Common genetic variants associated with thyroid function may be risk alleles for Hashimoto’s disease and Graves’ disease

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Summary

Background Recent studies have identified common genetic variants associated with TSH, free T4 and thyroid peroxidase antibodies, but it is unclear whether these differ between patients with Hashimoto’s disease and Graves’ disease.

Objective To examine whether 11 common genetic variants differ between Graves’ disease and Hashimoto’s disease.

Patients and measurements We genotyped 11 common variants in a discovery cohort of 203 Australian patients with autoimmune thyroid disease (AITD). Two variants with significant or suggestive associations were analysed in a replication cohort of 384 Danish patients.

Results For rs753760 (PDE10A), the minor allele frequency in Graves’ disease and Hashimoto’s disease was 0.38 vs. 0.23, respectively, \((P = 6.42 \times 10^{-4})\) in the discovery cohort, 0.29 vs. 0.24 \((P = 0.147)\) in the replication cohort and 0.32 vs. 0.24 in combined analysis \((P = 0.0021)\); all analyses adjusted for sex. In healthy controls from Busselton, the frequency was 0.29, significantly different from Hashimoto’s disease but not Graves’ disease. For rs4889009 (MAF gene region), the frequency of the minor G-allele in Graves’ disease and Hashimoto’s disease was 0.48 vs. 0.36 \((P = 0.0156)\) in the discovery cohort, 0.48 vs. 0.34 \((P = 1.83 \times 10^{-4})\) in the replication cohort and 0.48 vs. 0.35 in the combined analysis \((P = 7.53 \times 10^{-6})\); in controls, the frequency was 0.38, significantly different from Graves’ disease but not Hashimoto’s disease. After further adjustment for smoking, associations with rs4889009 remained significant, whereas those with rs753760 were not.

Conclusion Common variants in PDE10A and MAF gene regions may influence whether patients with AITD develop Graves’ disease or Hashimoto’s disease.

Introduction

The thyroid is targeted by autoimmune responses more frequently than any other organ. Clinically, the most common presentations of autoimmune thyroid disease (AITD) are hypothyroidism caused by Hashimoto’s disease and Graves’ hyperthyroidism. Both diseases are characterized by lymphocytic infiltration of the thyroid and the production of thyroid autoantibodies. In Graves’ disease, thyrotoxicosis results from the production of stimulating antibodies to the TSH receptor, whereas Hashimoto’s disease is characterized by tissue destruction and consequent hypothyroidism. Circulating thyroid peroxidase antibodies (TPOAbs) is detectable in approximately 90–95% of patients with Hashimoto’s disease and 75–85% of those with Graves’ disease, whereas antibodies against the sodium iodide symporter (NIS) and pendrin are very rare, and absent in healthy controls. In contrast, TPOAbs are also present in about 10% of the general population, but most TPOAb-positive individuals do not develop clinically overt thyroid disease.

The factors which trigger an autoimmune response to the thyroid and influence its progression to clinical thyroid disease are only partly understood. Environmental factors implicated in AITD include iodine status, infection and tobacco smoking; the latter appears to increase the risk of Graves’ disease while being protective against Hashimoto’s disease. Familial clustering of AITD is common, and in twin studies, its heritability is approximately 70%, indicating a strong genetic influence. Over the past two decades, considerable progress has been made in identifying susceptibility genes for AITD, including DMB1, CTLA-4, PTPN22, ARID5B, FCRL3, CD4, CD25, IL12B), many of which are also associated with other autoimmune diseases, and a smaller number of thyroid-specific genes (TSHR, TG). In a study...
published in 2011, however, known susceptibility genes for Graves’ disease accounted for less than 10% of the heritability of this disease in a Chinese Han population. In a recent meta-analysis of genomewide association (GWA) studies, Medici et al. reported 5 novel loci associated with TPOAb: common variants in TPO, ATXN2 and BACH2 were associated with TPOAb positivity, whereas variants in TPO, MAGI3 and KALRN were associated with TPOAb concentrations.

Most AITD susceptibility genes identified to date are not specific to Graves’ disease or Hashimoto’s disease, with the exception of TSHR, CD40 and CD25, which are associated with Graves’ disease. We previously reported that an IL12B polymorphism differed between Graves’ disease and Hashimoto’s disease in men but not women with AITD. In the study by Medici et al., the BACH2 variant was associated with hyperthyroidism but not hypothyroidism and with Graves’ disease in an independent cohort, suggesting that it may be specific to Graves’ disease, whereas the MAGI3 variant was associated with both hyperthyroidism and hypothyroidism.

TSH and free T4 are also heritable traits, and recent studies have advanced understanding of their genetic architecture. Two methods, and those from SNPTEST are presented. Correction for multiple testing was performed using the Bonferroni method, with significance set at $P < 0.0045$ (0.05/11 variants). In a secondary analysis, we further analysed for smoking habits (current, former, never), because of the recognized association between smoking and AITD phenotype. In the discovery cohort, smoking data were not recorded in the original study; for this study, we contacted participants to obtain these data, which were available from 50% of the cohort; the rest of the cohort was not included in this analysis. Smoking data were available for all members of the replication cohort. General linear modelling was performed to determine whether smoking was associated with AITD.

Written informed consent was obtained from participants. Ethical approval was obtained from Human Research Ethics Committees at Sir Charles Gairdner Hospital and Odense University Hospital.

**Results**

The discovery cohort comprised 203 Australian patients with AITD (104 with Hashimoto’s disease and 99 with Graves’ disease) and the replication cohort 384 Danish patients (169 with Hashimoto’s disease and 215 with Graves’ disease). Descriptive data are shown in Table 1. Smoking habit differed significantly between Graves’ disease and Hashimoto’s disease using Chi squared test ($P = 2.48 \times 10^{-9}$).

In the discovery cohort, 9 of the 11 variants analysed showed no significant difference in genotype frequency between Hashimoto’s disease and Graves’ disease ($P > 0.4$ for each). For
Table 1. Characteristics of the discovery cohort and replication cohorts. Data shown as number and percentage.

|                   | Perth          | Odense         |
|-------------------|----------------|----------------|
| Graves’ disease   | 99             | 215            |
| Males             | 14 (14%)       | 34 (16%)       |
| Females           | 85 (86%)       | 181 (84%)      |
| Smoking*          | 49             | 215            |
| Never             | 20 (41%)       | 73 (34%)       |
| Former            | 18 (37%)       | 33 (15%)       |
| Current           | 11 (22%)       | 109 (51%)      |
| Hashimoto’s disease | 104          | 169            |
| Males             | 10 (10%)       | 26 (15%)       |
| Females           | 94 (90%)       | 143 (85%)      |
| Smoking*          | 52             | 169            |
| Never             | 28 (54%)       | 92 (54%)       |
| Former            | 18 (35%)       | 43 (25%)       |
| Current           | 6 (12%)        | 34 (20%)       |

*Data available for 101 of 203 (50%) of participants in the Perth cohort.

rs753760 in PDE10A, there was a significant difference between groups ($P = 6.42 \times 10^{-4}$) (Table 2) after adjustment for sex, whereas for rs4889009 in the MAF region, after Bonferroni correction, there was only suggestive evidence of a difference ($P = 0.0156$). In the replication cohort, genotypes for rs753760 in PDE10A did not differ significantly between groups ($P = 0.147$), whereas for rs4889009 in the MAF gene region, there was a significant difference after Bonferroni correction ($P = 1.83 \times 10^{-4}$).

When results from both cohorts were combined, there was a significant difference in genotype frequency between Graves’ disease and Hashimoto’s disease for both variants. For rs753760 in PDE10A, the minor allele frequency was 0.24 for Hashimoto’s disease and 0.32 for Graves’ disease ($P = 0.0023$) with each additional copy of the minor allele (G) associated with a 33% decrease in the odds of an individual having Hashimoto’s disease vs Graves’ disease. In healthy controls free of thyroid disease, the minor allele frequency was 0.29; this was significantly different from Hashimoto’s disease ($P = 8.21 \times 10^{-3}$) but not from Graves’ disease ($P = 0.173$). For rs4889009 in the MAF gene region, the minor allele frequencies were 0.35 for Hashimoto’s disease and 0.48 for Graves’ disease in the combined analysis ($P = 7.53 \times 10^{-6}$), with each additional copy of the minor allele associated with a 68% increase in the odds of having Graves’ disease vs Hashimoto’s disease. The frequency of the minor G-allele for rs4889009 in healthy controls was 0.38; this was significantly different from Graves’ disease ($P = 1.01 \times 10^{-3}$) but not from Hashimoto’s disease ($P = 0.053$).

Smoking data were available for 50% of the discovery cohort and all of the replication cohort. After adjustment for sex and smoking habits, the difference in genotype frequency between Graves’ disease and Hashimoto’s disease in the combined analysis was no longer significant for rs753760 in PDE10A (minor allele frequency 0.30 vs. 0.24, $P = 0.0957$) but remained significant for rs4889009 in the MAF region (0.48 vs. 0.35, $P = 4.05 \times 10^{-4}$) (Table 3).

### Discussion

In this study, we examined common variants in 11 genes known to be associated with TPOAb, TSH or free T4 to ascertain whether their genotype frequency differed between Hashimoto’s disease and Graves’ disease. For two variants, there was strong or suggestive evidence of a difference between groups in the discovery and replication cohort, and in both cases, the difference was significant after adjustment for sex in the combined analysis.

The first of these was the single nucleotide polymorphism (SNP) rs753760, located in intron 1 of PDE10A, for which the minor allele (G) was less frequent in participants with Hashimoto’s disease compared with Graves’ disease and with healthy controls, suggesting that the major allele (C) may predispose to Hashimoto’s disease. rs753760 is reported by Haploreg v3.25 to alter a regulatory motif in MEF2C. MEF2C, among other functions, regulates the MAF region, after Bonferroni correction, there was only suggestive evidence of a difference between groups in the discovery and replication cohort, and in both cases, the difference was significant after adjustment for sex in the combined analysis.

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### Table 2. Genotyping results for rs753760 (PDE10A) and rs4889009 (MAF) in participants with Graves’ disease vs Hashimoto’s disease phenotype using SNPTEST adjusting for sex

|         | N  | 1-1 | 1-2 | 2-2 | MF |              |         | N  | 1-1 | 1-2 | 2-2 | MF | P          | β     | SE  |
|---------|----|-----|-----|-----|----|------------|---------|----|-----|-----|-----|----|------------|------|-----|
| rs753760 |    |     |     |     |    |            |         |    |     |     |     |    |           |      |     |
| Perth   | 213| 106 | 92  | 15  | 0.29| 169        | 101     | 55 | 13  | 0.24| 0.04| 0.02| 0.017     | -0.24| 0.16|
| Odense  | 312| 144 | 139 | 29  | 0.32| 273        | 160     | 97 | 16  | 0.24| 0.04| 0.02| 0.017     | -0.24| 0.16|
| Combined| 315| 248 | 227 | 47  | 0.37| 477        | 267     | 134| 77  | 0.24| 0.04| 0.02| 0.017     | -0.24| 0.16|

Data shown as number of subjects. For rs753760, allele 1 = C and allele 2 = G; for rs4889009, allele 1 = C and allele 2 = G. MF, minor allele frequency. For Perth cohort, 3 individuals failed genotyping for rs7889009 and for Odense cohort, 1 person failed genotyping for rs753760. Significant values in bold.
plays key roles in B lymphocyte formation and function, including antibody responses to T-cell-dependent antigens and induction of germinal centre B cells.26 The SNP is also in strong linkage disequilibrium (LD) \( r^2 \geq 0.8 \) with 15 genetic variants located at chr6:166040859-166060601 (hg19), but none of these has functional annotation that appears relevant to AITD. PDE10A encodes a cAMP-stimulated phosphodiesterase which is implicated in cAMP degradation in response to antibody responses to T-cell-dependent antigens and induction of germinal centre B cells.26 The SNP is also in strong linkage disequilibrium (LD) \( r^2 \geq 0.8 \) with 15 genetic variants located at chr6:166040859-166060601 (hg19), but none of these has functional annotation that appears relevant to AITD. PDE10A encodes a cAMP-stimulated phosphodiesterase which is implicated in cAMP degradation in response to TSH stimulation of thyrocytes,22,27 and in the meta-analysis by Porcu et al.22 the major C allele was positively associated with TSH in euthyroid participants, suggesting a physiological rather than pathological role. It is plausible, therefore that the variant influences disease ascertainment rather than pathogenesis, as individuals with thyroid autoimmunity who have the C allele will be more likely to have an elevated TSH level than those who do not and are therefore more likely to have Hashimoto’s disease diagnosed.

The second variant which differed between groups was rs4889009, located at chromosome 16q23, for which the minor allele was associated with an increased risk of Graves’ disease compared with Hashimoto’s disease and compared with healthy controls. In the study of Medici et al.17 there was suggestive evidence that this SNP was associated with TPOAb positivity, but the association was not genomewide significant. rs4889009 is an intergenic variant, reported by Haplolog v3 to be located in a weak enhancer region of chromatin regulatory states in mobilized CD34 primary cells. It is in strong LD \( r^2 \geq 0.8 \) with 45 other variants located chr16:79696939-79734249, none of which has functional annotation that seems relevant to AITD. The SNP is also in moderate LD \( r^2 = 0.686 \) for each with two variants: rs17767491, which is associated with thyroid volume28 and rs3813582, associated with serum TSH,22 whereas rs4889009 itself is not known not to be associated with TSH. In this region lies a third variant, rs3813579, associated with goitre28 but this is in low LD with rs4889009 \( (r^2 = 0.222) \). The three variants lie within 4 kb of each other and 110 kb upstream from \( MAF \), and rs17767491 and rs3813579 were found not to be in LD with \( MAF \).28 However, these variants do encompass the 3’-end of \( LOC440389 \) plus the region immediately downstream. \( LOC440389 \) is a predicted coding sequence previously removed from the NCBI database as a result of standard genome annotation processing. Teumer et al.28 have shown that sequenced cDNA from mRNA extracted from thyroid tissue matches the published \( LOC440389 \) mRNA sequence, suggesting that the removal of \( LOC440389 \) from the NCBI database may have been inappropriate. Teumer et al.28 also found this transcript to be threefold more abundant in thyroid vs skeletal muscle tissue, providing tentative evidence that \( LOC440389 \) is a thyroid-specific gene, but its function is unknown. That locus also maps within \( LOC102467146 \), a large noncoding RNA. Our data suggest that it may be a susceptibility locus for Graves’ disease.

In the present study, participants with Graves’ disease were significantly more likely to be current smokers than those with Hashimoto’s disease, consistent with previous reports.11,29 When the results were adjusted for smoking as well as sex, the associations with rs4889009 \( (MAF) \) remained significant, but results for rs753760 \( (PDE10A) \) were no longer significant. As information on smoking habits were not available for all participants, this may reflect a loss of statistical power as well as the confounding effect of smoking. Not all studies of genetic associations with AITD have adjusted for smoking, despite its association with AITD phenotype, and our study demonstrates the importance of this.

For the remaining nine variants studied, including five associated with TPOAb in the recent meta-analysis,17 there was no significant difference between Hashimoto’s disease and Graves’ disease. As TPOAb are associated with both Hashimoto’s disease and Graves’ disease, this may be because these variants are risk factors for AITD per se rather than a specific AITD phenotype; alternatively, it may be that our study was too small to detect genuine differences between Hashimoto’s disease and Graves’ disease because of the relatively small effect size of those risk

### Table 3. Genotyping results for rs753760 \( (PDE10A) \) and rs4889009 \( (MAF) \) in the participants with Graves’ disease vs Hashimoto’s disease phenotype using SNPTEST adjusting for sex and smoking

|                | Graves’ disease | Hashim.otype phenotype |
|----------------|-----------------|------------------------|
|                | \( N \) | 1-1 | 1-2 | 2-2 | \( MF \) | \( N \) | 1-1 | 1-2 | 2-2 | \( MF \) | \( P \) | \( \beta \) | SE |
| rs753760       |       |     |     |     |      |       |     |     |     |      |      |      |     |
| Perth          | 49    | 21  | 23  | 5   | 0.34 | 52    | 28  | 22  | 2   | 0.25 | 0.140 | -0.50 | 0.34 |
| Odense         | 213   | 106 | 92  | 15  | 0.29 | 169   | 101 | 55  | 13  | 0.24 | 0.214 | -0.22 | 0.17 |
| Combined       | 262   | 127 | 115 | 20  | 0.30 | 221   | 129 | 77  | 15  | 0.24 | 0.096 | -0.26 | 0.15 |
| rs4889009      |       |     |     |     |      |       |     |     |     |      |      |      |     |
| Perth          | 49    | 12  | 29  | 8   | 0.46 | 52    | 22  | 20  | 10  | 0.38 | 0.211 | -0.37 | 0.30 |
| Odense         | 214   | 65  | 94  | 55  | 0.48 | 169   | 75  | 74  | 20  | 0.34 | \( 8.18 \times 10^{-4} \) | -0.50 | 0.15 |
| Combined       | 263   | 77  | 123 | 63  | 0.47 | 221   | 97  | 94  | 30  | 0.35 | \( 4.05 \times 10^{-4} \) | -0.47 | 0.13 |

Data shown as number of subjects. For rs753760, allele 1 = C and allele 2 = G; for rs4889009, allele 1 = C and allele 2 = G. MF, minor allele frequency. For Odense cohort, 1 person failed genotyping for rs753760.

Significant values in bold.
alleles. Our study was adequately powered to detect variants with clinically relevant effect sizes; for example, for rs4889009 with a minor allele frequency of 0.38 associated with a 68% increase in the odds of having Graves’ disease vs Hashimoto’s disease per copy of the G-allele, the study had 93% power to detect an association at $\alpha = 0.05$.\(^{30}\) However, for a genetic variant with the same minor allele frequency but a lower effect size such as a 50% increase per copy of the risk allele, the power was slightly less: 77% at $\alpha = 0.05$.

Strengths of our study include the carefully defined phenotypes of Hashimoto’s disease and Graves’ disease established in specialist clinics. A limitation of our study is that we did not have smoking data from all participants in the discovery cohort, which reduced the power of the smoking-adjusted analyses.

In conclusion, this study provides evidence that common variants in the PDE10A and MAF/LOC440389 gene regions differ between patients with Hashimoto’s disease and Graves’ disease. These findings advance understanding of the genetic architecture and pathophysiology ofAITD. Further studies are required to establish the mechanisms underlying these associations and the extent to which rare variants (as opposed to common variants as studied here) contribute to the heritability and phenotype ofAITD. In addition, our study provides additional evidence for a role for LOC440389 in thyroid physiology, strengthening the case for its reinstatement to the NCBI database and for further research to determine the function of this gene and its role in thyroid biology.

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