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GRB10 Gene and Type 2 Diabetes in Whites

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GRB10 encodes for an inhibitor of insulin receptor signaling [1] and is therefore a candidate for type 2 diabetes (T2D). In a preliminary study, the minor allele (MA) of *GRB10* rs4947710 was associated with a reduced T2D risk in Whites from Italy, whereas a trend in the opposite direction, albeit not significant, was observed in Whites from the US [2], making the overall observation uncertain. A different *GRB10* single nucleotide polymorphism (SNP) (rs2237457) has been recently associated with T2D among Amish but not in other populations [3], suggesting the possibility of allelic heterogeneity. To further investigate the role of *GRB10* variability in modulating susceptibility to T2D in Whites, we genotyped rs4947710 and rs2237457 in a total of 3,433 diabetic cases (1899 males/1534 females; age=61.4±9.2 yrs; BMI=31.5±6.1 Kg/m^2) and 2,660 non-diabetic controls (1153 males/1507 females; age=45.5 ±16.0 yrs; BMI=27.8±6.1 Kg/m^2) of European origin included in the "GENetics of T2D in Italy and United States (GENIUS) Consortium". The clinical characteristics of these subjects have been previously reported in details [4]. All samples, which included those from the previous smaller study (2), were genotyped by TaqMan allelic discrimination assay. The average agreement rate of duplicate samples was >99%. Failure rate of genotyping was <3.0%. Both rs4947710 (MA frequency=0.073) and rs2247457 (MA frequency=0.39) were in Hardy Weinberg equilibrium in controls and cases. Since no genetic heterogeneity across the four centers of recruitment was evident (p values for heterogeneity = 0.11 and 0.16 for rs4947710 and rs2247457, respectively), data were analyzed after pooling the four data sets together and

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adjusting for center of recruitment, age and sex. No significant association with T2D was observed with either rs4947710 (allelic OR, 95% CI=1.11, 0.92-1.33, adjusted p=0.30) or rs2247457 (OR, 95%CI=0.98, 0.89-1.09, adjusted p=0.73). These results are in agreement with those from the DIAGRAM data set [5], which did not show a significant association between T2D and either rs4947710 (OR, 95% CI =1.08, 0.99-1.17; p=0.1) or rs2237457 (OR, 95% CI=1.06, 0.99-1.13; p=0.1). In conclusion, *GRB10* rs2237457 and rs4947710 do not seem to play a significant role in modulating susceptibility for T2D in individuals of European ancestry.

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