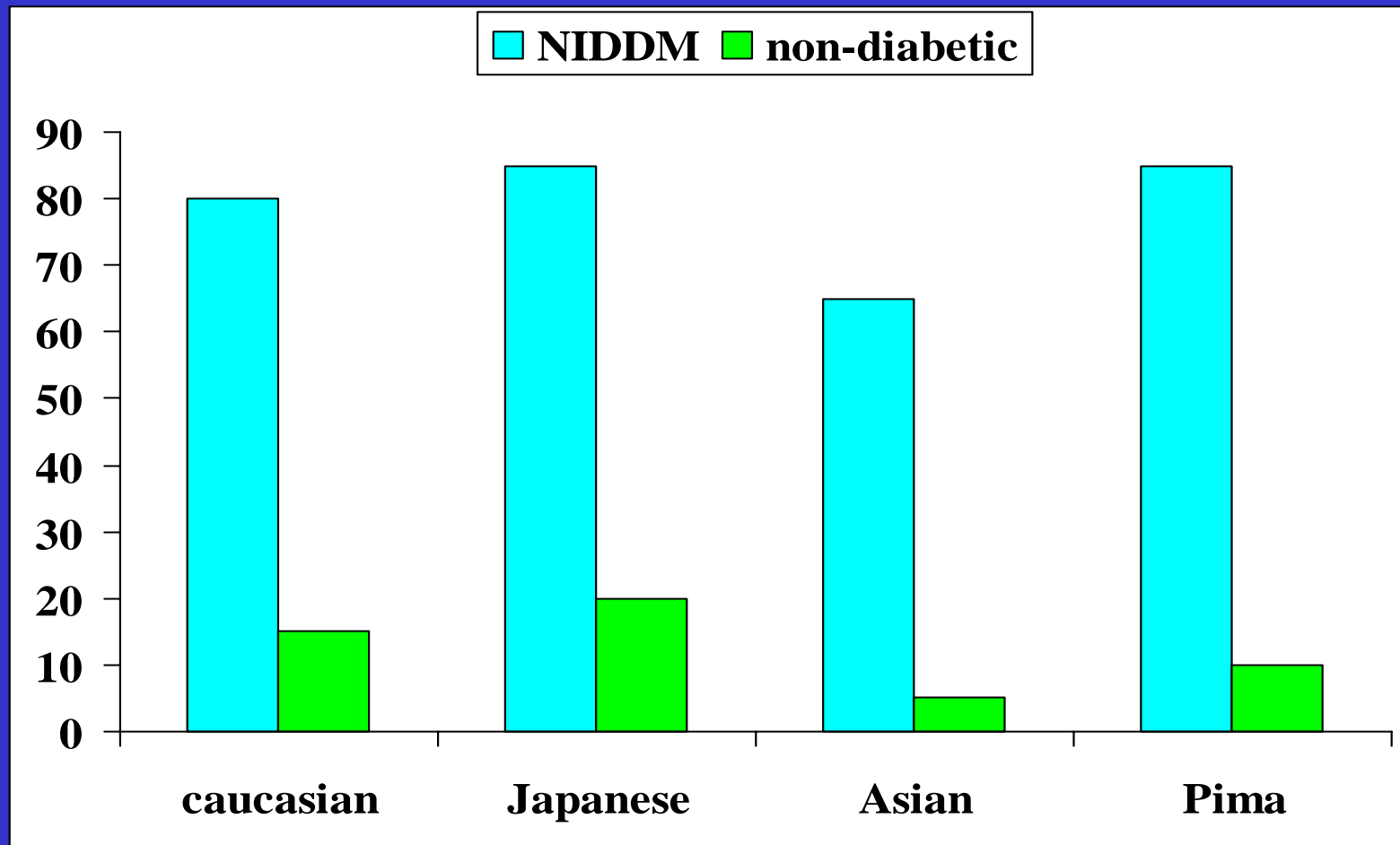


**Polarized light microscopy
of amyloid deposits**



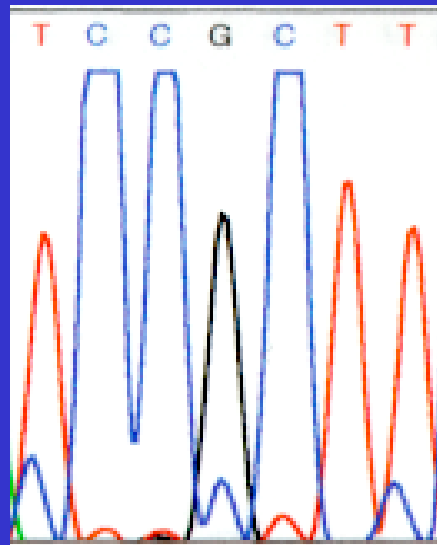
**Fibrils in amyloid deposits
Electron microscopy**

Prevalence of pancreas with Amyloid Studies in necropsies

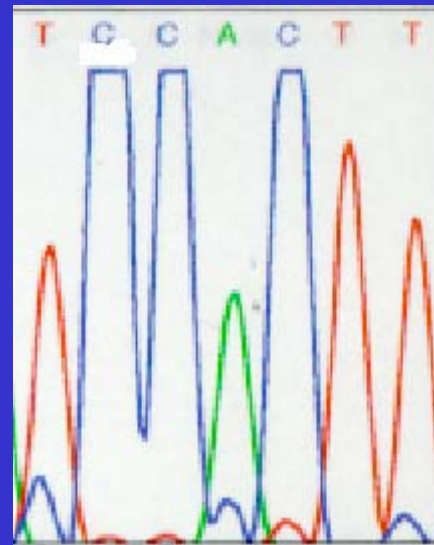


Westermarck et al., 1987

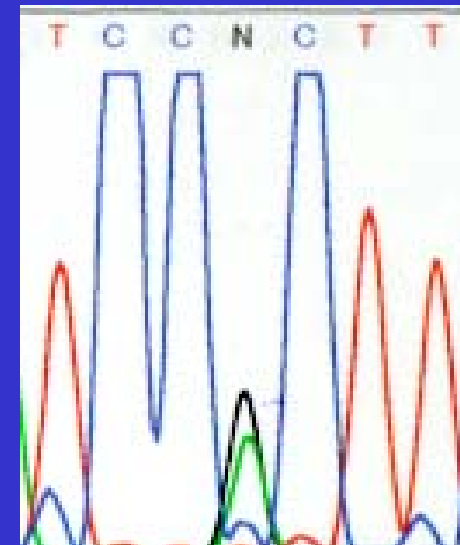
IDENTIFICATION OF -132 G/A MUTATION DNA SEQUENCE ANALYSIS OF THE PROMOTER REGION OF THE AMYLIN GENE



Non-carrier



Homozygote



Heterozygote

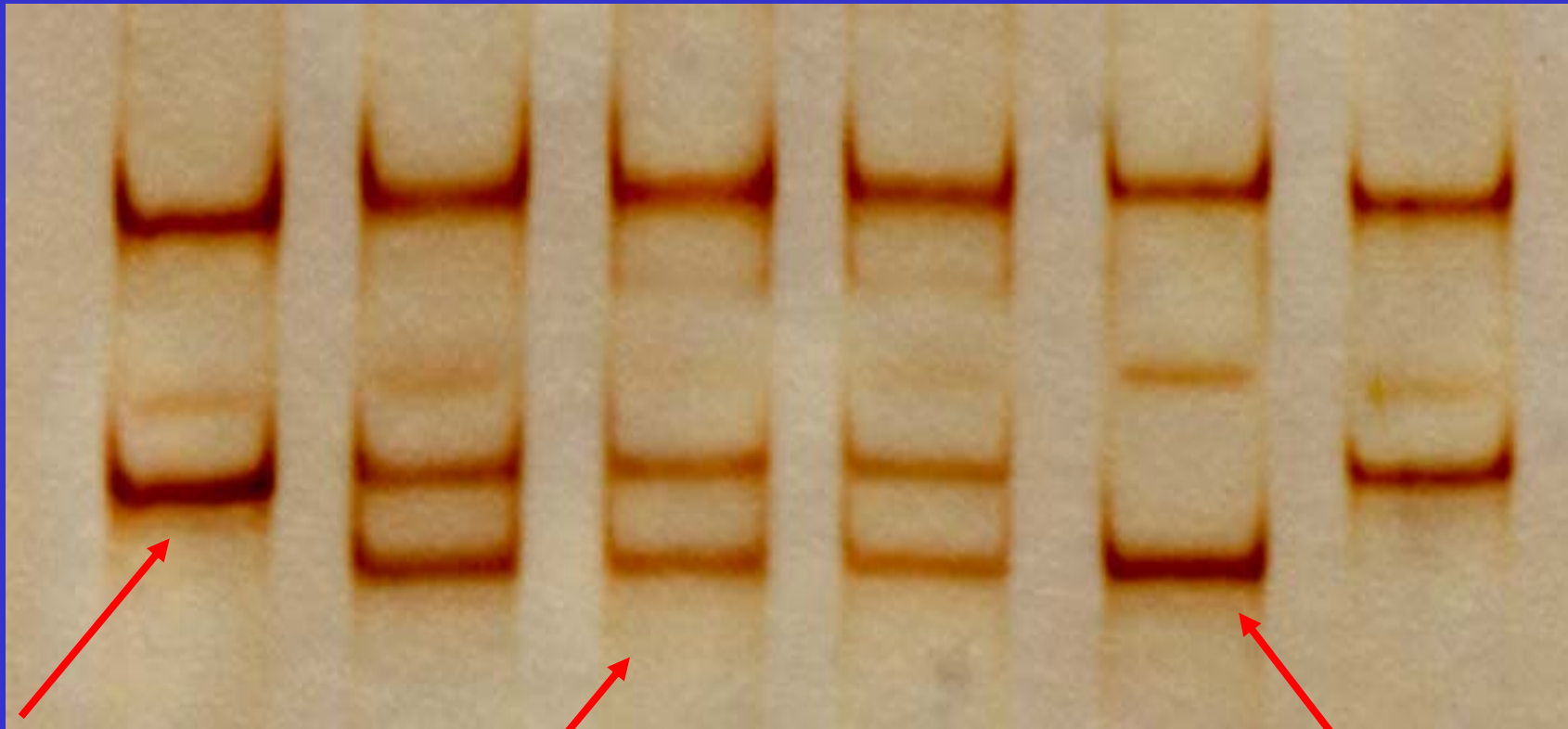
AIMS

- 1.** To investigate the prevalence of the mutation in a population of type 2 diabetic subjects
- 2.** To analyse the distinctive features of the patients carrying the mutation
- 3.** To analyse the glucose tolerance status of the relatives

Population

	Controls	DM 2	Relatives
N = 582	202	349	31
Age	48 ± 15	64 ± 11	40±15
Sex (M:F)	79:123	205:144	13:18
BMI (Kg/m²)	26± 5	28 ± 5	23±3
Duration diabetes (years)		12 ± 9	

SCREENING OF THE (-132 G/A) AMYLIN MUTATION USING SSCP ANALYSIS OF GENOMIC DNA



NORMAL

HETEROZIGOUS

HOMOZIGOUS

Results

The -132 G/A mutation of amylin gene was identified in 39 type 2 DM patients, in 16 relatives and in 3 controls.

	Genotype	
	Heterozigous	Normal
Controls (n=202)	3 (1.5%)	199 (98.5%)
Patients DM2 (n=349)	39 (11.2%)*	310 (88.8%)
Relatives (n=31)	16 (51.6%)	15 (48.4%)

p<0.001 patients versus controls

Odds ratio 8.33

CLINICAL CHARACTERISTICS

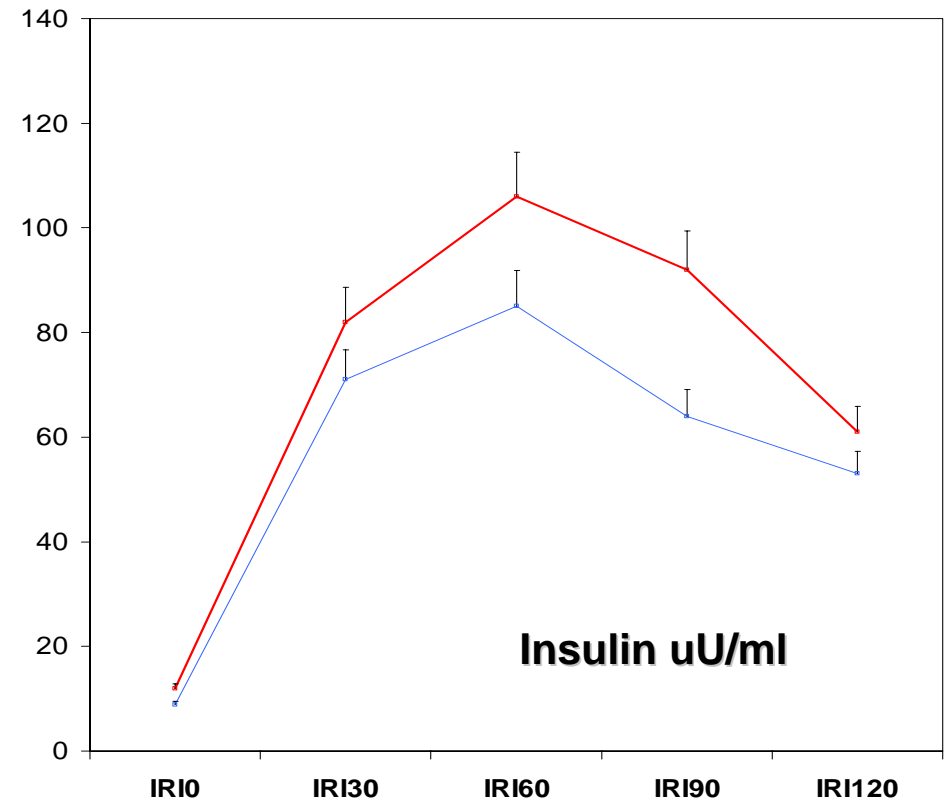
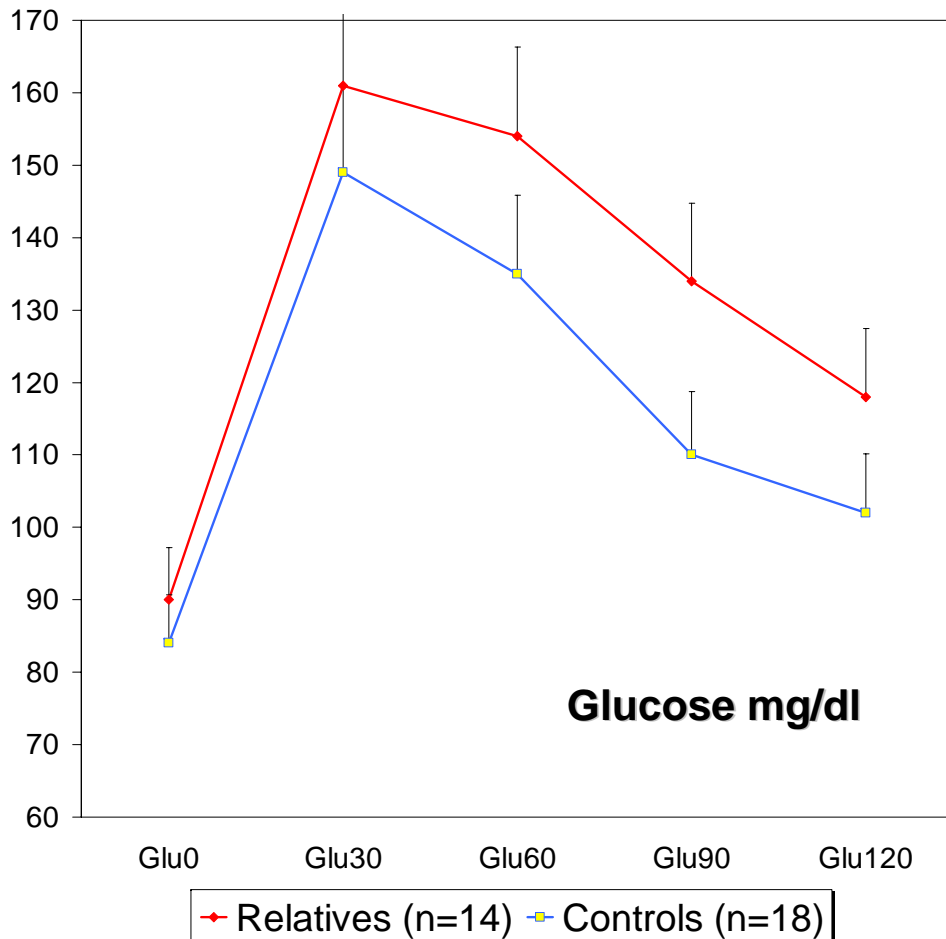
	GA Genotype (n =39)	GG Genotype (n = 310)	p
Age (years)	67 ± 9	64 ± 11	NS
Sex (M / F)	18 / 21	187 / 123	NS
BMI (Kg/m ²)	28 ± 4	28 ± 5	NS
Diabetes duration (years)	12 ± 9	13 ± 9	NS
Insulin therapy (%)	46	49	NS
Retinopathy (%)	37	33	NS
Nephropathy (%)	32	31	NS
Peripheral neuropathy (%)	32	45	NS
Coronary heart disease (%)	30	28	NS
Stroke (%)	13	7	NS
Distal arteriopathy (%)	14	17	NS
HTA (%)	74	57	<0.05
Dyslipidemia (%)	45	59	NS



CLINICAL CHARACTERISTICS

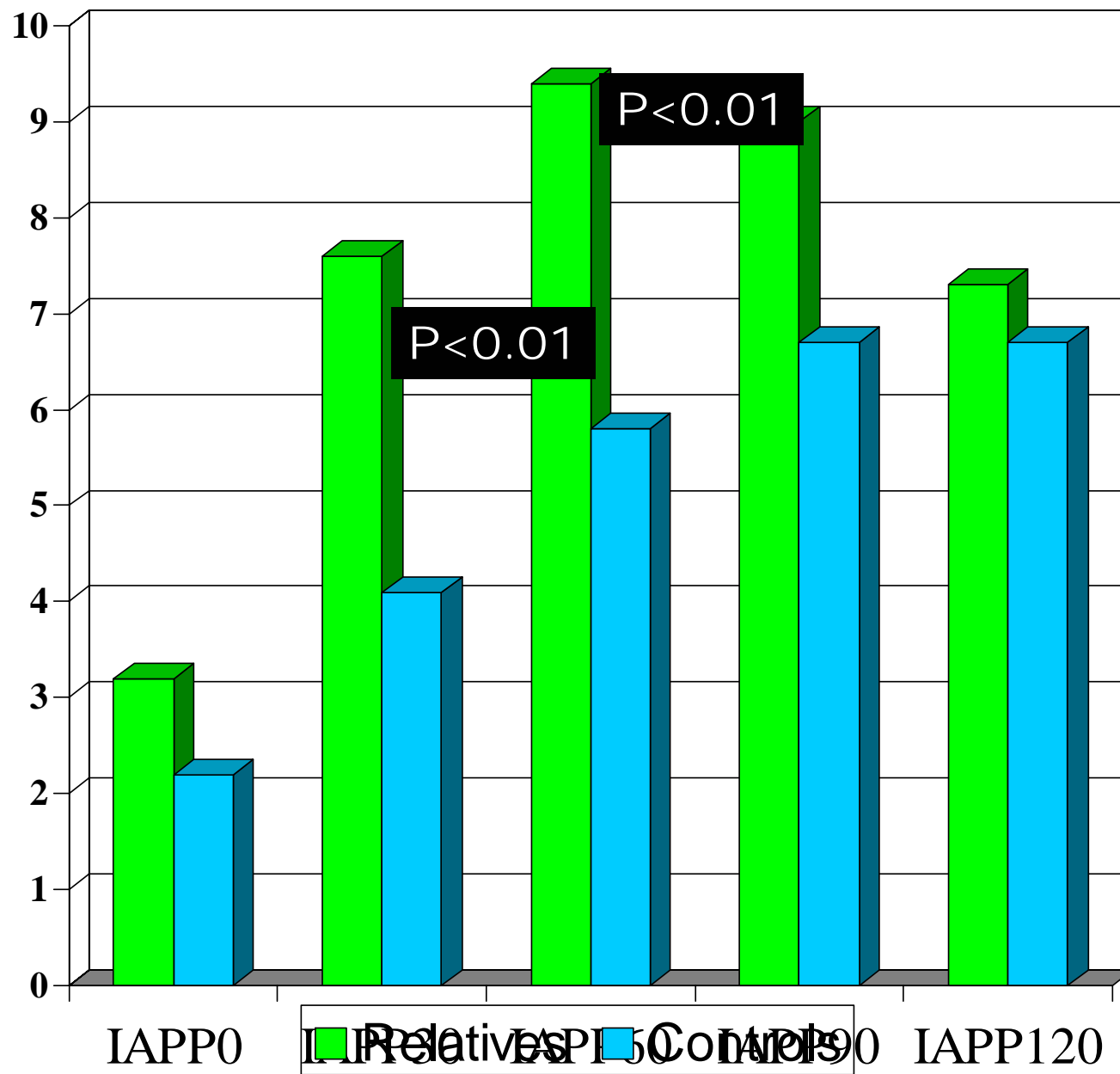
	GA Genotype (n =39)	GG Genotype (n = 310)	p
Fasting glucose (mg/dL)	164 ± 56	165 ± 60	NS
HbA1c (%)	7.5 ± 2	7.2 ± 2	NS
Total cholesterol (mg/dL)	199 ± 45	206 ± 38	NS
HDL-c (mg/dL)	58 ± 16	53 ± 15	NS
LDL-c (mg/dL)	123 ± 35	122 ± 31	NS
Triglycerides (mg/dL)	116 ± 19	161 ± 112	<0.001
Creatinine (mmol/L)	1.2 ± 1	1 ± 0.3	NS
Microalbuminuria (mg/day)	194 ± 646	180 ± 484	NS
Systolic BP (mmHg)	141 ± 19	136 ± 15	NS
Diastolic BP (mmHg)	77 ± 8	76 ± 10	NS
Abdominal circumference (cm)	107 ± 7	95 ± 9	NS

Glucose, Insulin and Amylin concentrations during an OGTT in non-diabetic relatives carriers of the mutation and in a control group



**Relatives group: 3 abnormal OGTT
(2 diabetes, 1 IGT)
Control group: no abnormal OGTT**

IAPP (pmol/L)



CONCLUSIONS

- The prevalence of the -132 (G/A) mutation of the amylin promoter region is higher in type 2 diabetic subjects and relatives than in controls.
- The mutation is associated with the development of hypertension.
- The higher amylin concentrations during OGTT in the relatives carrying the mutation could play a role in the development of diabetes in the future.