This article deals with the study of a rare genetic variant in the hypoxia inducible factor-1 alpha gene on type 1 and type 2 diabetes. 370 T2DM, 166 T1DM and 354 healthy subjects were enrolled in this study. Genotyping was validated by two independent methods, a Tsp45 I RFLPs protocol and a real time PCR approach using TaqMan probes. A protective effect of a rare genetic variant of HIF-1 alpha gene against type 2 diabetes was detected and, based on other findings, a possible overlap in the pathophysiological mechanism for T2DM and a T1DM is suggested.

This study has a very good potential, the results are clear and the molecular/statistical techniques are appropriate. The combination of two genotyping approaches is excellent. The data are in Hardy Weinberg equilibrium and detailed information dealing with the current literature is presented.

Minor comments:

1) A positive point of the article is that it presents some assumptions about the putative role of the gene polymorphism analyzed in the pathogenesis of diabetes. However, the inability of Hlatky et al (2007) and Nagy et al (this paper) to replicate former results presented by Yamada et al (2005) dealing with the HIF-1 alpha transcriptional activity make me a bit concerned as regards with the real functional significance of the polymorphism under study. Thus, I would avoid characterizing as “protective” the effect of this polymorphism; I would prefer the term “non-predisposing” rather than protective, given that this is still in fact one issue of debate in the literature, in case that alleles are found significantly more prevalent in controls than in patients.

2) I recommend a first approach to be done regarding the plausible role of the mutation analyzed in the conformation of the protein. This may give some explanations dealing with the functional significance of this SNP.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.