Chapter

Genetic Susceptibility to Differentiated Thyroid Cancer

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Abstract

Differentiated thyroid carcinoma (DTC) represents more than 90% of all thyroid cancer histological types. Its incidence has increased at a faster rate than most other malignancies during the last three decades and varies considerably around the world. The familial form of the disease has also become more common than previously reported, accounting for 5–15% of DTC cases. The main established risk factor of thyroid cancer is exposure to ionizing radiation, particularly if occurred during childhood. Thyroid cancer (including DTC) is also characterized by having one of the highest familial risks of any cancer supporting heritable predisposition. In spite of such a high familial risk, linkage analysis in non-syndromic DTC families (i.e. families where DTC is the primary cancer) performed two decades ago mapped several susceptibility loci but did not lead to the identification of high-penetrance causal germline variants. More recently, genome-wide association studies based on population case–control studies identified a limited number of DTC-associated loci and suggested that multiple low penetrance genes are involved in predisposition to DTC. This chapter reviews known genetic factors predisposing to DTC as well as approaches used to map them in various populations, and opens up on alternative strategies that could help to understand DTC tumorigenesis.

Keywords: differentiated thyroid cancer, familial risk, case–control study, genetic predisposition, genome-wide association study

1. Introduction

Almost 95% of patients with malignant thyroid tumors have non-medullary thyroid cancer (NMTC), which originates from follicular cells. Most NMTC are well-differentiated and include papillary thyroid carcinoma (PTC) (80–90%) and follicular thyroid carcinoma (FTC) (10–15%) while poorly differentiated thyroid carcinoma and anaplastic carcinoma are rare. C-cell-derived medullary thyroid carcinoma (MTC) are diagnosed in approximately 5% of patients [1]. Altogether differentiated thyroid carcinoma (DTC) represents more than 90% of all thyroid cancer histological types and the most frequent malignancy of the endocrine system (**Figure 1**) [2].

DTC incidence varies considerably around the world. High incidence was reported in some Pacific islands such as Hawaii, New Caledonia, and French Polynesia [3]. Ethnic differences in incidence within the same country have

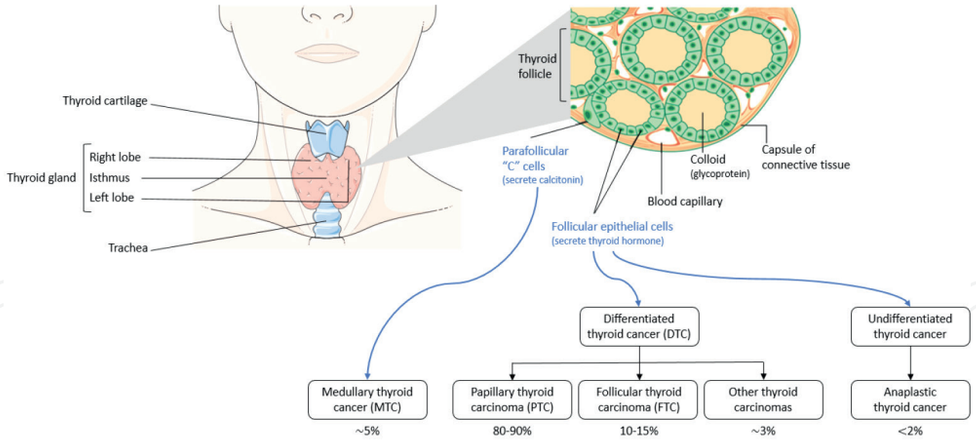

Figure 1.
Thyroid cancer subtypes classification.

been noted in Hawaii and New Caledonia with higher rates among Filipinos and Melanesians than in other ethnic groups [4]. The causes underlying these wide geographic and ethnic variations are still poorly understood. If this variation in incidence was attributed to screening practices, it was suggested that environment and inherited genetic risk factors may also play an important role [5]. Clinical awareness of potential risk factors, such as inherited genetic variants allows for earlier recognition of more vulnerable populations, earlier detection, proper treatment, and improved outcomes for patients and their families, justifying current efforts to identify and understand the causal factors and mechanisms of DTC so that effective interventions can be implemented.

Familial associations are often quantified in terms of familial relative risk (FRR). The FRR denotes the risk of disease when a family member is affected compared to the risk level in the general population. Specific types of familial relationships, like first-degree relatives, parent–child, or siblings are generally examined. Remarkably, thyroid cancer displays one of the strongest FRRs among cancers. Large case–control studies conducted in populations from Utah and Sweden showed that the FRR of thyroid cancer for first-degree relatives of probands was 8.5 and 12.4, respectively [6, 7]. Data from studies focusing on DTC conducted in Sweden, Iceland, and Norway showed that the standard incidence risk (SIR) of DTC was between 4.1 and 7.8 for male relatives and between 1.9 and 4.9 for female relatives of the proband [8–10]. The SIR for PTC was calculated in the Norwegian study as 5.8 and 4.1 for male and female relatives, respectively [10]. The family structures of non-medullary thyroid carcinoma (NMTC) patients in Taiwan were also studied. The prevalence of NMTC in the general population and in first-degree relatives of NMTC patients was 0.16% and 0.64%, respectively. This corresponds to a 5.5-fold increased risk of NMTC for first-degree family members [11].

Like many cancers, thyroid cancers may arise from mutations that may or may not be heritable. They can occur due to any mistake during DNA replication during cell division or may be induced due to the effect of carcinogens on DNA like ionizing radiation. Most thyroid cancers are the result of the accumulation of somatic mutations in the cancer genome, either driver mutations of oncogenesis or passenger mutations [12]. They are not present constitutionally in the individual but only in part of thyroid cells. By contrast, constitutional (germline) variants may predispose

to cancer susceptibility and are present in affected individuals in all the body's nucleic cells, as well as the cancer genome, and may therefore be heritable. Nonetheless, over 90% of all thyroid cancers are sporadic, *i.e.* occur in people with no family history of thyroid cancer. The remaining are familial forms of NMTC and MTC. Familial MTC is associated with well-known germline genetic alterations in the *RET* proto-oncogene [13, 14] and genotype–phenotype correlations have been described [15]. On the contrary, the genetic causes of familial NMTC (FNMTC) or follicular cell-derived carcinoma are poorly understood despite considerable effort to identify contributing loci. In this chapter, we summarize variants associated with risk of DTC in familial and sporadic settings, as well as approaches used to map them in various populations and to identify causal genes or variants, which would greatly facilitate the estimation of disease risk and prognosis.

2. Familial non-medullary thyroid cancers

Familial NMTC (FNMTC) is clinically defined as the presence of the disease in two or more first-degree relatives of the patient. It encompasses a heterogeneous group of diseases, including diverse syndromic-associated tumors with a preponderance of non-thyroidal tumors and non-syndromic tumors with a preponderance of NMTC. Hereditary cancer syndromes associated with FNMTC account for 5% of all familial cases and include familial adenomatous polyposis (FAP) and its variant Gardner syndrome, Cowden syndrome, Carney complex, Werner syndrome, and DICER1 syndrome. Other syndromes with less established links to the development of NMTC include McCune-Albright syndrome, Ataxia-telangiectasia, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome [16–20], also no epidemiological studies confirmed a significantly increased risk of NMTC for patients affected by these latter syndromes and for their relatives. Non-syndromic-associated conditions encompass pure familial PTC (fPTC) with or without oxyphilia, fPTC with papillary renal cell carcinoma, and fPTC with multinodular goiter [21–23]. The clinical characteristics of FNMTC are controversial. Several studies found an earlier age of onset, higher incidence of multifocality and lymph node metastasis, and a more aggressive outcome with more frequent relapses compared with sporadic disease [24], while other studies showed no significant increase in risk of recurrence or disease-related mortality in FNMTC cases compared to sporadic cases [25, 26]. Additionally, the second generation of parent-offspring FNMTC cases presents the disease at a younger age with more severe symptoms, indicating the presence of genetic anticipation [27].

Understanding the genetic basis of a heterogeneous disease such as FNMTC and the identification of biomarkers of disease aggressiveness can help to better stratify risk, allowing predictive screening of at-risk family members, improved surveillance guidance, and clinical management plan.

2.1 Genetic variants associated with risk of syndromic-associated disorders

Germline mutation (or "pathogenic variants") accounting for syndromic FNMTC are highly penetrant and actionable, meaning that targeted genet testing is recommended when the clinician recognizes the clinical phenotype of the syndrome. Clinical characteristics and genes involved in the predisposition to syndromic FNMTC are summarized hereafter.

Familial adenomatous polyposis (FAP) is inherited as an autosomal dominant trait characterized by young-onset multiple gastrointestinal adenomatous polyps, especially of the colon, with malignant potential. In about 90% of cases, FAP is caused by germline loss-of-function variants in the tumor suppressor gene *APC* (*adenomatous polyposis coli*) located on chromosome 5q21 and encoding an inhibitor of Wnt signaling pathway. Ten to 25% of germline pathogenic *APC* variants arise *de novo.* Patients with FAP or with **Gardner syndrome,** a subset of FAP in which patients also develop extra-colonic manifestations [28], have a 160-fold greater risk than unaffected individuals of developing PTC [29–31]. Two to 12% of patients with FAP develop PTC [32], and 70% to 90% of these latter are diagnosed with a cribriform-morular variant of PTC (CMV-PTC), an extremely rare variant accounting for less than 1% of all PTC in the general population [33].

Cowden syndrome (also called **PTEN-hamartoma tumor syndrome**) is an autosomal dominant disorder characterized by hamartomatous changes and epithelial tumors of the breast, thyroid, kidney, colon, and endometrium caused by germline pathogenic variants in the tumor suppressor gene *PTEN* (*Phosphatase and TENsin homolog*) on chromosome 10q23.3 in about 9% of tested probands [34]. Up to 60% of patients with Cowden syndrome have thyroid nodules and 25% of patients have thyroid cancer [35]. These patients develop principally PTC (55.1%), followed by follicular variants of PTC (19.5%) and FTC (10%) [35]. Germline pathogenic variants in genes *SDHB*, *SDHC,* and *SDHD* encoding the subunits of the succinate dehydrogenase have also been described, as well as an epimutation in the promoter of the *killin* (*KLLN*) gene [35]. Succinate dehydrogenase belongs to mitochondrial complex II that participates in both the electron transport chain and Krebs cycle, and *KLLN* is a p53-regulated gene located upstream of *PTEN* and sharing a bidirectional promoter region.

Carney complex is a dominantly inherited syndrome characterized by a classic triad of spotty skin pigmentation, endocrine overactivity, and myxomas. About 5% of patients develop thyroid nodules (follicular adenoma) and cancer (PTC or FTC). Inactivating pathogenic variants in the *PRKAR1A* gene located at 17q22–24 are identified in 73% of patients and their penetrance has been estimated to be 97.5% [36]. The gene encodes the protein kinase cAMP-dependent type I regulatory subunit alpha. Phosphorylation mediated by the cAMP/protein kinase A signaling pathway is involved in the regulation of metabolism, cell proliferation, differentiation, and apoptosis [37]. Remarkably, the *PRKAR1A* gene can fuse to the RET protooncogene by gene rearrangement and form the thyroid tumor-specific chimeric oncogene known as *PTC2* [38].

Werner syndrome is an autosomal recessive genetic instability and progeroid ('premature aging') syndrome associated with loss-of-function variants in the *WRN* (*Werner syndrome RecQ like helicase*) gene located at 8p11–21 [39]. The *WRN* gene encodes a member of the RecQ subfamily of DNA helicase protein. This nuclear protein is involved in important functions required for the maintenance of genome stability such as replication, transcription, DNA repair, and telomere maintenance. Patients with Werner syndrome develop features reminiscent of premature aging beginning in the second decade of life, including bilateral cataracts, graying and loss of hair, scleroderma-like skin changes, diabetes mellitus, and osteoporosis. They are also at elevated risk for common, clinically important age-dependent diseases, such as cancer and atherosclerotic cardiovascular disease, which are the most common causes of death at a median age of 54 years [40]. Sixteen percent of patients with Werner syndrome develop thyroid cancer, with FTC being the most common histological subtype, followed by PTC and anaplastic thyroid cancers [40].

DICER1 syndrome, also known as **pleuropulmonary blastoma familial tumor and dysplasia syndrome**, is a rare pediatric autosomal dominant inherited disorder that predisposes individuals to various benign and malignant tumors. It is caused by germline pathogenic variants in the *DICER1* gene located at 14q32.13. The gene encodes a member of the ribonuclease III (RNaseIII) family involved in the generation of micro-RNA (miRNAs) and modulates gene expression by interfering with mRNA function. In the thyroid, germline *DICER1* loss-of-function variants disrupt the correct timing and expression of miRNA production necessary for normal thyroid differentiation and function [41, 42]. Patients with DICER1 syndrome are at higher risk of early-onset multinodular goiter and thyroid carcinomas. In particular, in DICER1 syndrome families, carriers of a *DICER1* pathogenic variant have a 16-fold increase in risk of DTC as compared to noncarriers [43].

2.2 Genetic variants associated with risk of non-syndromic-associated disorders

Initial efforts to identify DTC susceptibility genes were conducted in the late 90s – early 2000s by conducting genome-wide linkage analysis in multigenerational families with multiple affected members, usually with attempt to replicate best hits in an independent set of smaller families. Some candidate genes within the mapped regions have been subsequently screened. To date, seven loci involved in FNMTC susceptibility have been mapped (1q21, 2q21, 8p23.1-p22, 8q24, 12p14, 14q32, 19p13.2), where the causal genes remain to be identified or confirmed in independent family sets. With the introduction of massive-parallel sequencing technologies in diagnostic and research laboratories in the 2010s, some of these regions have been more extremely screened highlighting new candidates (*AK023948* at 8q24, *SRGAP1* at 12p14, *DICER1*

Locus (name)	Family/ cases in the discovery study	Candidate gene	Replication study	Ref.	Approach
14q32 (*MNG1*)	1 French Canadian family, 18 MNG cases, 2 cases also with PTC	*DICER1*	Investigation of 37 NMTC families (88 DTC cases) indicates that only a small proportion of FNMTC is attributable to *MNG1*.	[23, 44]	Linkage analysis [44]; sequencing of *DICER1; in vitro* assays to assess expression level of miRNA in *DICER1* variant carriers [23].
19p13.2 (*TCO)*	1 French family, 9 PTC cases (atypical carcinomas and adenomas with cell oxyphilia); 1 family, 3 cases	*MYO1F*	No linkage in subsequent study involving 56 NMTC families [45]; WES in the original family identified *MYO1F* c.400G>A (p.Gly134Ser) but targeted sequencing of *MYO1F* in 192 FNMTC cases showed no evidence of association with FNMTC [46].	[45–47]	Linkage analysis [45, 47]; WES + functional assay + sequencing of *MYO1F* in extended sets of FNMTC families.

Locus (name)	**Family/ cases in the discovery study**	**Candidate gene**	**Replication study**	**Ref.**	**Approach**
1q21 (*fPTC1/ PRN1)*	1 family, 5 PTC cases, 2 family members with papillary renal neoplasia	*N-RAS, NTRK1, PRCC*	No replication study.	[22]	Linkage analysis
2q21 (*NMTC1)*	1 Tasmanian family, 8 PTC cases	*ACVR2, RAB6/ RALB, LRP-DIT*	Linkage confirmed in an independent set of 80 families.	[48]	Linkage analysis
8p23.1-p22 (*FTEN)*	1 Portuguese family, 5 PTC cases, 11 members with benign thyroid lesions	17 candidates excluded.	No replication study.	[49]	Linkage analysis + gene expression profiling + sequencing + LOH analysis.
8q24	1 family with PTC and melanoma	*AK023948* noncoding RNA (*TG* and *SLA* excluded)	Linkage confirmed using 25 additional PTC families (86 cases and 13 obligate carriers)	[50]	Linkage analysis + target sequencing+ gene expression analysis.
12q14	38 families, 108 PTC cases	*SRGAP1*	Association study on tag SNPs spanning the locus performed in 2 cases-control series from Ohio and Poland; biochemical assays showed that missense variants p.Gln149His and p.Arg617Cys impair the ability of SRGAP1 to inactivate CDC42.	[51]	Linkage analysis + association study + sequencing of *SRGAP1* + *in vitro* assays.
4q32	1 US family, 11 PTC cases and 2 cases with anaplastic thyroid carcinoma	(putative enhancer)	Not replicated in 38 NMTC families; rare single nucleotide variant absent in 2676 sporadic cases and 2470 controls from Poland and Ohio.	[52]	Linkage analysis + functional study
HABP2 (10q25.3)	1 family, 6 PTC cases	*HABP2*	Target sequencing of *HABP2* in probands of 12 Chinese PTC families [53]; sequencing of *HABP2* exon 13 in tumor from 217 sporadic PTC patients did not identify the variant [54].	[53, 54]	WES + investigation of the expression of HABP2 in thyroid tissue samples + functional assay on variant p.Gly534Glu [53]; target sequencing of *HABP2* exon 13 [54]

Locus (name)	Family/ cases in the discovery study	Candidate gene	Replication study	Ref.	Approach
16p13.3	1 family, 6 PTC cases	*SRRM2*	Identified variant c.1037C>T (p.Ser346Phe) not found in 138 familial PTC cases; association study involving 1170 sporadic PTC cases and 1404 controls confirmed association with PTC.	[55]	WES, then genotyping of identified variant in 138 other PTC; association study in sporadic PTC and unrelated controls; RNA-Seq to assess effect on efficiency of RNA splicing machinery.
15q23	34 Chinese families, 77 cases	*MAP2K5*	Variants c.961G>A and c.1100T>C identified in 2 families of the original Chinese study [56] not found in 33 Italian FNMTC families [57].	[56, 57]	WES + functional study [56]; targeted sequencing to search for the 2 previously described variants only [57]
19q13.33	1 family with 5 NMTC cases	*NOP53*	Variant rs78530808 (NOP53 p.Asp31His) identified in 3 of 44 additional families and absent in unaffected spouses; Functional studies showed oncogenic function but high frequency in the general population (MAF 1.8%) suggests a low-penetrant variant, possibly a modifier.	[58]	WES + targeted sequencing of candidate variants in familial cases and controls + functional assays.
22q12.1	5 NMTC families, 23 cases	Variants enrichment in MAPK/ ERK and PI3K/AKT signaling pathways	No replication study.	[59]	WGS
14q12	1 family with 10 members affected with PTC and/or melanoma + 23 NMTC families, 34 cases	*TINF2*	No replication study.	[60, 61]	WGS in the key family with PTC and melanoma + target sequencing of *TINF2* + gene expression analysis + quantification of relative telomere length in variant carriers and noncarriers.

Locus (name)	Family/ cases in the discovery study	Candidate gene	Replication study	Ref.	Approach
7q31.33	1 NMTC family, 8 cases	*POT1*	Another germline likely pathogenic variant in *POT1* already reported in a melanoma-prone family with occurrence of thyroid cancers [62]. Lack of likely pathogenic *POT1* variants in 7 FNMTC families [63].	[59, 64]	WGS + functional analysis, including quantification of relative telomere length in variant carriers and noncarriers

GWAS: genome-wide association study, LOH: loss of Heterozygosity, MAF: minor allele frequency, Ref.: reference, WES: whole-exome sequencing, WGS: whole-genome sequencing.

Table 1.
DTC susceptibility loci evidenced in family studies on non-syndromic NMTC (in chronological order of discovery).

Figure 2.
DTC susceptibility loci evidenced in family studies (in red) and in genome-wide association studies (GWAS) on NMTC (in blue). Only GWAS loci replicated in independent samples are shown.

at 14q32, *MYO1F* at 19p13.2). In addition, whole-exome or whole-genome sequencing followed in most instances by functional assays allowed identification of potentially causal variants in other genes (*HABP2*, *SRRM2*, *MAP2K5*, *NOP53*, *TINF2*, *POT1*) located elsewhere in the genome. The details of these studies and clinical features of non-syndromic FNMTC families used in the discovery steps and replication steps are reported in **Table 1** and summarized in **Figure 2**.

3. Genetic factors associated with sporadic DTC

3.1 Findings from association studies

Sporadic DTC, which represents the majority of all NMTC, is considered as a complex disease caused by multiple environmental and genetic risk factors. Common polymorphisms in low-penetrance genes or altering their expression are hypothesized to play an important role in sporadic DTC. The numerous association studies conducted in the general population used a case–control design that compares the distribution of the polymorphisms in a population of affected versus unaffected individuals. Two types of association studies can be performed: the candidate gene approach that focuses on a limited number of polymorphisms located in genes select based on *a priori* knowledge of their biological function and the genome-wide association studies (GWAS) approach that consists in screening the association between the disease and the genetic variants along the genome without prior hypothesis.

The candidate gene approach usually focuses on functional or tags polymorphisms located in specific genes selected based on their potential functional impact on the gene product or on its potential interaction with known environmental/lifestyle risk factors for the disease. Candidate genes selected for analysis in association studies on DTC are mostly involved in the following biological pathways: DNA repair, cell cycle regulation, and apoptosis, xenobiotic metabolism, thyroid function, MAPK pathway, immune response and inflammation, and obesity [65–67].

Figlioli et al. [67] proposed an exhaustive review of polymorphisms investigated in association studies published before September 2013. They reviewed 100 original articles and five meta-analyses and reported 91 significant SNPs (over 316 analyzed) from 127 genes. They also conducted a meta-analysis on 46 SNPs, which were reported by at least two studies, and reported 13 significant SNPs, of which six are located in the coding sequence of candidate genes: *ADPRT* (rs1136410; p.Val762Ala), *BRCA1* (rs16942; p.Lys1183Arg), *XRCC7* (rs7830743; p.Ile3434Thr), *TP53* (rs1042522; p.Pro72Arg), *MTHFR* (rs1801133; p.Ala222Val), *RET* (rs1800862; p.Ser836Ser), one is intronic (rs4658973 in *WDR3*) and six SNPs are located in intergenic regions highlighted by GWAS. Therefore, many candidate genes and polymorphisms were considered in association with DTC but only a few were properly replicated.

With the completion of the human genome sequencing in 2003, GWAS involving hundreds of thousands to millions of SNPs across the human genome became more and more common. GWAS are usually composed with one discovery phase that aims to analyze a large number of variants, followed by a replication phase consisting of validation of the most significant variants in an independent sample. Since 2009, seven GWAS were published on NMTC risk, of which six were conducted in individuals of European ancestry [68–73] and one was conducted in individuals of Asian ancestry from Korea [74] (**Table 2**). The latest GWAS conducted by Truong et al. [73] also included a small discovery sample of individuals of Oceanian ancestry but with no replication set. Among the GWAS conducted in the European ancestry population, one study focused on radiation-related PTC, with cases recruited in Belarus and aged 0–18 years old at the time of the Chernobyl accident [69]. All these GWAS were based on a relatively low number of cases compared to other cancers GWAS and the largest study included 3,001 cases is a meta-analysis of several studies with no replication phase [72].

Reference	Populations	Histology	Number of cases/ controls in discovery phase	Number of cases/controls in replication phase
[68]	Iceland	NMTC	192 /37,196	
	Spain	NMTC		89 /1,343
	USA (Columbus)	PTC		294/384
[69]	Belarus (Gomel) and Russia	PTC	401/620	259/648
	Age <18 years old at the time of Chernobyl accident			
[70]	Italy	PTC	701/499	
	Italy	DTC		1213/989
	Italy	DTC		326/730
	Poland	DTC		468/470
	UK	DTC		509/1,118
	Spain	DTC		443/420
[71]	Spain	DTC	398/502	
	Italy	DTC		541/532
	Spain (Galicia)	DTC		240/531
	Spain (Catalonia)	DTC		354/408
[74]	Korea	DTC	470/8,279	615/605
[72]	Iceland	NMTC	1,003/278,991	
	Netherlands	NMTC	85/4,956	
	USA (Columbus)	PTC	1,580/1,628	
	USA (Houston)	PTC	250/363	
	Spain (Zaragosa)	NMTC	83/1,612	
[73]	European descents from France, French Polynesia, New Caledonia, Belarus, Cuba	DTC	1,554/1,973	
	Oceanian from France Polynesia, New Caledonia	DTC	301/348	
	USA (Columbus)	PTC		1,580/1,628
	Italy	DTC		649/431

NMTC: non-medullary thyroid carcinoma, DTC: differentiated thyroid carcinoma, PTC: papillary thyroid carcinoma, TSH: thyroid stimulating hormone

Table 2.
Details on published genome-wide association studies on NMTC risk.

Tables 3 and **4** summarize the significant and suggestive loci highlighted by these seven GWAS. All these variants are located in intronic or intergenic regions, except rs6793295 which is a missense variant in *LRRC34* at 3q26.2. The loci that were replicated in independent studies are shown in **Figure 2**. The most robust associations, *i.e.* the ones that were reported by several GWAS and independent sample sets, are for variants at 9q22.33, 14q13.3, 2q35, and 8p12.

Locus	Nearest gene(s)	Location	Lead SNPs	EA/OA	EAF	OR	p-value	Ref.	Ancestry	Remarks	Replicated
9q22.33	FOXE1,	PTCSC2 intron	rs965513	A/G	0.34	1.75	1.7×10^{-27}	[68]	Eur		[75–89]
	PTCSC2				0.34	1.65	4.8×10^{-12}	[69]	Eur	radiation-related DTC	
					_	1.78	2.7×10^{-10}	[70]	Eur		
					0.33	1.65	2.7×10^{-23}	[71]	Eur		
		PTCSC2 intron	rs1588635	A/C	0.40	1.69	2.0×10^{-58}	[72]	Eur	r2 = 0.99 with rs965513 in EUR	
					0.39	1.64	2.1×10^{-21}	[73]	Eur		
		Intergenic	rs72753537	C/T	0.07	1.41	7.7×10^{-6}	[74]	Asian	r2 = 0.001 with rs965513 in EAS	
14q13.3	NKX2-1,	PTCSC3 promoter	rs944289	T/C	0.57	1.37	2.0×10^{-9}	[68]	Eur		[75, 79, 80, 82–84, 87–89, 92–94]
	PTCSC3			T/C	0.56	1.24	1.5×10^{-5}	[71]	Eur		
				T/C	0.46	1.25	1.4×10^{-6}	[74]	Asian		
		Intergenic	rs116909374	T/C	0.03	1.81	1.1×10^{-16}	[72]	Eur	r2 = 0.006 with rs944289 in EUR	[79, 82, 88, 93]
					0.06	2.33	1.6×10^{-10}	[73]	Eur		
		Intergenic	rs368187	G/C	0.58	1.39	5.1×10^{-23}	[72]	Eur	r2 = 0.70 with rs944289 in EUR	[93]
					0.63	1.47	3.8×10^{-13}	[73]	Eur	r2<0.01 with rs116909374 in EUR	
		Intron	rs34081947	T/C	0.41	1.27	1.2×10^{-7}	[74]	Asian	r2 = 0.61 with rs944289 in EAS r2 = 0.90 with rs368187 in EAS	

Locus	Nearest gene(s)	Location	Lead SNPs	EA/OA	EAF	OR	p-value	Ref.	Ancestry	Remarks	Replicated
2q35	DIRC3	Intron	rs6759952	T/C	0.38	1.25	6.4×10^{-10}	[70]	Eur		[108]
		Noncoding transcript	rs11693806	C/G	0.32	1.43	1.5×10^{-24}	[72]	Eur	r2 = 0.45 with rs6759952 in EUR	
		Noncoding transcript	rs3821098	T/C	0.28	1.39	1.1×10^{-10}	[73]	Eur	r2 = 0.98 with rs11693806 in EUR	
		Intron	rs12990503	G/C	0.63	1.34	3.5×10^{-9}	[74]	Asian	r2 = 0.97 with rs11693806 in EAS	
8p12	NRG1	Intron	rs2466076	G/T	0.48	1.32	1.5×10^{-17}	[72]	Eur	r2 = 0.94 with rs2439302 in EUR	
		Intron	rs142450470	T/-	0.35	1.33	1.5×10^{-7}	[73]	Eur	r2 = 0.45 with rs2439302 in EUR Significant for PTC ($p = 9.4 \times 10^{-9}$)	
		Intron	rs2439302	G/C	0.21	1.37	1.4×10^{-9}	[74]	Asian	r2 = 0.95 with rs2466076 in EAS r2 = 0.39 with rs142450470 in EAS	[73, 84, 88, 89, 92, 94, 98]
		Intron	rs6996585	G/A	0.23	1.39	1.1×10^{-10}	[74]	Asian	r2 = 0.67 with rs2439302 in EAS	
		Intron	rs12542743	C/T	0.25	1.36	4.6×10^{-10}	[74]	Asian	r2 = 0.37 with rs2439302 in EAS	

EA: effect allele, OA: other allele, EAF: effect allele frequency, lead SNP: SNP with the lowest p-value in the locus, OR: Combined odds ratio for EA versus OA from the meta-analysis of the discovery and replication sets, Ref.: Reference of the GWAS, EAS: East Asian ancestry population from the 1000 genomes project, EUR: European ancestry population from the 1000 genomes project

Table 3.
Findings from genome-wide association studies on NMTC at robust susceptibility loci (in chronological order of discovery).

Locus	Nearest gene(s)	Location	Lead SNPs	EA/OA	EAF	OR	p-value	Ref.	Ancestry	Remarks	Replicated
1q42.2	*PCNXL2*	Intron	rs12129938	A/G	0.79	1.32	4.0×10^{-11}	[72]	Eur		[109]
	PCNXL2	Intron	rs4649295	T/C	0.82	1.43	6.0×10^{-8}	[74]	Asian	r2 = 0.67 with rs12129938 in EAS	[109]
10q.24.33	*OBFC1*	Intergenic	rs7902587	T/C	0.11	1.41	5.4×10^{-11}	[72]	Eur		
5q22.1	*EPB41L4A*	Intron	rs73227498	A/T	0.87	1.37	3.0×10^{-10}	[72]	Eur		
15q22.33	*SMAD3*	Intron	rs2289261	C/G	0.68	1.23	3.1×10^{-9}	[72]	Eur		
	SMAD3	Intron	rs56062135	T/C	0.25	1.24	4.9×10^{-9}	[72]	Eur		
16q23.2	*MAF*	Intergenic	rs16950982	G/A	0.37	1.22	4.7×10^{-9}	[73]	Eur		
12q14.3	*MSRB3*	Intron	rs11175834	T/C	0.15	1.37	4.3×10^{-8}	[74]	Asian		
1p13.3	*VAV3*	Intron	rs4915076	T/C	0.70	1.33	8.5×10^{-8}	[74]	Asian		[110]
3q26.2	*LRRC34*	Exon, p.Ser249Gly	rs6793295	T/C	0.76	1.23	2.7×10^{-8}	[72]	Eur		
5p15.33	*TERT*	Intron	rs10069690	T/C	0.27	1.20	3.2×10^{-7}	[72]	Eur		[111, 112]
	TERT	Intron	rs7726159	A/C	0.39	1.17	5×10^{-6}	[73]	Eur	$r^2 = 0.44$ with rs10069690 in EUR	
19p12	*ZNF257*	Intron	rs7260863	T/C	0.20	1.22	8.7×10^{-7}	[73]	Eur		
4q21.1	*SEPT11*	Intergenic	rs1874564	G/A	0.69	1.31	2.0×10^{-7}	[74]	Asian		
3p14.2	*FHIT*	Intergenic	rs9858271	G/A	0.43	1.26	6.8×10^{-7}	[74]	Asian		
1p31.3	*NFIA*	Intron	rs334729	C/T	0.05	1.43	7.6×10^{-7}	[73]	Eur		
7q31.1	*IMMP2L*	Intron	rs7800391	T/C	0.34	1.25	5.7×10^{-6}	[70]	Eur	Specific to Italian pop	
	IMMP2L	Intron	rs10238549	C/T	0.63	1.27	4.1×10^{-6}	[70]	Eur	Specific to Italian pop	
3q25.32	*RARRES1*	Intron	rs7617304	A/G	0.25	1.25	4.6×10^{-5}	[70]	Eur	Specific to Italian pop	

Locus	Nearest gene(s)	Location	Lead SNPs	EA/OA	EAF	OR	p-value	Ref.	Ancestry	Remarks	Replicated
10q26.12	*WDR11-AS1*	Intron	rs1254167	C/G	0.08	1.38	5.9×10^{-5}	[71]	Eur		
	WDR11-AS1	Intron	rs10788123	T/C	0.20	1.69	3.2×10^{-5}	[71]	Eur		
9q34.3	*SNAPC4/ CARD9*	Intergenic	rs10781500	C/T	0.60	1.23	3.5×10^{-5}	[70]	Eur	Specific to Italian pop	
19p13.2	*INSR*	Intron	rs7248104	A/G	0.36	1.22	2.0×10^{-5}	[74]	Asian		
6q14.1	*HTR1B*	Intergenic	rs4075570	G/A	0.35	0.82	2.0×10^{-4}	[71]	Eur		[113]

EA: effect allele, EAF: effect allele frequency, lead SNP: SNP with the lowest p-value in the locus, OR: Combined odds ratio for EA versus OA from the meta-analysis of the discovery and replication sets, Ref.: Reference of the GWAS, EAS: East Asian populations from the 1000 genomes project, EUR: European populations from the 1000 genomes project.

Table 4.
Other significant or suggestive susceptibility loci highlighted by genome-wide association studies on DTC (ordered by significance of association).

3.1.1 Locus 9p22.33

At 9p22.33, the most robust association reported in GWAS was for rs96551 or rs1588635, a highly correlated proxy (r^2 = 0.99 in the European population from the 1000 Genomes Project). Rs965513 has been associated with radiation-related DTC as well as with sporadic DTC, and it was subsequently consistently replicated in several different populations of European ancestry [75–82], of Asian ancestry [81, 83–85] as well as in admixed populations from Oceania [79, 86], Cuba [87], Colombia [88], or Kazakhstan [89].

In 2009, a study focusing on the role of *FOXE1* in DTC risk [90] suggested rs1867277 as a causal variant at 9p22.33. This variant is located in the 5' UTR of *FOXE1* (also known as *TTF2,* for *Thyroid Transcription Factor 2*) and was shown to affect the transcription of *FOXE1* which is involved in the development and regulation of the thyroid gland, and in the proliferation and differentiation of thyroid follicular cells. However, rs1867277 is less consistently replicated in other populations and the linkage disequilibrium (LD) between rs1867277 and rs965513 is moderate in Europeans (r2 = 0.3 in Europeans from the 1000 Genomes project) and even weaker in populations of Asian or African ancestries (r^2<0.01 in the 1,000 Genomes Project). Rs965513 is located 60 kb upstream of rs1867277, in an intron of the long intergenic noncoding RNA (lincRNA) *PTCSC2* that was reported for the first time in 2015 by He et al. [91]. The risk allele [A] of rs965513 was shown to significantly decrease the expression of unspliced *PTCSC2*, FOXE1, and TSHR in normal thyroid tissue.

3.1.2 Locus 14q13.3

Rs944289 was the first variant identified by GWAS at 14q13.3 [68]. This association was replicated in subsequent studies conducted in diverse populations [75, 79, 80, 82–84, 87–89, 92–94]. However, the most recent GWAS, conducted in several European populations [72, 73] and in one Asian population from Korea [74], analyzed a higher number of SNPs (using genotyped and imputed SNPs) and reported the strongest signal for respectively rs368187 and rs34081947 (r^2 = 0.98 in Europeans and r^2 = 0.90 in East Asians from the 1000 Genomes Project), which are in moderate LD with rs944289 (r^2<0.70 in Europeans or East Asians from the 1000 Genomes Project). The recent European GWAS also reported an independent signal at rs116909374 and rs368187. Rs116909374 replicated only in studies on European ancestry populations [79, 82, 88, 93] as this SNP is monomorphic or very rare in Asian populations. Interestingly, rs368187 is in high LD with rs34081947, which was highlighted by the GWAS conducted in the Korean population (r2 = 0.98 in East Asians from the 1000 Genome Project) (**Table 3**).

In 2012, Jendrzejewski et al. [95] described a novel lincRNA named *PTCSC3* located 3.2 kb downstream of rs944289. They showed that the expression of *PTCSC3* was strongly down-regulated in thyroid tumor tissue and that the risk allele [T] of rs944289 was associated with up-regulation of *PTCSC3* in normal thyroid tissue, suggesting that *PTCSC3* could act as a tumor suppressor gene. Most recent fine-mapping analyses [79, 93] confirmed that multiple independent SNPs are involved in DTC risk at 14q13.3, but the clinical significance of all these SNPs is still unknown.

3.1.3 Locus 2q35

The association between DTC and variants at 2q35 was first highlighted in 2009 in a GWAS that investigated genetic factors associated with thyroid stimulating hormone

(TSH) levels in blood in 27,758 Icelandic individuals. The authors further investigated the role of the top SNPs associated with circulating TSH levels in DTC susceptibility of which rs966423 at 2q35 [82]. Another GWAS on DTC risk, conducted in 2013 in an Italian population [70], reported rs6759952 as the lead SNP at 2q35, which is moderately correlated to rs966423 (r^2 = 0.69 in Europeans from the 1000 Genomes project). The most recent GWAS from 2017 [72–74] reported three new SNPs (rs11693806, rs3821098, and rs12990503) with the strongest signal at 2q35, which are highly correlated to each other but only moderately with the two previous reported SNPs (**Table 2**).

Finally, the recent *in silico* fine-mapping analysis at 2q35 conducted in a multiethnic study pinpointed rs16857609 as a possible causal SNP [96]. This SNP was strongly correlated to the three SNPs reported by recent GWAS and was associated with the expression of the two nearby genes *DIRC3* and *IGFBP5* in thyroid tumor cells. Interestingly, this SNP had also been previously associated with breast cancer risk [97].

3.1.4 Locus 8p12

At 8p12, rs2439302 was first highlighted in the Icelandic GWAS on TSH levels, and it was found to be associated with DTC risk in subsequent analyses [82]. The association between DTC and rs2439302 was then replicated in different populations [84, 88, 89, 92, 94, 98].The recent GWAS [72–74] replicated this SNP and also reported several other variants within the gene *NRG1* that were independently associated with DTC in European and Asian ancestry populations (rs142450470, rs6996585, and rs12542743) (**Table 2**).

In 2018, He et al. [99] reported that the risk allele [G] of rs2439302 was associated with the expression of multiple NGR1 isoforms in normal thyroid tissue. They also suggested that multiple enhancer variants exist at this locus that may have a combinatory effect on the expression of *NRG1* and possibly on the susceptibility to DTC.

3.1.5 Other loci

Among the other loci reported by GWAS, only SNPs at four loci (1q42.2, 5p15.33, 1p13.3, 6q14.1) were replicated in independent studies on DTC (**Table 4**). Interestingly, some of the variants reported in **Table 4** were also previously associated with other diseases or traits. For instance, the SNPs at 5p15.33 (*TERT*) were shown to be associated with telomere length in European and Asian populations [100–102] as well as with risk of breast or ovarian cancers [100, 103]. Rs7902587 at 10q24.33 (*OBFC1*) was significantly associated with ovarian cancer [104], rs56062135 (*SMAD*) at 15q22.33 was also highlighted by a GWAS on coronary artery disease [105], the missense variant rs6793295 (*LRRC34*) at 3q26.2 was associated to systemic sclerosis [106], and rs7248104 (*INSR*) at 19p13.2 was associated to triglyceride levels [107].

3.2 Polygenic risk scores

Based on findings from GWAS, polygenic risk scores (PRS), which are calculated by computing the sum of risk alleles of identified susceptibility SNPs weighted by the effect size estimate from the GWAS, were proposed to predict DTC risk. Several studies evaluated a DTC PRS in different populations [114–118]. The most recent studies used PRS including 10 to 12 SNPs reported by the meta-analysis of GWAS [72] and estimated odds ratios per standard deviation of PRS from 1.55 to 2.31. Liyanarachchi et al. [118] estimated that about 8% of the genetic predisposition to PTC could be

accounted for by 10 SNPs (rs12129938, rs11693806, rs6793295, rs73227498, rs2466076, rs1588635, rs7902587, rs368187, rs116909374, rs2289261). They also estimated that individuals of European ancestry in the highest decile of PRS had a 6.9 higher risk to develop PTC than individuals in the lowest decile group. A recent study reported that the PRS improved significantly predictive scores based on clinical factors in the prediction of subsequent thyroid cancers in childhood cancer survivors of European ancestry [119]. Future studies should investigate the combined effect of PRS and exposure to lifestyle and environmental factors in order to enhance individualized DTC risk prediction. There is also a need to extend the DTC PRS to other ethnic groups.

4. Conclusion

Despite the solid evidence for heritability of thyroid cancer, only a handful of variants have been significantly associated with an increased risk of DTC representing the most common form of thyroid cancer. The high heritability of the disease is likely due to the contribution of rare high-penetrance variants in some cases and the combination of common low-penetrance variants in others, as well as the influence of common shared environmental factors in DTC-prone families or in specific groups of the general population. So far, efforts to identify DTC predisposing genes outside of syndromic FNMTC led to the identification of mainly low-to-moderate penetrance genes, and routine genetic testing for these genes is not recommended. Further large studies to characterize their penetrance and function and to identify new DTC-associated loci or alternative hereditary mechanisms such as epigenetic modifications are required to improve our understanding of DTC tumorigenesis. Ultimately, risk prediction models integrating family history of DTC, PRS, and some modifiable risk factors (obesity, exposure to ionizing radiations from medical diagnostic procedure, etc.) may help stratify individuals according to their risk of developing DTC, which can be useful for elaborating screening policies. Moreover, inherited genetic factors can also impact the final outcome of the disease such as histological subtypes, localization of metastases, or molecular profiling of the tumor, and their characterization can help to predict effectiveness of the initial treatment [120].

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