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The PAX4 gene variant A1168C is not associated with early onset Type 1 diabetes in a UK population.

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The PAX4 gene variant A1168C is not associated with early onset Type 1 diabetes in a UK population

Biason-Laubert and colleagues have recently reported an association between a single nucleotide polymorphism (SNP; rs712701) in PAX4 (A1168C) and Type 1 diabetes (T1D) [1]. The C/C genotype was over-represented in T1D compared with control subjects (76.7 vs. 31.2% Swiss, 71.5 vs. 33.9% German; $P < 0.0001$). They also reported that pancreatic β cells expressing both PAX4A and PAX4C efficiently proliferate when stimulated with glucose, unlike cells expressing the PAX4C variant alone. They concluded that the polymorphism may be considered a predisposition marker that assists in the identification of individuals prone to develop T1D.

We have replicated the study in the Northern Ireland population, employing both case-control and family-based association analyses.

Probands ($n = 437$; mean age at diagnosis 6.8 years) were derived from a Northern Ireland register of newly diagnosed early onset patients with Type 1 diabetes [2]. All subjects were white Caucasians with parents and grandparents born in Northern Ireland. DNA from both parents was available for

283 probands. These trios were employed for the family-based association study. Control subjects ($n = 419$; mean age 13.5 years) were derived from a random sample of healthy Northern Ireland school children [3]. All subjects were genotyped for the PAX4 A1168C polymorphism by the Taqman 5'-nuclease assay (C 7563629 10) on an ABI Prism 7000 Sequence detection system (Applied Biosystems, Warrington, UK).

A slight increase in C/C genotype in cases compared with control subjects was observed (66.8 vs. 60.6%; $P = 0.06$; OR = 1.31, 95% CI 1.0, 1.7), however, the association was weaker than the stratified odds ratio of 6.14 (95% CI 4.7, 8.2) calculated from the results of Biason-Laubert and colleagues [1]. We also found no significant transmission distortion of the PAX4 1168C allele from informative parents to affected individuals, 105 (53.6%) transmissions vs. 91 (46.4%) non transmissions ($P = 0.32$). Similarly, stratification for age at diagnosis of diabetes (< 5 years and ≥ 5 years) and for the case's HLA-DR risk group (DR3/DR4 heterozygotes, other carriers of DR3, other carriers of DR4) showed no association of the A1168C SNP with T1D in both case-control and transmission disequilibrium test analyses (TDT, data not shown).

The present case-control study comprises a larger cohort of T1D samples than those investigated by Biason-Laubert *et al.* (Northern Ireland $n = 437$, Swiss $n = 249$, German $n = 130$). Indeed, our case-control study was of sufficient size to have almost 80% power to detect as statistically significant ($P < 0.05$) a 50% increase in T1D risk among those with the C/C genotype. The validity of Biason-Laubert and colleagues findings has also recently been challenged by Paterson [4] and Maier *et al.* [5]. Errors in the original statistical analyses (χ^2 test and odds ratio), along with significant departures from Hardy-Weinberg equilibrium (HWE), have been noted [4]. In reply, the original authors confirmed their findings [6], suggesting that deviation from HWE is the result of heterozygote advantage at the PAX4 A1168C polymorphism; a theory supported by their expression studies [1]. However, this study and a recent multipopulation study [5] failed to find an association between PAX4 and T1D. Indeed, both studies found the frequency of the C/C genotype in cases and control subjects (66.8 vs. 60.6% Northern Ireland; 62.2 vs. 60.4% Great Britain) to be considerably higher than those reported by Biason-Laubert *et al.* (76.7 vs. 31.2% Swiss, 71.5 vs. 33.9% German).

In conclusion, our findings do not support association of the PAX41168CC genotype with T1D in the Northern Ireland population.

Competing interests

None declared.

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