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


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Biason-Lauber 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 \(\beta\) 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. Proband (\(n = 437\); 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-Lauber and colleagues [1]. We also found no significant transmission distortion of the PAX4 A1168C 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 \(\geq 5\) 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-Lauber 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-Lauber and colleagues findings has also recently been challenged by Paterson [4] and Maier et al. [5]. Errors in the original statistical analyses (\(\chi^2\) 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-Lauber et al. (76.7 vs. 31.2% Swiss, 71.5 vs. 33.9% German).

In conclusion, our findings do not support association of the PAX4 A1168C variant with T1D in the Northern Ireland population.

Competing interests
None declared.

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