REVIEW

Genetic Predisposition for Nonmedullary Thyroid Cancer

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Abstract Nonmedullary thyroid cancer (NMTC) can be sporadic or can occur as a component cancer as part of several well-described hereditary cancer syndromes. NMTC, particularly papillary thyroid cancer, also can occur by itself in families and is often termed familial NMTC or familial papillary thyroid cancer. The occurrence of NMTC in families, along with extensive population-based evidence from patients with sporadic thyroid cancer, together suggest that NMTC has a strong genetic component, only a small proportion of which has been characterized to date. Advances in genetic and genomic technology have rapidly advanced our understanding of the complex nature of NMTC susceptibility, although much remains to be explained. Herein, we describe the current state of knowledge, starting with a brief review of hereditary syndromic causes and moving on to describe recent data using modern genomic approaches to identifying genes involved in the predisposition to NMTC.

Introduction

Papillary thyroid carcinoma is the most common form of thyroid cancer, accounting for more than 80 % of cases, and has the most rapidly rising incidence of all cancers in the USA and worldwide [1]. It arises from the follicular cells of the thyroid, which play an important role in iodine metabolism and ultimately thyroid hormone production. Papillary thyroid cancer, follicular thyroid carcinoma, Hürthle cell carcinoma, and their variants are collectively referred to as differentiated thyroid cancer or nonmedullary thyroid cancer (NMTC) [2]. While mortality rates for NMTC are low, the associated morbidity constitutes a significant public health challenge.

The most recognized factor that predisposes to the development of NMTC, particularly PTC, is radiation exposure [3–6]. Although well-defined, this exposure accounts for only a small percentage of clinical NMTCs and most commonly develops through somatically acquired gene translocations that activate oncogenic signaling cascades (reviewed in [7]). For patients without this risk factor, the causative factors leading to NMTC development are incompletely defined. Interestingly, in many populations, one of the strongest risk factors for NMTC is having a family history of the disease [8–12]. In rare instances, NMTC can be seen as a component tumor in several well-defined hereditary cancer syndromes. Alternatively, NMTC can occur by itself in families, a situation termed familial NMTC or FNMTC. The occurrence of NMTC in families, along with the overwhelming evidence from large population-based case control studies and twin studies [8, 10, 13], suggests that NMTC has a strong genetic component, only a small proportion of which has been characterized to date.

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Although the first descriptions of FNMTC date back to the mid 1990s, not much was known about the underlying hereditary causes until very recently. Advances in genetic and genomic technology have rapidly advanced our understanding of NMTC susceptibility, and as highlighted in this review, it is clear that the predisposition to NMTC is highly complex.

Hereditary Syndromes

Nonmedullary thyroid cancer is a feature of several rare hereditary cancer syndromes, including Cowden syndrome, familial adenomatous polyposis (FAP), and Carney complex (CNC) and Werner Syndrome (Table 1). In the following sections, each of these defined tumor syndromes will be briefly described:

Cowden Syndrome

Cowden syndrome (CS) is a multisystem disorder characterized by benign hamartomatous growths of the skin, buccal mucosa and tongue, thyroid, breast, uterine, and colon as well as an increased lifetime risk of several cancers [14, 15]. It has a prevalence of 1/200,000 and is caused by germline mutations in the PTEN gene [16, 17]. Approximately 75 % of individuals with CS will develop benign thyroid disease, most commonly multiple nodules, such as follicular adenomas, or adenomatous goiter. Individuals with CS also have an increased risk for several types of cancer, including nonmedullary thyroid cancer. Although papillary thyroid cancer and follicular variant papillary thyroid carcinoma are commonly diagnosed in individuals with CS, follicular carcinoma is overrepresented to a greater degree when compared to the general background risk [18]. The lifetime risk of NMTC in CS is 3–10 % [14]. Screening recommendations for thyroid cancer in individuals with CS have been developed [14] but are based on expert opinion only.

Familial Adenomatous Polyposis

FAP is characterized by the development of hundreds to thousands of adenomatous polyps throughout the colon and rectum, with an extremely high lifetime risk of colon cancer. It is an autosomal dominant condition caused by germline mutations in the adenomatous polyposis coli (APC) gene and affects about 1 in every 5,000–10,000 people. Several extra-colonic cancers, including NMTC, also occur more commonly in FAP [19, 20]. A rare variant of papillary thyroid carcinoma—referred to as the cribriform morular variant—occurs in approximately 2 % of individuals with FAP [21, 22]. This is more common in female carriers and presents at an average age of 28 years [19, 20]. Based on expert opinion, individuals with FAP are recommended to be screened for thyroid nodules by neck ultrasound at diagnosis and periodically thereafter [23].

Carney Complex

CNC is an autosomal dominant condition caused by mutations in the PRKAR1A gene. It is characterized by pigmented abnormalities of the skin, myxomas, schwannomas, and endocrine tumors [24]. Approximately 75 % of individuals with CNC will have multiple follicular adenomas or other thyroid nodules [25]. Papillary and follicular carcinomas may occur, especially in individuals with a history of thyroid nodules.

Werner Syndrome

Werner syndrome is a rare autosomal recessive disorder caused by mutations in the WRN gene often classified as one of the progeria syndromes associated with premature aging. Clinical features include scleroderma-like skin changes, bilateral cataracts, graying and loss of hair, diabetes mellitus, osteoporosis, atherosclerosis, and an increased risk for several malignancies, including melanoma, meningioma, soft tissue

Table 1 Hereditary cancer syndromes pre-disposing to differentiated thyroid carcinoma

Syndrome	Gene	Thyroid cancer type	Lifetime thyroid cancer risk	Other features
Cowden syndrome	PTEN	FTC, PTC	3–10 %	Breast cancer, endometrial cancer, goiter, macrocephaly, uterine fibroids, colon polyps, and Lhermitte-Duclos disease
Familial adenomatous polyposis	APC	PTC, cribriform morular variant	2 %	Marked colonic polyposis, congenital hypertrophy of the retinal pigment epithelium
Carney complex	PRKAR1A	FTC, PTC	Unknown	Pigmented abnormalities of the skin, myxomas, schwannomas, and endocrine tumors
Werner syndrome	WRN	FTC	Unknown	Scleroderma-like skin changes, bilateral cataracts, graying and loss of hair, diabetes mellitus, and other cancers

sarcoma, leukemia, osteosarcoma, and differentiated thyroid cancer [26, 27], most commonly follicular carcinoma [28].

Familial (Nonsyndromic) Nonmedullary Thyroid Cancer

Although the term FNMTC has been used in the literature for over 20 years, a clear and consistent definition and detailed description is still lacking. Criteria around the required number of affected relatives and their necessary degree of relationship (e.g., first degree, second degree, etc.), the inheritance pattern, histologic subtypes, and the frequency of preexisting or concurrent benign thyroid disease have been widely discussed but have not been universally defined [29–31]. Moreover, screening methods for nodules (e.g., ultrasound) or laboratory evaluations have not been consistently applied in families. Currently, FNMTC is most commonly characterized by at least two or three cases of NMTC in first- or second-degree relatives, typically (but not always) following an autosomal dominant pattern and in the absence of a known hereditary cancer syndrome that would explain the cancer history (e.g., Cowden syndrome) [30]. Papillary thyroid carcinoma is the most common histologic subtype within FNMTC, followed by PTC follicular variant, FTC, and very rarely anaplastic carcinoma. Although other cancers including breast cancer, melanoma, and renal cell carcinoma may be overrepresented within FNMTC families [8, 32], the evidence to support these observations is limited.

Candidate Loci in Multi-Case Families

The hereditary nature of NMTC had been largely under-recognized until the 1990s when several reports of multi-case families were reported in the literature. Moreover, at that time, it was posited that PTCs in individuals with FNMTC were characterized by a more aggressive course than sporadic cases [33–36]. Prior to this, evidence regarding the heritability of NMTC came mostly from twin studies and population-based registry studies [8–13]. Although this evidence was striking, with NMTC showing some of the highest relative risks and standardized incidence ratios of all cancers, reports describing multi-case families were sparse. The first series of published results in the late 1990s/early 2000s described several new loci in relatively small collections of families with two or more cases. In one Canadian family in which two individuals were affected with PTC and 18 individuals with multinodular goiter, a genome-wide search for linkage gave tentative evidence (highest multipoint LOD score 4.88) at 14q32 when all 20 affected individuals were scored as "affected" [37]. In a French family in which three individuals were affected with PTC of the distinct oxyphilic histology and six additional family members had multi-nodular goiter, a multipoint LOD score of 3.01 at 19p13.2 was obtained when

all nine individuals with either PTC or goiter were scored as affected [38]. A large study including 191 members of 80 families recruited world-wide disclosed evidence of linkage to 2q21 (LOD score 3.07), and the proportion of all the families showing linkage to that locus was estimated at 36 % [39]. Analyzing 10 families with NMTC, 9 with the oxyphilic subtype (including the family previously reported in) strengthened evidence of linkage to the 19p locus. Interestingly, all 10 of these families showed evidence of linkage not only to 19p but also to the 2q21 locus as well [39]. Another study of one family in which six members had PTC and two members had renal papillary cancer (one individual had both cancers), an LOD score of 3.58 at 1q21 was obtained for linkage when members with either cancer type were scored as affected [32]. In a report of a Portuguese family with 5 cases of NMTC and an additional 11 cases with benign thyroid disease, linkage to chromosome 8p23.1–p22 was reported (LOD score of 4.41, theta=0.0) [40]. The disease haplotype segregated in 14 of the 16 individuals with benign or malignant thyroid disease and the critical region was narrowed down to a 7.46-Mb region. LOH analysis of tumors from seven family members was negative, and sequencing of 17 of the 32 genes in the linkage region was negative for mutations. Although no gene has been identified to date, the linkage data suggest a candidate gene for PTC and multinodular goiter in the 8p21–22 region. Finally, in a pooled linkage analysis of 38 families, Suh et al. demonstrated linkage to chromosome 1q21 and 6q22 [41]. The SNP in the 1q21 locus is within the same region as that identified in the PTC renal cell carcinoma family described by Malchoff et al. [32], but it is unclear if these represent two distinct loci. Despite these relatively promising findings with several common, but large linkage locations, no genes in these regions of interest have been found to date, almost 15–20 years after publication of the first report. However, these studies support the notion of a multigenic model for NMTC predisposition and provided important clues for future investigation.

Candidate Genes/Mutations

More recent linkage studies have led to the identification of several putative and/or causative genes in a handful of families. He et al. utilized genome-wide linkage to identify two candidate loci at chromosomes 8q24 and 12q14 [42, 43]. The locus at 8q24 produced an NPL score of 7.03 in one large family with multiple cases of papillary thyroid cancer ($n=6$), melanoma ($n=2$), or both ($n=2$). The region of linkage included the thyroglobulin (TG) gene and the Src-like adapter (SLA) gene, the latter being encoded by the antisense strand of 3′ introns of the TG gene. A search for causative mutations including all coding exons of both genes was negative by Sanger sequencing. This highly complex genetic region also contained three noncoding RNA genes residing in the introns of the SLA gene. While no mutations were found in the

noncoding genes, one of the genes is significantly under-expressed in PTC tumor vs. normal thyroid, providing rationale for further analysis of this particular gene.

He et al. also reported linkage to 12q14 in a genome-wide linkage study of 38 families with 2 or more individuals with NMTC [43]. Twenty-one families had an NPL Z-score above 1.0, suggesting possible linkage. These families were investigated further using microsatellite marker genotyping, followed by a targeted association study in two large cohorts of sporadic cases and healthy controls. The SNP showing the highest association (rs2168411) in the microsatellite marker study fell within the linkage region and was located in an intron of the SRGAP1 gene. SRGAP1 regulates the small G-protein CDC42 in a Slit-Robo-dependent manner in neurons and affects cell motility [44]. CDC42 acts as a signal transduction convergence point in intracellular signaling networks, mediates multiple signaling pathways, and plays a role in tumorigenesis. Sequencing of the SRGAP1 gene in the 21 linkage positive families identified 5 different nonsynonymous missense variants in 5 different families. Four of the five mutations segregated with disease, and three were predicted to be disease-causing by in silico models. Functional studies demonstrated subsequently that two of the four variants (Q149H and R617C) decrease the CDC42-GAP activity of SRGAP1, suggesting that they may be the causative mutations for thyroid tumors in these families. The authors suggest that these may represent low penetrance mutations; however, confirmatory studies in additional families have not yet been reported.

In some cases, mutations identified through linkage studies have potential to be highly penetrant and therefore highly predictive of disease in individual families. One such family with 13 cases of nonmedullary thyroid cancer, including two individuals with anaplastic carcinoma, was recently reported to have a point mutation in an enhancer at chromosome 4q32 (4q32A>C) [45]. The enhancer region contained potential binding sites for the POU2F1 and YY1 transcription factors, and functional studies showed decreased levels of enhancer RNA from the 4q32 region in tumor versus normal thyroid as well as decreased transcription in the presence of the POU2F1 and YY1 transcription factors. Although the 4q32A>C mutation appears to be the only highly penetrant mutation known to cause FNMTC to date, it was not found in 38 additional FNMTC kindreds or in over 2,000 sporadic cases of NMTC and 2,000 healthy controls. This suggests that it is an extremely rare or even "private" mutation and is unlikely to be found in other FNMTC kindreds. However, identification of the target(s) of the 4q32 enhancer could elucidate additional pathways in thyroid cancer development in both sporadic and familial cases.

MicroRNA also plays a role in thyroid cancer development, both at the somatic and germline level. MicroRNAs (miRs) are small noncoding RNA molecules that negatively regulate mRNAs at the posttranscriptional level by binding to miR-specific sequences in 5′ untranslated sequences. Thus, each miR downregulates expression of specific proteins. Altered expression and mutations in miRs are known to occur at the somatic level in tumors, and activation and disruption of specific miRs regulate tumor formation and progression. In addition to somatic changes in miRs, a common G/C polymorphism in miR 146a in the germline is associated with predisposition to papillary thyroid cancer [46]. Individuals who are heterozygous have an odds ratio of 1.62 ($p=$ 0.000007), while those who are homozygous for the C or the G allele have low odds ratios suggesting a protective effect. This occurs through production of three different mature miRs in heterozygotes resulting in differential regulation of target genes as compared to homozygotes [47]. Although this SNP has not been implicated in familial NMTC, identification of its targets may prove useful in understanding the underlying genetic mechanisms in both sporadic and familial cases.

Sporadic NMTC

Targeted Association Studies

Another classical approach used to identify susceptibility genes is the association study, in which large cohorts of cases (i.e., patients with NMTC) and controls are genotyped and the frequency of various SNPs is compared between the two groups. SNPs that appear significantly more frequently in cases than in controls can be studied further for possible causation. Several different approaches can be used including a targeted, candidate gene approach or a more broad genome-wide approach (GWAS). The former approach has identified SNPs in multiple genes known to be involved in insulin resistance and obesity [48, 49], thyroid hormone metabolism [50], and other important cellular processes such as DNA damage response [51–56], telomere length and stability [57], autophagy [58], metabolism and detoxification [59], immune function [60], and others, but the findings thus far have been mixed and the odds ratios are small. Several studies have assessed the potential interaction between SNPs and lifestyle factors such as cigarette smoking, but the evidence supporting these associations appears to be relatively weak [61].

Genome-Wide Association Studies

Five GWAS in NMTC have been performed to date [62–66]. Collectively, these studies have uncovered a total of 19 SNPs with odds ratios ranging between 1.16 and 2.09 in combined populations (see Table 2). The associations between NMTC and SNPs at 9q22 and 14q13.3, and to a lesser degree 2q35

Table 2 Thyroid cancer SNPs identified through GWAS

Variant (risk allele), chromosome	Gene(s)	Combined OR (95 % CI)	p value	Reference	Replicated in other populations? (references)
rs965513[A], 9q22.33	FOXE1, XPA, C9orf156, HEMGN	1.75 (1.59, 1.94)	1.7×10^{-27}	[61]	Yes (60, 62, 64–69)
rs944289[T], 14q13.3[a]	NKX2-1, BRMS1L, MBIP, SFTA3	1.37 (1.24, 1.52)	2.0×10^{-9}	[61]	Yes (60, 62, 64–69)
rs966423[C], 2q35[b,c]	DIRC3	1.34 (1.22, 1.47)	1.3×10^{-9}	[60]	Yes (62, 63, 65)
rs2439302[G], 8p12[c]	NRG1	1.36 (1.23, 1.50)	2.0×10^{-9}	[60]	Yes (60, 65)
rs116909374[T], 14q13.3[a]	MBIP, NKX2-1	2.09 (1.68, 2.60)	4.6×10^{-11}	[60]	No
rs11823005 [C], 11q25	SNX19	1.35 (1.12–1.62)	1.7×10^{-3}	[62]	No
rs6759952 [T], 2q35[b]	DIRC3	1.30 (1.18–1.43)	7.3×10^{-8}	[62]	No
rs10238549 [C], 7q21	IMMP2L	1.27 (1.15–1.40)	4.1×10^{-6}	[62]	No
rs7800391 [T], 7q21	IMMP2L	1.25 (1.14–1.38)	5.7×10^{-6}	[62]	No
rs7617304 [A], 3q25.32[c]	RRARES1	1.25 (1.12–1.39)	4.6×10^{-5}	[62]	No
rs10781500 [C], 9q34.3	SNAPC4	1.23 (1.12–1.36)	3.5×10^{-5}	[62]	No
rs2633322 [C], 10q22	PLAU	1.21 (1.06–1.38)	5.3×10^{-3}	[62]	No
rs9951245 [G], 18q22	GTSCR1	1.20 (1.09–1.33)	9.8×10^{-4}	[62]	No
rs7267944[C] 20q12	DHX35	1.32 (1.20–1,46)	1.34×10^{-8}	[63]	No
rs10136427[C] 14q24	BATF	1.30 (1.17–1.44)	9.30×10^{-7}	[63]	No
rs1159444 [T], 3p22	GPD1L	1.23 (1.09–1.39)	9.13×10^{-4}	[63]	No
rs13184587[G] 5q13-14c	ARSB	1.17 (1.07–1.27)	7.16×10^{-4}	[63]	No
rs2245026[G] 13q21-22	DACH1	1.17 (1.06–1.30)	2.09×10^{-3}	[63]	No
rs1220597[C] 13q11c	SPATA13	1.16 (1.07–1.25)	2.64×10^{-4}	[63]	No
rs2281016[A] 1q23-24	TIPRL	1.16 (1.06–1.27)	2.03×10^{-3}	[63]	No

[a] The 14q13.3 SNPs rs966423 and rs116909374 are in separate linkage disequilibrium regions and associations at each SNP remained significant after controlling for the other

[b] The 2q35 SNPs rs966423 and rs6759952 are within the same linkage disequilibrium region and likely represent one association signal

[c] Intragenic SNPs

and 8p21, have been replicated in several unique thyroid cancer populations [66–71] and confirmed through meta-analyses [72, 73], while confirmation of the remaining SNPs is currently lacking, mainly due to their recent description. Key findings from these GWAS and notable follow-up studies are summarized below.

The first GWAS in differentiated thyroid cancer was published in 2009 and utilized an Icelandic population of 192 cases and 37,196 controls followed by replication studies in individuals of European ancestry [63]. Two variants, one at 9q22 (rs965513) and the other at 14q13.3 (rs944289), showed a significant association with DTC with odds ratios of 1.75 ($p=1.7\times10-27$) and 1.37 ($p=2.0\times10-9$), respectively. Interestingly, both SNPs are located near genes with well-known biological function in the thyroid gland: FOXE1 (also known as thyroid transcription factor 1 or TTF-1) on 9q22.33 and NKX2-1 (also known as thyroid transcription factor 2 or TTF-2) on 14q13.3. A separate analysis of these SNPS in ~12,000 Icelanders without thyroid cancer showed that both alleles were also associated with low TSH levels. A second GWAS

focusing on radiation-induced papillary thyroid cancer confirmed the association with the 9q22 SNP rs965513 [66].

Two follow-up studies of the 14q13.3 region have been done in an attempt to characterize the mechanism of thyroid cancer predisposition due to the FOXE1 locus. Landa et al. performed a targeted association study using SNPs within the FOXE1 region and identified a functional SNP rs1867277 with an OR of 1.49 that affects transcriptional regulation of the FOXE1 gene [74]. In 2012, Jendrzejewski et al. identified a long intergenic noncoding RNA gene (lincRNA) called PTCSC3 ~3.2 kb downstream of the original 14q13 SNP rs944289 [75]. PTCSC3 is expressed in the thyroid and expression is strongly downregulated in thyroid tumors compared to normal thyroid tissue. Normal expression of the PTCSC3 gene in thyroid cancer cell lines results in inhibition of cell growth and affects expression of genes involved in key cellular processes such as DNA replication, recombination and repair, and cell death. The authors suggest that the PTCSC3 gene is an important tumor suppressor gene in thyroid cancer, although many questions as to the

mechanism through which PTCSC3 influences thyroid cancer development remain. Although it appears that the FOXE1 locus plays a role in the susceptibility to thyroid cancer, the mechanism through which it acts appears quite complex and may involve more than one gene.

A third GWAS in 2011 was designed to further focus on the potential association with TSH level and PTC suggested in the prior study described above [62]. This new study took a novel approach, using whole-genome sequencing data from 475 Icelanders and imputing ~16 million SNP genotypes into 27,758 individuals without thyroid cancer who had TSH measurements [64]. The initial associations with TSH were then compared to associations in previously genotyped individuals with NMTC. SNPs within close proximity or in regions of overlap in the two groups were studied further. Strong association with the previously identified 9q22 locus was confirmed but not studied further. Five additional SNPs were then studied in three separate case-control groups of individuals of European descent from the Netherlands, USA, and Spain. Importantly, three alleles remained significant in all three validation cohorts. These were rs966423 on 2q35, rs2439302 on 8p12, and rs116909374 on 14q.13.3. These three SNPs had odds ratios ranging between 1.34 and 2.09 in the combined populations, and all were highly statistically significant. The rs116909374 SNP at 14q13.3 is in a separate linkage disequilibrium region from the previously identified 14q13 SNP rs944289, and associations at each SNP remained significant after controlling for the other, suggesting unique associations. Genes closest to these SNPs include the DIRC3 gene at 2q35, the NRG1 gene at 8p12, and the MBIP and NKX2-1 genes on chromosome 14q13. To date, limited functional data is available for these loci.

Two more recent GWAS in several large Italian cohorts have both confirmed previous associations and identified several new promising SNPs [64, 65]. The first study in an Italian population with a high incidence of thyroid cancer confirmed the association with the 9q22 NKX2-1 locus [64]. The remaining eight most significant associations in this cohort also included the previously described 2q35 locus. Validation studies for the eight SNPs were first replicated in two additional Italian populations and then in three lower-incidence populations from the UK, Poland, and Spain. Combined analysis of all populations confirmed the association for rs6759952 (DIRC3) on 2q35 but not for the other seven loci. The analysis of the Italian cohorts alone, however, showed suggestive associations with rs7617304 (within the RARRES1 gene) on 3q25.32, rs10238549 and rs7800391 (near the IMMP2L gene) on 7q21, and rs10781500 (near the SNAPC4 gene) on 9q34.3 [64]. A second report from this same high incidence Italian population investigated an additional 45 SNPs that were identified through the first Italian GWAS [65]. This provided evidence of association with rs10136427 near BATF (OR=1.40, p value=4.35×10−7)

and rs7267944 near DHX35 (OR=1.39, p value=2.13×10−8). A possible role in the Italian populations was also found for rs13184587 (ARSB, p value=8.54×10−6) and rs1220597 (SPATA13, p value=3.25×10−6). Only the associations between rs10136427 and rs7267944 and DTC risk were replicated in the Polish and the Spanish populations with little evidence of population heterogeneity (GWAS and all replications combined, OR=1.30, p value=9.30×10−7 and OR=1.32, p value=1.34×10−8, respectively). In silico analyses on several of these variants suggest a possible role in thyroid cancer predisposition, but functional studies have not yet been reported.

Conclusions

Although great strides have been made over a very short period of time, much remains to be discovered with regard to the inherited causes of NMTC, particularly for the majority of patients with sporadic disease. Taken together, the results of the aforementioned studies suggest the following: (1) The predisposition to nonmedullary thyroid cancer is extremely complex and is most likely due to multiple low to moderate risk mutations, with the exception of rare families with very high disease prevalence. Early evidence suggests that in the sporadic population, these SNPs may interact with each other in a cumulative manner [76, 77]. However, it is unclear how such a mechanism might work in familial cases, since various mutations and SNPs would presumably segregate independently through a family. It is possible that in NMTC families, a single gene mutation of moderate penetrance is the main driver of risk, and the presence of additional but different modifier genes or environmental factors is required for thyroid cancer to develop. These complexities will make predictive testing for differentiated thyroid cancer susceptibility difficult as genetic testing for certain mutations may not be informative for all individuals and families. (2) Many of the genes identified to date are regulatory in nature (e.g., noncoding RNA genes) which has implications regarding future gene discovery approaches; for example, gene hunting approaches that utilize whole exome sequencing will not detect these mutations; (3) additional loci are likely to be identified, but not all of these loci and the mutations within them are likely to account for a significant proportion of the disease. This is especially relevant for those SNPs or mutations identified in a small proportion of familial cases or through targeted association studies rather than through GWAS, as they may be extremely rare in the larger population with sporadic thyroid cancer. As more variants are identified, predictive models for clinical use can be developed. Several groups have tested this approach using the SNPs located at 2q35,

8p12, 9q22.0 and the two SNPs at 14q13.3 with mixed results [76, 77]. It is likely, however, that an adequate number of SNPs will eventually be identified for such models to be useful in risk predictions and genetic counseling in clinical practice.

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