FOXE1 Gene and Subclinical Hypothyroidism

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Abstract

Thyroid diseases, including autoimmune thyroid diseases , thyroid cancer and subclinical thyroid dysfunctions , 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.

Keywords: FOXE1 gene, subclinical Hypothyroidism

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Introduction

Thyroid diseases, including autoimmune thyroid diseases , thyroid cancer and subclinical thyroid dysfunctions , 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. **(Chadwick et al. 1997).**

In GWAS of 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. **(Cuesta et al. 2007).**

Regarding thyroid function, many susceptibility loci for levels of TSH and free T4 have been identified through genome-wide analyses. **(Fernandez et al. 2015).**

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, providing insights into the pathogenesis of thyroid diseases and disease co-clustering within families and individuals. **(Fernandez et al. 2015).**

The FOXE1 gene (otherwise known as Thyroid Transcription Factor 2) is a member of the forkhead family of transcription factors that plays a vital role in thyroid gland morphogenesis. The FOXE1 gene is expressed in a range of cells and tissues with mRNA extracted from liver, pancreas, muscle, brain and fat tissue **(Taylor, et al., 2015).**

The gene is located on the long arm of chromosome 9 (9q22) (De Lloyd,2015), has 1 exon and ~1/3rd of the gene is coding sequence **(Venza, et al., 2011).**

The FOXE1 gene is expressed in a range of cells and tissues with mRNA extracted from liver, muscle, heart, brain and fat tissue, and the protein demonstrated in hair follicle outer root sheath and testis **(Genecards human gene database; FOXE1 (www.genecards.org).**

FOXE1 is a thyroid-specific transcription factor that, together with PAX8 and NKX2-1, coordinately maintains the differentiated state of the thyroid gland and is essential for its correct development . FOXE1 is also a key player in thyroid organogenesis, as its expression during early thyroid development is required for thyrocyte precursor migration **(Fernandez, et al. 2015).**

FOXE1 regulates the expression of the thyroglobulin (TG) and thyroid peroxidase (TPO) genes; the expression of both genes is essential to the synthesis of T3 and T4 hormones, and these are necessary for maintaining a differentiated state of the thyroid gland. In addition, thyroid hormones play an important role in different organs, where they participate in cell metabolism, growth, development and differentiation **(Gandarilla-Esparza, et al., 2021).**

FOXE1 is an intronless gene. These variants near FOXE1 have been previously associated with increased risk for both papillary and follicular thyroid cancer. Of note, the rs965513 minor allele has been shown to confer risk of thyroid cancer in this and prior studies, whereas the major allele confers risk to primary hypothyroidism (PH) **(Gudmundsson, et al., 2009).**

Mutations in the coding region of FOXE1 have also been associated with a rare form of syndromic congenital hypothyroidism (Bamforth-Lazarus syndrome: hypothyroidism, cleft palate, choanal atresia, spiky hair), and cleft lip with or without cleft palate and isolated cleft palate) **(Marazita, et al., 2009).**

Most thyroid diseases, including autoimmune thyroiditis and thyroid cancer, have been recognized to have high heritability **(Vaidya, et al., 2002).**

A study of autoimmune hypothyroidism showed a 55% concordance in monozygotic twins

(Brix, et al., 2000).

For Hashimoto's thyroiditis (HT), the sibling risk ratio was 28 based on data from the National Health and Nutrition Examination Survey III , and a similar risk was confirmed in data from Germany **(Dittmar, et al., 2011).**

These pieces of evidence suggest the existence of a genetic predisposition to autoimmune thyroid diseases.Thyroid function, including levels of thyroid hormone and thyroid stimulating hormone (TSH), is regulated within a narrow range in individuals, although the inter-individual variability is large . This suggests that every individual has his or her own set point of thyroid function **(Hansen, et al., 2004).**

About 40% to 60% of variation in thyroid function has been estimated to be determined by genetic factors **(Panicker, et al., 2008).**

Research into the genes responsible for thyroid disease has identified several candidates **(Cooper, et al., 2012).**

However, candidate gene studies have been controversial and have shown very few reproducible findings.In the last decade, Genome-Wide Association studies (GWAS) have been extensively used to identify genes involved in thyroid diseases. **(Wellcome, et al., 2017).**

GWAS have facilitated the screening of a large proportion of the genome and discovereda variety of susceptibility genes. GWAS have been widely applied in autoimmune thyroid diseases, thyroid function, and thyroid cancer, and have identified susceptibility genes for thyroid-related phenotypes. **(Wellcome, et al., 2017).**

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[PDE10A], capping actin protein of muscle Z-line subunit beta [CAPZB], MAP, vascular endothelial growth factor A [VEGFA], nuclear receptor subfamily 3 group C member 2 [NR3C2], insulin like growth factor binding protein 5 [IGFBP5], SRY-box 9 [SOX9], nuclear factor I A [NFIA], fibroblast growth factor 7 [FGF7], PR/SET domain 11 [PRDM11], microRNA 1179 [MIR1179], insulin receptor [INSR], ABO, inositol-tetrakisphosphate 1-kinase [ITPK1], neuregulin 1 [NRG1],MAP3K12 binding inhibitory protein 1 [MBIP], SAM and SH3 domain containing 1 [SASH1], and GLIS family zinc finger 3 [GLIS3]) and levels of free T4 (iodothyronine deiodinase 1 [DIO1], LIM homeobox 3 [LHX3], FOXE1, aminoadipate aminotransferase [AADAT], lysophosphatidylcholine acyltransferase 2 [LPCAT2]/calpain small subunit 2 [CAPNS2], neuropilin and tolloid like 1 [NETO1]/F-box protein 15 [FBXO15]) **(Porcu, et al., 2013).**

A GWAS of TSH levels was also conducted in 1,346 Chinese Han individuals. Which confirmed previously reported TSH susceptibility loci near FOXE1 and CAPZB and identified

novel variants in XK related 4 (XKR4) **(Zhan, et al., 2014).**

Whole-genome sequence-based analysis was performed to examine the genetic architecture for levels of free T4 and TSH, and further identified novel variants on synapsin II (SYN2), PDE8B, and beta-1,4-galactosyltransferase 6 (B4GALT6) **(Taylor, et al., 2015).**

They also found a rare functional variant (minor allele frequency=0.4%) in the transthyretin (TTR) gene, which is located near B4GALT6. This study showed that common variants explained over 20% of the variance in TSH and free T4 and that a substantial amount of heritability of thyroid function could be explained by rare variants with larger effects. Results of GWAS for thyroid function are summarized in **Table (1).**

Table (1): Susceptibility Loci for Levels of TSH or Free T4 (Gudmundsson J, et al., 2017).

Phenotypes	locus	gene	Protein function	population
TSH	*5q13.3*	*PDE8B*	*Role in hydrolysis of the secondmessenger cAMP*	*European, USA, , UK*
	6q27	*PDE10A*	*Role in regulation of the intracellular concentration of cyclic nucleotides*	*European, UK*
	1p36.13	*CAPZB*	*Regulating actin filament dynamics*	*European, UK, Chinese,Germany*
	16q23.2	*MAF*	*Role in increased T-cell susceptibility to apoptosis*	*European, UK,Germany*
	6p21.1	*VEGFA*	*Proliferation and migration of vascular endothelial cells*	*European, UK*
	4q31.23	*NR3C2*	*Role in aldosterone actions*	*European, Germany,UK*
	2q35	*IGFBP5*	*Encoding insulin like growth factorbinding protein 5*	*European*

	17q24.3	*SOX9*	*Role in chondrocyte differentiation*	*European*
	9q22.33	*FOXE1*	*Encoding TTF-2, role in thyroid morphogenesis*	*Chinese Han, USA, UK*
	2q35	*IGFBP2*	*Encoding insulin like growth factorbinding protein 2*	*UK*
	3p25.2	*SYN2*	*Binding to small synaptic vesicles*	*UK*
Free T4	*1p32.3*	*DIO1*	*Encoding iodothyronine deiodinase 1*	*European, UK*
	9q34.3	*LHX3*	*Role in pituitary development*	*European, UK*
	9q22.33	*FOXE1*	*Encoding TTF-2, role in thyroid morphogenesis*	*European*
	4q33	*AADAT*	*Role in L-lysine catabolism*	*European, UK*
	16q12.2	*LPCAT2-CAPNS2*	*Role in membrane biogenesis*	*European*
	18q12.1	*B4GALT6*	*Role in biosynthesis of glycosphingolipids*	*UK*

TSH, thyroid stimulating hormone; **PDE8B**, phosphodiesterase 8B; **cAMP**, cyclic adenosine monophosphate; **PDE10A**, phosphodiesterase 10A; **CAPZB**, capping actin protein of muscle Z-line subunit beta; **VEGFA**, vascular endothelial growth factor A; **NR3C2**, nuclear receptor subfamily 3 group C member 2; **IGFBP5**, insulin like growth factor binding protein 5; **SOX9**, SRY-box 9; **FOXE1**, forkhead box E1; **IGFBP2**, insulin like growth factor binding protein 2; **SYN2**, synapsin II; T4, thyroxine; **DIO1**, iodothyronine deiodinase 1; **LHX3**, LIM homeobox 3; **AADAT**, aminoadipate aminotransferase; **LPCAT2**, lysophosphatidylcholine acyltransferase 2; **CAPNS2**, calpain small subunit 2; **B4GALT6**, beta- 1,4-galactosyltransferase6.

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