Association between the *Leu262Val* polymorphism of presenilin associated rhomboid like protein (PSARL), diabetes and metabolic phenotype in an Irish case-control population.

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Aims/hypothesis:

Mitochondrial dysfunction is of increased interest in obesity, insulin resistance and Type 2 diabetes (T2DM). PSARL is a mitochondrial protein shown to be associated with T2DM in Psammomys obesus[1]. In particular, a SNP variant (Leu262Val) in PSARL has been associated with hyperinsulinaemia in an age-dependent manner in a non-diabetic, mainly Caucasian, cohort[1].

Methods:

We studied the PSARL gene in an Irish Caucasian T2DM case-control population. A PCR-RFLP genotyping assay was optimised to study the *Leu*262*Val* polymorphism (Figure 1), in a cohort of 611 subjects, 419 with T2DM and 192 with normal glucose tolerance (Table 1). The *Leu*262*Val* polymorphism is due to a substitution of C for G.

Figure 1.

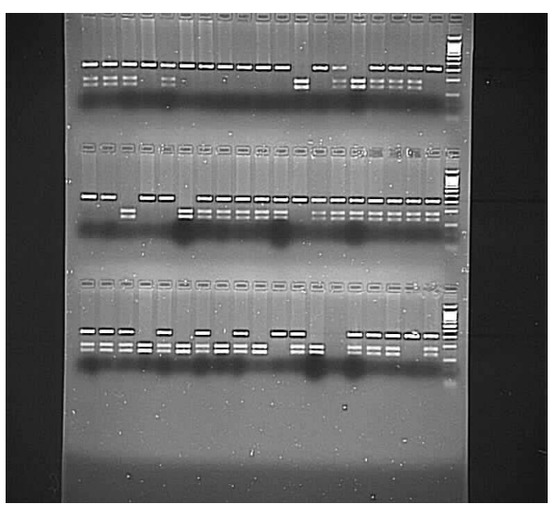

Table1

	Controls	T2DM	P-Value
Male Sex %	40.0	60.6	<0.05
Age: years	45.2±1.0	62.5±0.6	<0.05
Systolic BP: mmHg	117.9±1.4	133.7±0.9	<0.05
Diastolic BP:mmHg	73.9±0.7	78.5±0.4	<0.05
Weight: kg	79.3±1.3	85.8±0.9	<0.05
Height: m	168.7±0.8	167.3±0.6	NS
BMI: kg/m^2	27.9±0.4	30.4±0.3	<0.05
Waist circumf: cm	93.1±1.0	103.0±0.7	<0.05
Hip circumf: cm	107.3±0.9	110.0±0.6	<0.05
Waist : hip ratio	0.87±0.01	0.93±0.003	<0.05
Fast Insulin: µU/ml	8.0±0.8	13.2±0.5	<0.05
Fast C-peptide: µg/l	2.2±0.4	3.4±0.3	<0.05
F. Glucose: mmol/l	4.9±0.2	8.4±0.1	<0.05
HbA1c	5.5±0.1	7.6±0.1	<0.05
T. Cholesterol : mmol/l	4.9±1.4	6.0±0.9	NS
HDL: mmol/l	1.4±0.02	1.2±0.01	<0.05
LDL: mmol/l	2.6±0.1	2.9±0.05	<0.05
Triglycerides : mmol/l	1.7±0.3	2.2±0.2	<0.05
U. Microalbumin:mg/l	20.4±4.9	42.8±3.2	<0.05
U. Creatinine: mmol/l	12.5±0.5	11.4±0.3	NS
U. Albumin:Creatinine Ratio	1.9±0.6	4.5±0.4	<0.05

Values are presented as mean ± SEM

Results:

The frequency of the C allele in controls was 0.47 and in the group with T2DM was 0.46, consistent with Hardy-Weinberg equilibrium. In the control group 27.4 % were GG homozygotes, 51.5 % CG heterozygotes and 21.1 % were CC homozygotes. In the group with T2DM 30.6 % were GG homozygotes, 47.8 % CG heterozygotes and 21.6 % were CC homozygotes. A One-way ANOVA showed significant difference (p<0.05) for the following variables between genotypes Table 2.

Table 2

	CC	CG	GG	P value
Controls				
Weight: kg	82.9 ±2.9	76.2 ±1.8	82.3 ±2.5	0.047
Waist Circ: cm	97.7 ±2.3	90.1 ±1.4	95.2 ±2.0	0.011
Hip Circ: cm	110.4 ±2.0	104.9 ±1.2	109.4±1.7	0.03
F.Insulin: mU/l	10.6 ±2.1	6.9 ±0.5	8.3 ±1.0	0.04
F.Glucose: mmol/l	5.15 ±0.1	4.8 ±0.1	4.9 ±0.1	0.031
T2DM				
F. Insulin: mU/l	10.9 ±1.3	14.1 ±0.1	13.3 ±1.1	0.11
F. Triglycerides: mmol/l	3.3 ±0.1	1.9 ±0.1	1.9 ±0.1	0.023
U. Albumin:Creatinine ratio	7.0 ±1.4	4.4 ±0.5	2.8 ±0.5	0.003
U. Microalbumin: mg/l	58.3 ±7.9	46.1 ±5.2	26.6 ±6.6	0.007
Age at diagnosis	56.7 ±1.3	55.9 ±0.9	52.7 ±1.1	0.048

Values are presented as mean ± SEM

Conclusion:

We have confirmed a genotype distribution in our population similar to the recently published cohort. Furthermore, genetic variation at *Leu*262*Val* of PSARL may be a risk factor for centripetal obesity, hyperglycaemia and hyperinsulinaemia in the normo glycaemic population and in population with T2DM a worse cardiovascular risk profile.

Reference:

1.Walder K, *et al*. The mitochondrial rhomboid protease PSARL is a new candidate gene for type 2 diabetes. Diabetologia. 2005 Mar; 48(3): 459 - 68.

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