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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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Abstract

Type 1 diabetes and autoimmune thyroid disease (AITD) have been linked to HLA haplotypes with allelic variation of the T cell activation gene PTPN22 and the T cell regulatory gene CTLA4. We compare the relationship between these loci and type 1 diabetes patients with and without thyroid peroxidase autoantibodies (TPOAbs), an indicator of thyroid autoimmunity. People with type 1 diabetes from all over Great Britain had their TPOAbs measured. 67% were under the age of 18. Genotyping was done on these cases and controls from the same area.

Keywords: Autoimmunity; CTLA4; Human; Diabetes; Thyroid antibodies

Introduction

The 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 specific 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 effect 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 effect 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 significant difference reported. The CTLA-4 gene was found to be linked to type 1 diabetes and AITD, an autoimmune polyendocrine syndrome (APS), in three additional studies [2]. Thyroid peroxidase autoantibodies (TPOAbs) and other autoantibodies to thyroid gland components frequently precede AITD diagnosis. The 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% confidence intervals. By incorporating a regional variable into the regression, analyses were stratified according to 12 geographical regions as cases and controls were collected from all over Great Britain. As a result, any confusion brought about by differences 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 effect between genotype or haplotype and the presence of TPOAbs. By regressing gender on TPOAbs status, we also tested whether gender explained the variation in TPOAbs. Gender was included as a confounder in all TPOAb analyses by including a gender variable in the regression because gender was found to be a significant determinant of TPOAb status.

Thyroid autoantibodies help keep type 1 diabetes under genetic control

With a 6.2% increase in the disease-associated G allele frequency in the TPOAb-positive group and almost twice the risk of having both type 1 diabetes and TPOAbs, associated with the G allele or G/G genotype odds ratio of the G/G genotype = 2.63 in the TPOAb-positive group compared to 1.37 in the TPOAb-negative group, with no overlap in the 95% confidence intervals, CTLA4 demonstrated a convincing distinction between TPOAbs subgroups [5]. The mode of inheritance of the locus is another interesting difference in the association of CTLA4 with TPOAbs positive type 1 diabetes cases: The G allele has a dominant effect, with no significant difference between the G/A heterozygote risk (OR = 2.16) and the G/G homozygous genotype risk (P = 0.0097 against this model), indicating that the disease risk of the alleles does not align with the multiplicative model. This is demonstrated by the fact that AITD and type 1 diabetes both fall outside of this model [6]. Take note that neither the age at diagnosis of type 1 diabetes overall nor the age at diagnosis of type 1 diabetes in TPOAbs-positive cases is affected by the CTLA4 rs3087243 G allele, nor is it associated differently with males and females.

Discussion

Allelic variation at CTLA4 strongly regulates this disease form. As an inhibitory regulator of T cell activation, proliferation, and apoptosis,

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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 findings 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 affects 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 find these in our case samples. Our interpretation of this result differs from that of a recent Japanese study, which came to the conclusion that the G allele of the CTLA4 rs3087243 SNP has no direct effect 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 affect 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 effect of CTLA-4 gene allelic variation on type 1 diabetes susceptibility [8]. The region of mouse chromosome 1 containing the CTLA-4 gene and the Idd5.1 susceptibility locus has a significant impact on disease susceptibility, as demonstrated by genetic analysis of the NOD mouse model of type 1 diabetes. The 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-independent (liCTLA-4) alternative isoform of CTLA-4. In addition, it has been demonstrated that liCTLA-4 inhibits T cell activation. Studies on NOD mice have also demonstrated that a variety of autoimmune phenotypes, including liver disease and AITD, as well as type 1 diabetes with varying rates of progression, can result from various combinations of alleles from multiple susceptibility genes [9-10].

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