Genome-Wide Association Studies of Autoimmune Thyroid Diseases, Thyroid Function, and Thyroid Cancer

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Thyroid diseases, including autoimmune thyroid diseases and thyroid cancer, are known to have high heritability. Family and twin studies have indicated that genetics plays a major role in the development of thyroid diseases. Thyroid function, represented by thyroid stimulating hormone (TSH) and free thyroxine (T4), is also known to be partly genetically determined. Before the era of genome-wide association studies (GWAS), the ability to identify genes responsible for susceptibility to thyroid disease was limited. Over the past decade, GWAS have been used to identify genes involved in many complex diseases, including various phenotypes of the thyroid gland. In GWAS of autoimmune thyroid diseases, many susceptibility loci associated with autoimmunity (human leukocyte antigen [HLA], protein tyrosine phosphatase, non-receptor type 22 [PTPN22], cytotoxic T-lymphocyte associated protein 4 [CTLA4], and interleukin 2 receptor subunit alpha [IL2RA]) or thyroid-specific genes (thyroid stimulating hormone receptor [TSHR] and forkhead box E1 [FOXE1]) have been identified. Regarding thyroid function, many susceptibility loci for levels of TSH and free T4 have been identified through genome-wide analyses. In GWAS of differentiated thyroid cancer, associations at FOXE1, MAP3K12 binding inhibitory protein 1 (MBIP)-NK2 homeobox 1 (NKX2-1), disrupted in renal carcinoma 3 (DIRC3), neuregulin 1 (NRG1), and pecanex-like 2 (PCNXL2) have been commonly identified in people of European and Korean ancestry, and many other susceptibility loci have been found in specific populations. Through GWAS of various thyroid-related phenotypes, many susceptibility loci have been found, providing insights into the pathogenesis of thyroid diseases and disease co-clustering within families and individuals.

Keywords: Genome-wide association study; Graves disease; Hashimoto disease; Thyroid neoplasms; Thyroid function

INTRODUCTION

Most thyroid diseases, including autoimmune thyroiditis and thyroid cancer, have been recognized to have high heritability [1,2]. In twin studies, a high concordance rate for Graves’ disease (GD) in monozygotic twins was reported, in the range of 50% to 70%, compared with 3% to 25% in dizygotic twins [1,3]. A study of autoimmune hypothyroidism likewise showed a 55% concordance in monozygotic twins [4]. Familial clustering of autoimmune thyroid disease has been consistently reported [5-7]. Hemminki et al. [7] showed that the familial standardized incidence ratios for GD were 4.49 for individuals with an affected parent, 5.04 for those whose singleton sibling was affected, 310 when two or more siblings were affected, and 16.45 in twins. For Hashimoto’s thyroiditis (HT), the sibling risk ratio was 28 based on data from the National Health and Nutrition...
Several candidate gene studies identified putative susceptibility variants for GD, but only the human leukocyte antigen (HLA) locus and the cytotoxic T-lymphocyte associated protein 4 (CTLA4), thyroid stimulating hormone receptor (TSHR), and protein tyrosine phosphatase, non-receptor type 22 (PTPN22) loci were confirmed in subsequent replication studies [21-25]. The first genome-wide analysis using 14,436 nonsynonymous single-nucleotide polymorphisms (SNPs) for GD was performed by the Wellcome Trust Case Control Consortium, and showed that three loci (HLA, TSHR, and Fc receptor like 3 [FCRL3]) were associated with GD [26]. A subsequent GWAS with >500,000 SNPs confirmed previously reported loci and identified a novel region of susceptibility loci at 6q27 (the ribonuclease T2 [RNASET2]-FGFR1 oncogene partner [FGFRIOP]-CCR6) and an intergenic region at 4p14 (GDCG4p14) [27].

Several GWAS of autoimmune thyroid diseases (GD, HT, and PTC) have been performed for a variety of phenotypes including self-reported hypothyroidism, biochemical hypothyroidism with positive antibodies, antibody positivity, and level of antibodies, caution is needed when interpreting the results. Several types of hypothyroidism might not have an autoimmune etiology, and autoimmunity does not necessarily lead to hypothyroidism. Thus, careful consideration regarding the phenotype is required when interpreting the biological mechanisms of the associated genes identified through GWAS of autoimmune thyroid diseases.

A heterogeneity analysis between GD and HT showed that GD and HT share several susceptibility loci (HLA, PTPN22, and CTLA4), while an association with TSHR was exclusively seen in GD patients. The majority of genes associated with autoimmune thyroid disease are thought to play a major role in autoimmune processes, including disrupted T-cell regulation and peripheral immune tolerance [37]. Variants in thyroid-specific loci, including TSHR and forkhead box E1 (FOXE1), could affect the immune recognition of autoantigens and antibody generation [37].

**GWAS OF THYROID FUNCTION**

Thyroid function, including levels of free thyroxine (T4) and TSH, is highly heritable even in euthyroid subjects. A large meta-analysis of GWAS of serum levels of TSH and free T4, in 26,420 and 17,520 euthyroid European individuals, respectively, was performed, identifying many susceptibility loci for levels of TSH (phosphodiesterase 8B [PDE8B], phosphodiesterase 10A...
| Gene       | Locus    | Population                        | Protein function                                                                 |
|------------|----------|-----------------------------------|----------------------------------------------------------------------------------|
| PTPA2      | 1p13     | UK, USA                           | Role in T-cell signaling                                                         |
| ITGAM      | 2q33.1   | UK, China, USA                    | Inhibition of CD25                                                                |
| C4orf15    | 1q21.32  | European                          | Cyclic adenosine monophosphate (cAMP) kinase activity                              |
| TG         | 2q21.1   | Chinese Han, USA                  | Role in regulating actin filament dynamics                                         |
| TG         | 1p34.3   | US, Japan                         | Role in coordinating transcription activation and repression by MAFK              |
| DPP2       | 2q33.2   | Chinese Han                       | Negative regulator of hematopoietic cell growth and survival                       |
| ITGAM      | 4q31.2   | UK, Chinese Han                   | Role in regulating actin filament dynamics                                         |
| CTNFP6     | 10p15.1  | European                          | Role in actin cytoskeletal rearrangements and transcriptional alterations          |
| ENM         | 20p15.1  | European                          | Role in circadian entrainment                                                     |
| GRIN3A     | 20p15.1  | European                          | Role in p75 NTR-mediated signaling and EPH-ephrin signaling                       |
| BACH2      | 20p15.1  | European                          | Role in mediating cell fate decisions during hematopoiesis                         |

**Table 1. Susceptibility Loci for Autoimmune Thyroid Disease Detected by Genome-Wide Association Studies**

**Phenotypes**
- GD: Graves’ disease
- HT: Hashimoto’s thyroiditis
- TPOAb: Anti-thyroid peroxidase antibody
- TgAb: Anti-thyroglobulin antibody
- GD, HT: Graves’ disease and Hashimoto’s thyroiditis
- GD, TPOAb: Graves’ disease and anti-thyroid peroxidase antibody
- GD, HT, TPOAb: Graves’ disease, Hashimoto’s thyroiditis, and anti-thyroid peroxidase antibody

**Protein function**
- Role in cell-cell adhesion and cell mobility
- Role in NEDD8-specific protease activity
- Role in coordinating transcription activation and repression by MAFK
- Role in apoptosis of hematopoietic cells
- Role in actin cytoskeletal rearrangements and transcriptional alterations
- Role in circadian entrainment
- Role in mediating cell fate decisions during hematopoiesis

**Reference**
- European refers to European ancestry from various countries.

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- [GWAS for Thyroid Diseases](http://www.e-emm.org)
The first GWAS of thyroid cancer was reported in 2009 and showed that common variants located on 9q22.33 (FOXE1) and 14q13.3 (NK2 homeobox 1 [NKX2-1]) were associated with DTC [41]. Associations at FOXE1, MBIP/NKX2-1, disrupted in renal carcinoma 3 (DRC3), and NRGI have been identified and repeatedly confirmed in individuals of European ancestry [41-44]. Several markers associated with DTC, including inner mitochondrial membrane peptidase subunit 2 (IMMP2L), retinoic acid receptor responder 1 (RARRES1), small nuclear RNA activating complex polypeptide 4 (SNAPC4), basic leucine zipper ATF-like transcription factor (BATF), DEAH-box helicase 35 (DHX35), UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminytransferase-like 4 (GALNTL4), 5-hydroxytryptamine receptor 1B (HTR1B), forkhead box A2 (FOXA2), and WDR11 antisense RNA 1 (WDR11-AS1), were identified but not replicated in other studies [43-46]. A recent meta-analysis of GWAS including a total of 3,001 DTC patients and 287,550 controls from five study groups of European populations found five novel loci (pecanex-like 2 [PCNX2L1], telomerase RNA component [TERC], neuronal regeneration related protein [NREP]-erythrocyte membrane protein band 4.1 like 4A [EPB41L4A], oligosacchride-binding folds containing 1 [OBFC1], and SMAD family member 3 [SMAD3]) [47]. Table 3 provides the susceptibility loci identified in GWAS of thyroid cancer [38-40,48,49]. The most robust signals were detected on 9q22.33 (FOXE1) in Caucasians [41,50]. The FOXE1 locus was also reported to be a susceptibility gene for radiation-related thyroid cancer [50]. A functional study showed that common variants on FOXE1 regulated FOXE1 transcription through the recruitment of the upstream stimulatory factor 1 (USF1)/USF2 transcription factors [51]. Several reports demonstrated that variants of FOXE1 were related to aspects of the clinical aggressiveness of papillary thyroid cancer (PTC), such as tumor stage, size, lymphocytic infiltration, and extrathyroidal extension [52,53].

Recently, we reported 15 variants from 11 loci associated with DTC in a Korean GWAS including 1,085 cases of DTC and 8,884 controls [54]. The most robust signals were detected in the NRGI gene, and expression quantitative trait loci analysis showed that variants on NRGI were also associated with NRGI expression in thyroid tissues [54]. He et al. [55] also showed that the expression levels of NRGI isoforms were significantly correlated with genotypes. NRGI encodes neuregulin-1, which acts on the erb-b2 receptor tyrosine kinase (ERBB) family of tyrosine kinase receptors. In a study of the intrinsic resistance of PTC to a B-Raf inhibitor, ERBB2/ERBB3 activation was found to be dependent on autocrine production of neuregulin-1 [56].
NRG1 dysregulation is also closely related with the phosphoinositide 3-kinase (PI3K)-AKT and mitogen-activated protein kinase (MAPK) signaling pathway via ERBB [57]. Our gene set enrichment analysis data showed that variants on NRG1 were associated with many pathways related to cellular growth or cancer, and the ERBB-MAPK signaling pathway was
| Locus     | Gene                | Protein function                                           | Population                                      | References                  |
|-----------|---------------------|------------------------------------------------------------|-------------------------------------------------|----------------------------|
| 9q22.33   | FOXE1               | Encoding TTF-2, role in thyroid morphogenesis              | Iceland, USA, Spain, Netherlands, Belarus, Italy, Poland, Korea | [41,42,46-50,54]             |
| 14q13.3   | MBIP-NKX2-1         | Encoding TTF-1                                              | Iceland, USA, Spain, Netherlands, Italy, Poland, Korea | [41,42,46,47,54]            |
| 2q35      | DIRC3               | Non-coding RNA                                             | Iceland, USA, Spain, Netherlands, Italy, Poland, UK, Korea | [42,43,47,54]               |
| 8p12      | NRG1                | Role in the growth and development of multiple organ systems| Iceland, USA, Spain, Netherlands, Korea          | [42,54]                    |
| 7q31.1    | IMMPL2              | Catalytic activity of the mitochondrial inner membrane peptidase complex | Italy, USA, Spain, Netherlands, Korea | [43]                        |
| 3q25.32   | RARRES1             | Encoding a type 1 membrane protein.                        | Italy, Poland, UK, Spain                        | [43]                        |
| 9q34      | SNAPC4              | Role in RNA polymerase II and III transcription from small nuclear RNA promoters | Italy, Poland, UK, Spain | [43]                        |
| 14q24.3   | BATF                | Negative regulator of AP-1/ATF transcriptional events      | Italy, Poland                                   | [44]                        |
| 20q11.23  | DHX35               | Putative RNA helicases                                      | Italy, Poland                                   | [44]                        |
| 5q14      | ARSB                | Role in the regulation of cell adhesion, cell migration and invasion | Italy, Poland, Spain                            | [44]                        |
| 13q12     | SPATA13             | Role in regulation of cell migration and adhesion assembly and disassembly | Italy, Poland, Spain                            | [44]                        |
| 11p15.3   | GALNTL4             | Role in initial reaction in O-linked oligosaccharide biosynthesis | Italy, Poland, Spain                            | [45]                        |
| 20p11     | FOXA2               | Activators for liver-specific genes such as albumin and transthyretin | Italy, Poland, Spain                            | [45]                        |
| 10q26.12  | WDR11-AS1           | Non-coding RNA                                             | Italy, Spain                                    | [46]                        |
| 6q14.1    | HTR1B               | Role in activity of adenylate cyclase and the release of serotonin, dopamine, and acetylcholine | Italy, Spain                                     | [46]                        |
| 1q42.2    | PCNXL2              | Role in tumorigenesis                                       | Iceland, USA, Spain, Netherlands, Korea          | [47,54]                    |
| 10q24.33  | OBFC1               | Role in initiation of DNA replication                      | Iceland, USA, Spain, Netherlands                 | [47]                        |
| 5q22.1    | NREP-EPB41L4A       | Role in interactions between the cytoskeleton and plasma membrane | Iceland, USA, Spain, Netherlands                 | [47]                        |
| 15q22.33  | SMAD3               | Signal transducers and transcriptional modulator            | Iceland, USA, Spain, Netherlands, Korea          | [47]                        |
| 3q26.2    | TERC-LRRC34         | Encoding telomerase RNA component                           | Iceland, USA, Spain, Netherlands                 | [47]                        |
| 5p15.33   | TERT                | Encoding telomerase reverse transcriptase                   | Iceland, USA, Spain, Netherlands                 | [47]                        |
| 12q14.3   | MSRB3               | Role in reduction of methionine sulfoxide to methionine     | Korea                                           | [54]                        |
| 1p13.3    | VAV3                | Role in actin cytoskeletal rearrangements and transcriptional alterations | Korea                                           | [54]                        |
| 4q21.1    | SEPT11              | Role in cytokinesis and vesicle trafficking                 | Korea                                           | [54]                        |
| 3p14.2    | FHIT                | Role in purine metabolism                                  | Korea                                           | [54]                        |
| 19p13.2   | INSR                | Encoding insulin receptor                                   | Korea                                           | [54]                        |
| 12q24.13  | SLC24A6             | Role in cellular calcium homeostasis                        | Korea                                           | [54]                        |

FOX1, forkhead box E1; TTF, thyroid transcription factor; MBIP, MAP3K12 binding inhibitory protein 1; NKX2-1, NK2 homeobox 1; DIRC3, disrupted in renal carcinoma 3; NRG1, neuregulin 1; IMMPL2, inner mitochondrial membrane peptidase subunit 2; RARRES1, retinoic acid receptor responder 1; SNAPC4, small nuclear RNA activating complex polypeptide 4; BATF, basic leucine zipper ATF-like transcription factor; AP-1, activator protein 1; ATF, activating transcription factor; DHX35, DEAH-box helicase 35; ARSB, arylsulfatase B; SPATA13, spermatogenesis associated 13; GALNTL4, UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 4; FOXA2, forkhead box A2; WDR11-AS1, WDR11 antisense RNA 1; HTR1B, 5-hydroxytryptamine receptor 1B; PCNXL2, pecanex-like 2; OBFC1, oligosaccharide-binding folds containing 1; NREP, neuronal regeneration related protein; EBP41L4A, erythrocyte membrane protein band 4.1 like 4A; SMAD3, SMAD family member 3; TERC, telomerase RNA component; LRRC34, leucine rich repeat containing 34; TERT, telomerase reverse transcriptase; MSRB3, methionine sulfoxide reductase B3; VAV3, vav guanine nucleotide exchange factor 3; SEPT11, septin 11; FHIT, fragile histidine triad; INSR, insulin receptor; SLC24A6, solute carrier family 24 member A6.
the most significantly enriched. This evidence indicates that NRG1 expression in thyroid tissue could contribute to increased DTC risk via ERBB signaling.

Our results confirmed previously reported loci (FOXE1, NKX2-1, D IRC3, and PCNXL2) from GWAS of European populations and found novel susceptibility loci (vav guanine nucleotide exchange factor 3 [VAV3], INSR, MRSB3, fragile histidine triad [FHIT], septin 11 [SEPT11], and solute carrier family 24 member A6 [SLC24A6]) associated with DTC. Specially, a variant of SLC24A6 was associated with a specific risk of follicular thyroid cancer, for which the genetic factors that increase the risk of thyroid cancer may vary depending on the cancer subtype. Signals on VAV3, INSR, MRSB3, FHIT, SEPT11, and SLC24A6 were only identified in Koreans, suggesting between-study heterogeneity in GWAS of DTC.

In GWAS in European and Korean populations, some genetic loci (FOXE1, NKX2-1, D IRC3, NRG1, and PCNXL2) were commonly found, while certain susceptibility loci were only found in either the European or Korean population. In addition, the risk allele frequency of commonly found SNPs differs by race, and the DTC risk by genotype varies across ethnicities. For example, the risk allele frequencies of variants on FOXE1 were reported to be 0.14 to 0.34 in Europeans and 0.08 to 0.13 in Asians, suggesting ethnic differences in allele frequencies and a small genetic contribution of variants on FOXE1 to the development of DTC in East Asians [58]. Moreover, common variants on FOXE1 were associated with an increased risk of DTC, with an odds ratio (OR) of 1.80 in the European population, but the OR was 1.35 in East Asians [58]. A comparison of these associations, including effect size (OR) and P values, between Europeans and Koreans is shown in Fig. 1 [54].

CONCLUSIONS

Twin and family studies of autoimmune thyroid diseases and thyroid cancer have indicated high heritability, suggesting that genetic factors play a key role in disease onset. Previous candidate-gene studies have limitations, such as lack of reproducibility and small sample sizes with limited statistical power. In the last decade, GWAS have unraveled the many forms of genetic predisposition to autoimmune thyroid disease, thyroid function, and thyroid cancer. These genetic discoveries provide insight into the pathogenesis of these diseases and provide opportunities to develop new therapies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.
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