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LETTER TO THE EDITOR

A common polymorphism in MIR155 gene promoter region is associated with a lower risk to develop type 2 diabetes

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Dear Editor,

We read with great interest the paper "Polymorphisms in genes encoding miR-155 and miR-146a are associated with protection to type 1 diabetes mellitus" by Assmann et al. [1]. The authors described the association between two polymorphisms in *MIR155* and *MIR146A* genes and susceptibility to type 1 diabetes. It is known that these miRNAs are involved in immunity and inflammation pathways; therefore, it is conceivable that they could also play a role in type 2 diabetes mellitus (T2DM) susceptibility. In a previous publication, we had investigated *MIR146a* rs2910164 polymorphism in relation to T2DM susceptibility but we did not observe significant differences of frequencies between T2DM patients and healthy controls [2].

Since, at present time, there are no data in literature related to the effect of *MIR155* polymorphisms in the susceptibility to T2DM, we examined the *MIR155* rs767649 (A/T) in 233 patients with T2DM recruited from outpatients attending the Diabetic Clinic of the Policlinico Tor Vergata (PTV) in Rome and 303 ethnically and age-matched healthy controls. DNA was extracted from peripheral blood and the polymorphism was genotyped using TaqMan Genotyping Assay (Thermo Fisher Scientific, Foster City, CA, USA). A case/control association study and a genotype/phenotype correlation analysis have been performed using the SPSS program (SSPS Inc., IL, USA).

In Table 1a, we reported the distribution of genotypes and alleles frequencies in patients with T2DM and in the healthy controls. No subject homozygous for the low frequency A allele was observed. As shown, we observed a significant association between the rs767649 polymorphism and T2DM susceptibility. Individuals heterozygous for this genetic variant showed a lower risk to develop T2DM in comparison with wild-type individuals (OR 0.55, $P=0.029$). The lower risk was observed also at the allelic level (OR 0.58 and $P=0.035$). Therefore, the A allele seems to play a protective role for the development of T2DM, similarly to what observed in type 1 diabetes [1].

Subsequently, we performed a genotype/phenotype correlation analysis between the *MIR155* polymorphism and clinical characteristics of patients with T2DM (Table 1b). Interestingly, the A allele of rs767649 polymorphism was significantly less frequent in patients with central obesity (OR 0.29, $P=0.039$), suggesting a protective effect also for this condition. Conversely, we observed that the same genotype was associated with a significantly increased risk to develop coronary artery disease (CAD) (OR 3.49, $P=0.02$).

The rs767649 polymorphism is located in the promoter region of gene encoding miR-155 and was reported to be able to alter transcriptional activity of this miRNA [3]: specifically, the A allele upregulates the mir expression. Dysregulation of the miR-155 has been observed in several inflammatory diseases, such as cardiovascular or autoimmune diseases. Since one of the pathophysiological derangements of diabetes is chronic inflammation, an altered level of miR-155 caused by rs767649 A allele could explain the association. Decreased serum levels of miR-155 have been previously observed in obese patients [4]; on the contrary, CAD patients showed a higher miR-155 expression level when compared to control subjects [5]. Thus, the lower and higher frequencies of the A allele that we found in association with central obesity and CAD, respectively, seem to be consistent with the data of lower and higher miR-155

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Table 1 (a) Genotypes and alleles frequencies of MIR155 polymorphism (rs767649) in T2DM patients and healthy controls, (b) significant genotype-phenotype correlations in T2D patients

	T2DM ($n=233$)	CTRL ($n=303$)	P*	OR (95% CI)*
(a)				
Genotypes				
TT	211 (90.6%)	255 (84.2%)	0.029	0.55 (0.32–0.97)
TA	22 (9.4%)	48 (15.8%)		
AA	0	0		
Alleles				
T	444 (95.3%)	558 (92.1%)	0.035	0.58 (0.34–0.97)
A	22 (4.7%)	48 (7.9%)		
	Central obesity		P*	OR (95% CI)*
	Without	With		
(b)				
Genotypes				
TT	35 (83.3%)	85 (94.4%)	0.039	0.29 (0.09–0.99)
TA	7 (16.7%)	5 (6.5%)		
	Coronary artery disease			
	Without	With		
Genotypes				
TT	128 (92.8%)	22 (78.6%)	0.02	3.49 (1.15–10.58)
TA	10 (7.2%)	6 (21.4%)		

The variables evaluated and not significantly associated (data not shown) were: sex, age, disease duration, BMI, microalbuminuria, HbA1c, total cholesterol, HDL, LDL, triglycerides, serum creatinine, hypertension, peripheral vascular disease, retinopathy

*P value and Odds ratios (ORs) evaluated by Pearson χ^2 test

expression level reported in the two conditions [4, 5]. However, the different genotype-phenotype patterns, supposed to be present in central obesity and CAD, are not easily compatible with a unifying hypothesis. They might be interpreted in the light of the multiple (inflammatory and immune) pathways implicated in the diabetic complications and potential targets of miR-155.

The involvement of the miR-155 in T2DM, cardiovascular diseases and obesity was already known. However, this is the first study that evaluated the association between the *MIR155* rs767649 polymorphism and T2DM and its complications. Our results, although preliminary, are consistent with the protective role of rs767669 polymorphism described by Assmann in T1D, further supporting the miR-155 role in diabetes pathogenesis. These findings surely require additional independent studies, including both functional studies and a higher number of patients, to confirm and clarify the possible contribution of this polymorphism to the development of T2DM and its complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments

Informed consent Informed consent was obtained from all individual participants included in the study.

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