Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease

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Autoimmune thyroid diseases (AITD) are common, affecting 2-5% of the general population. Individuals with positive thyroid peroxidase antibodies (TPOAbs) have an increased risk of autoimmune hypothyroidism (Hashimoto's thyroiditis), as well as autoimmune hyperthyroidism (Graves' disease). As the possible causative genes of TPOAbs and AITD remain largely unknown, we performed GWAS meta-analyses in 18,297 individuals for TPOAb-positivity (1769 TPOAb-positives and 16,528 TPOAb-negatives) and in 12,353 individuals for TPOAb serum levels, with replication in 8,990 individuals. Significant associations (P<5Œ10(-8)) were detected at TPO-rs11675434, ATXN2-rs653178, and BACH2-rs10944479 for TPOAb-positivity, and at TPO-rs11675434, MAGI3-rs1230666, and KALRN-rs2010099 for TPOAb levels. Individual and combined effects (genetic risk scores) of these variants on (subclinical) hypo- and hyperthyroidism, goiter and thyroid cancer were studied. Individuals with a high genetic risk score had, besides an increased risk of TPOAb-positivity (OR: 2.18, 95% CI 1.68-2.81, P = 8.1Œ10(-8)),

a higher risk of increased thyroid-stimulating hormone levels (OR: 1.51, 95% CI 1.26-1.82, P = 2.9Œ10(-6)), as well as a decreased risk of goiter (OR: 0.77, 95% CI 0.66-0.89, P = 6.5Œ10(-4)). The MAGI3 and BACH2 variants were associated with an increased risk of hyperthyroidism, which was replicated in an independent cohort of patients with Graves' disease (OR: 1.37, 95% CI 1.22-1.54, P = 1.2Œ10(-7) and OR: 1.25, 95% CI 1.12-1.39, P = 6.2Œ10(-5)). The MAGI3 variant was also associated with an increased risk of hypothyroidism (OR: 1.57, 95% CI 1.18-2.10, P = 1.9Œ10(-3)). This first GWAS meta-analysis for TPOAbs identified five newly associated loci, three of which were also associated with clinical thyroid disease. With these markers we identified a large subgroup in the general population with a substantially increased risk of TPOAbs. The results provide insight into why individuals with thyroid autoimmunity do or do not eventually develop thyroid disease, and these markers may therefore predict which TPOAb-positives are particularly at risk of developing clinical thyroid dysfunction.

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