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Review Article

A systematic review of genetic studies of thyroid disorders in Taiwan

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Abstract

A systematic review of genetic studies of thyroid disorders in Taiwan identified studies of gene mutations involved in the synthesis and binding of thyroid hormone, as well as mutations of proto-oncogenes and tumor suppressor genes in thyroid cancer. Studies related to gene polymorphisms in patients with autoimmune thyroid disease (AITD) and thyroid cancer were also reviewed. The most prevalent mutations in the Han-Chinese population were c.2268insT in the thyroid peroxidase (*TPO*) gene and c.919-2A>G in the Pendred syndrome (*PDS*) gene. Additional mutations have also been revealed in the genes encoding TPO ($n = 5$), thyroglobulin (TG; $n = 6$), pendrin ($n = 2$), and thyroxine-binding globulin (TBG; $n = 2$), which were novel at the time they were reported. The prevalence of various somatic mutations in differentiated thyroid cancer was similar in Taiwan and Western countries, with the *RAS kinase* mutation and tyrosine receptor kinase (*TRK*) and rearranged during transfection (*RET*) proto-oncogenes being detected in lower frequencies and the B-type RAF kinase (*BRAF*) mutation accounting for the majority of cases. Recent microRNA analysis revealed an association between miR146b and the *BRAF* mutation, which was associated with poor prognosis of papillary thyroid carcinoma (PTC). Susceptibility to Graves' disease (GD) was linked to the human leukocyte antigen (HLA) region. The associated alleles were different in Han-Chinese and Caucasians; HLA-DPB1*0501, the major allele in Taiwan, has a low frequency in the West. By contrast, a high frequency of HLA-DRB1*0301 was detected in Caucasians but not Han-Chinese. In addition to the HLA region, cytotoxic T lymphocyte-associated molecule-4 (*CTLA4*) gene polymorphisms +49G>A and +6230G>A (CT60) were positively associated with GD. The GG genotype and G allele of single nucleotide polymorphism (SNP) +49G>A were also related to relapse of Graves' hyperthyroidism after antithyroid drug withdrawal. Differences in the genetic patterns between Han-Chinese and Caucasians for some thyroid disorders suggest the importance of variable genetic influences in different populations.

Keywords: gene; mutation; Taiwan; thyroid

1. Introduction

Thyroid disorders may be categorized into two general groups, including functional disorders such as hyperthyroidism and hypothyroidism, and structural abnormalities, including goiter and thyroid neoplasia. The basis of some thyroid disorders may reflect the effect of a mutation in a single gene (e.g., monogenic) or the effects of polymorphisms in multiple genes. Among the monogenic diseases, germline mutations can affect thyroid hormone synthesis or thyroid hormone binding in serum. However, somatic mutations play a major role in thyroid neoplasia pathogenesis. Impaired synthesis of thyroid hormone may result in congenital hypothyroidism while mutations in the genes encoding thyroid hormone carrier proteins lead to clinically euthyroid patients with falsely abnormal thyroid function tests. In addition, an increased risk for autoimmune thyroid disease (AITD) or thyroid neoplasia has been associated with genetic polymorphisms at various loci (Fig. 1). The current review will

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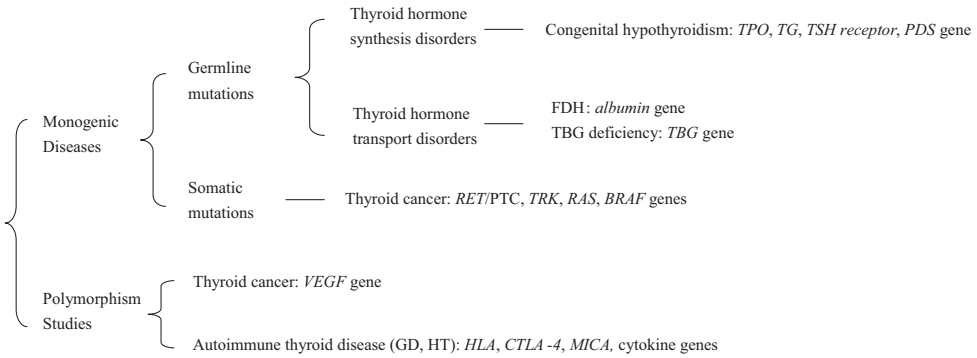

Fig. 1. Schematic diagram for genetic studies of thyroid disorders in Taiwan. BRAF = B-type RAF kinase; CTLA-4 = cytotoxic T lymphocyte-associated molecule-4; FDH = familial dysalbuminemic hyperthyroxinemia; GD = Graves' disease; HLA = human leukocyte antigen; HT = Hashimoto thyroiditis; MICA = major histocompatibility complex class I-chain related gene A; PDS = pendred syndrome/pendrin; PTC = papillary thyroid carcinoma; RET = rearranged during transfection; TBG = thyroxine-binding globulin; TG = thyroglobulin; TPO = thyroid peroxidase; TRK = tyrosine receptor kinase; TSH = thyroid stimulating hormone; VEGF = vascular endothelial growth factor.

summarize the results of major genetic studies performed in Taiwan regarding thyroid disorders to provide a basis for further understanding of the thyroid genetics in the Han-Chinese population.

2. Genetic basis of congenital hypothyroidism

The prevalence of congenital hypothyroidism in Taiwan ranges from 1 in 1992 live births to 1 in 5788 live births,[1,2] which is similar to the 1 in 4000 live births reported in European and North American populations.[3,4] Thyroid dysgenesis, such as agenesis, hypoplasia, ectopy, and hemiagenesis, accounts for 80−85% of congenital hypothyroidism; thyroid dyshormonogenesis contributes to the remaining 15−20% of cases.[5,6] Congenital hypothyroidism may be the result of impaired thyroid stimulating hormone (TSH) signaling, abnormal thyroid hormone synthesis, or defective thyroid hormone action in target tissues (Fig. 2).[6] The majority of genetic studies in Taiwan have focused on germline mutations involving the thyroid hormone synthesis pathways, such as pendrin for the trapping of iodide into thyroid follicular cells, and thyroid peroxidase (TPO), which regulates iodide organification by binding iodide to thyroglobulin (TG) and further coupling to form thyroxine (T4) and triiodothyronine (T3).[7−9]

The severity of thyroid dyshormogenesis is based on whether there is a total or partial defect in the organification of iodide. Mutation in the *TPO* gene is the major contributing factor for total iodide organification defect (TIOD); mutation in the Pendred syndrome (*PDS*) gene usually causes partial iodide organification defect (PIOD).[7,10] Despite an intact thyroid hormone synthesis pathway in the thyroid follicular cells, synthesis of thyroid hormone remains impaired in the absence of a signal from pituitary thyroid stimulating hormone (TSH) to a functional thyroid TSH receptor. Loss-of-function mutations in the *TSH receptor* gene may induce TSH resistance and subsequent congenital hypothyroidism.[11] Mutations in the thyroid hormone receptor alpha and beta have been reported to result in impaired thyroid hormone action in target tissues; however, we failed to identify any study in Taiwan regarding this issue.[12,13]

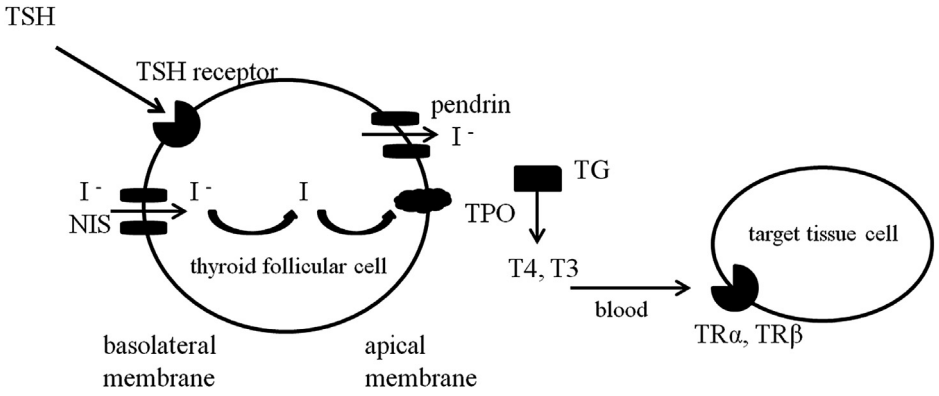

Fig. 2. Mutations that may lead to congenital hypothyroidism include those in the TSH receptor causing impaired TSH signaling, mutations involved in the synthesis of thyroid hormone, and mutations in TRα and TRβ, causing defective thyroid hormone action in target tissues. Key elements involved in thyroid hormone synthesis include the NIS and pendrin for iodide trapping, TPO for facilitating iodide binding to TG, and further coupling to form T4 and T3. NIS = sodium iodide symporter; TG = thyroglobulin; TPO = thyroid peroxidase; TRα = thyroid hormone receptor alpha; TRβ = thyroid hormone receptor beta; TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine.