

PTPN2 gene polymorphisms are associated with type 1 *diabetes mellitus* in Brazilian subjects?

Polimorfismos no gene PTPN2 estão associados com diabetes melito em brasileiros?

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We appreciated the correspondence by Liu and cols. that was sent to this journal regarding our manuscript “The rs1893217 (T/C) polymorphism in PTPN2 gene is not associated with type 1 *diabetes mellitus* in subjects from Southern Brazil” (1).

We agree with Liu and cols. regarding the potential role of PTPN2 in the pathogenesis of type 1 *diabetes mellitus* (T1DM), which has been reinforced by several experimental studies (2). However, our study found no evidence of a significant association between the PTPN2 rs1893217 (T/C) polymorphism and T1DM risk (1), while Espino-Paisan and cols. (3) reported that in subjects from Spain the minor allele of the PTPN2 rs2542151 polymorphism was more prevalent in early-onset T1DM patients (age of onset < 16 years) as compared to late-onset patients and non-diabetic controls. No significant difference was found between control and T1DM late-onset groups. Of note, the rs2542151 polymorphism is in strong linkage disequilibrium with the rs1893217 polymorphism in subjects of European descent (4). One possible explanation for these discordant results is that Espino-Paisan and cols. (3) only observed an association between the rs2542151 polymorphism and early-onset T1DM. Thus, our results are in agreement with their data regarding an absence of association with late-onset T1DM. It is worth noting that in our sample the mean age of T1DM onset was 17.3 ± 10.1 years (1), more similar to that of their late-onset group. Another possible explanation is different genetic backgrounds and environmental risk factors between Brazilian (1) and Spanish populations (3). It is well known that genetically different individuals exposed to varied environmental factors will have different pathways leading to β -cell loss and, consequently, disease onset and evolution (2).

Moreover, Steck and cols. (5) reported that the PTPN2 rs1893217 polymorphism seems to predict islet autoimmunity (hazard ratio = 1.42, 95% CI 1.02-1.99) but not T1DM development, after controlling for family history of T1DM and HLA high-risk genotypes. The absence of an association with T1DM is in agreement with our reported data (1). Unfortunately, we did not analyze HLA-high risk genotypes in our population to know if this genetic background would modify the association between the rs1893217 polymorphism and T1DM in different subgroups. Interactions with non-HLA genes also might influence the effects of the rs1893217 polymorphism on T1DM susceptibility.

Therefore, we agree that available evidence suggests that PTPN2 may play a potential role in the pathogenesis of T1DM, and may have a therapeutic potential for this disease. However, different therapeutic strategies might be required depending on the genetic background of the affected individuals. Furthermore, multicenter studies with larger sample numbers, and controlling for HLA-high risk genotypes and

presence of autoantibodies are necessary to define the role of *PTPN2* polymorphisms in the Brazilian population as well as in other populations. Prospective studies following children since the development of islet autoimmunity to progression to T1DM are also needed as they may offer further insights regarding the association of the *PTPN2* rs1893217 polymorphism and T1DM.

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