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Failure to develop Tolerance to Thyroid Peroxidase at an Early Age and a Strong Ctla-4 Gene Association Define Female-Dominated Type 1 Diabetes Subgroup

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Introduction

e CTLA-4 gene, which encodes a crucial negative immunoregulatory receptor in T cell activation and expansion, has also been linked to AITD and type 1 diabetes, in addition to associations with HLA class II alleles and haplotypes, particularly the lymphoid speci c phosphatase (LYP) T cell activation gene PTPN22. Single nucleotide polymorphisms (SNPs) in the 3'UTR of the gene are the strongest candidates for the variant(s) that are to blame for the AITD association. SNP with the greatest disease association [1]. However, the e ect is much smaller in type 1 diabetes, and a recent study of 769 Japanese type 1 diabetes cases found that the G allele of the CTLA4 rs3087243 SNP has no direct e ect on susceptibility to type 1 diabetes. Furthermore, the study found that the association with type 1 diabetes is secondary to anti-thyroid autoimmunity, and that CTLA4 is only associated with AITD. However, there was no statistically signi cant di erence reported. e CTLA-4 gene was found to be linked to type 1 diabetes and AITD, an autoimmune polyendocrine syndrome (APS), in three additional studies [2]. yroid peroxidase autoantibodies (TPOAbs) and other autoantibodies to thyroid gland components frequently precede AITD diagnosis. e CTLA-4 gene is linked to the production of TPOAbs. In the USA, 4.8% of people matured 12-19 years have thyroid peroxidase autoantibodies, while 10 to 30% of patients with type 1 diabetes have thyroid antibodies, and up to half of these advancement to clinical AITD. We have gathered plasma and DNA tests from more than 4,000 instances of type 1 diabetes, for the most part from pediatric facilities from across Incredible England [3].

Methods

Statistical approaches

Using the genotype as a reference at OR = 1.0, logistic regression was used to test for association and calculate odds ratios (OR) within STATA8 with 95% con dence intervals. By incorporating a regional variable into the regression, analyses were strati ed according to 12 geographical regions as cases and controls were collected from all over Great Britain. As a result, any confusion brought about by di erences in allele frequency across Britain was minimized [4]. Using TPOAbs status as the outcome variable, a case-only logistic regression strategy was used to investigate whether type 1 diabetes cases had an interaction e ect between genotype or haplotype and the presence of TPOAbs.

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CTLA-4's critical role in peripheral tolerance, as well as its roles in the functions of antigen presenting cells and T regulatory cells, supports this conclusion. We hypothesize those individuals with the SNP A/A genotype, which is associated with protection from autoimmune diseases and increased peripheral tolerance, are more likely to have T cells that are more hyperactive and respond more strongly to peripheral antigens than those with the rs3087243 G allele [7]. However, our ndings also suggest that the allelic variation of CTLA4 has a much smaller impact in approximately 90% of cases of type 1 diabetes. Since anti-thyroid autoimmunity a ects more than 15% of European type 1 diabetes cases, the OR in the TPOAb-negative subgroup would probably be reduced to one or very close to it if we were able to nd these in our case samples. Our interpretation of this result di ers from that of a recent Japanese study, which came to the conclusion that the G allele of the CTLA4 rs3087243 SNP has no direct e ect on susceptibility to type 1 diabetes and that the association with type 1 diabetes is secondary to anti-thyroid autoimmunity. By predisposing individuals with a G allele to reduced tolerance, a multiplicity of peripheral antigens, and possibly even a form of autoimmune polyendocrine syndrome (the occurrence in patients with two or more endocrine autoimmune diseases), we propose that allelic variation of CTLA4 does directly a ect type 1 diabetes. Additionally, type 1 diabetes almost always develops more than a decade before clinical AITD in patients with both types of diabetes. However, research on the NOD mouse provides the strongest evidence for a direct e ect of CTLA-4 gene allelic variation on type 1 diabetes susceptibility [8]. e region of mouse chromosome 1 containing the CTLA-4 gene and the Idd5.1 susceptibility locus has a signi cant impact on disease susceptibility, as demonstrated by genetic analysis of the NOD mouse model of type 1 diabetes. e causal variant has been mapped to a SNP in Ctla4's exon 2 where the NOD allele inhibits the splicing and expression of the ligand-