

Original article

Integrated analysis of bioinformatic databases to identify thyroid cancer drug target candidates

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Abstract

Background: Thyroid cancer is an endocrine malignancy whose global incidence continues to rise. Although it generally has a favourable prognosis, aggressive subtypes, such as anaplastic thyroid cancer, remain a therapeutic challenge. Drug repurposing strategies offer the opportunity to accelerate the development of therapies by utilising available drugs with an established safety profile.

Objectives: This study aimed to identify candidate thyroid cancer risk-associated genes by analyzing GWAS and PheWAS data and to evaluate their potential therapeutic relevance through drug recycling.

Methods: Significant gene variants were obtained from these databases and functionally annotated using HaploReg, ClinVar, SIFT, PolyPhen, CADD, cis-eQTL, and a review of PubMed literature. Candidate genes from seven functional annotations with scores ≥ 2 were designated as risk-associated and further analyzed using the STRING database. Drug candidates were searched for in DrugBank and ClinicalTrials.gov.

Results: Ten risk-associated genes may be involved in thyroid cancer pathogenesis, with *DIRC3* having the highest score. However, no drugs that could directly interact with these genes were recognized. These findings highlight the therapeutic gap between thyroid cancer risk-associated genes and available drugs.

Conclusion: This study identified ten risk genes involved in thyroid cancer pathogenesis, with *DIRC3* as the topmost candidate. Although no approved drugs directly targeted these genes, the findings highlight their potential as biomarkers and novel therapeutic targets. Integrative genomics and drug repurposing approaches remain promising strategies for advancing precision therapy in thyroid cancer.

Keywords: Bioinformatics, drug repurposing, GWAS, PheWAS, thyroid cancer.

Thyroid cancer (TC) is one of the most common cancers of the endocrine system ^(1, 2) and most frequently diagnosed cancers among individuals aged 15–29 years.⁽³⁾ Over the past four decades, the incidence of thyroid cancer has been increasing, with

821,214 new cases and 47,507 deaths reported globally.⁽⁴⁾ Women are ~3 times more prone to TC than men.⁽⁵⁾ Thyroid cancer is of three main histological types: differentiated (papillary and follicular), undifferentiated (poorly differentiated and anaplastic), and medullary.⁽⁶⁾ Major risk factors include radiation exposure, genetic predisposition, and family history.⁽⁷⁾

Treatment choice is determined by type and stage. Surgical removal of the thyroid gland remains the primary approach for most cases.⁽⁸⁾ Certain antidiabetic drugs are the focus of studies regarding thyroid cancer therapy, given that they show potential

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antitumor effects.⁽⁹⁾ Most patients with thyroid cancer have a good prognosis, especially if detected early and treated promptly. However, aggressive types such as anaplastic thyroid cancer have a very low survival rate, suggesting an urgent need for more effective therapeutic strategies, and regular follow-up is essential to monitor for signs of recurrence.⁽¹⁰⁾ The application of bioinformatics and artificial intelligence (AI) in biomarker analysis is expanding. These approaches enable deciphering complex bionetworks and predicting treatment outcomes by integrating genome-wide association study (GWAS) catalogs.^(11, 12) Big data analysis can identify potential biomarkers, providing more complete information for thyroid cancer therapy.⁽¹³⁾

These susceptibility genes and associated variants may play an important role in thyroid cancer to discover novel drug-target and drug-phenotype associations.⁽¹⁴⁾ Genome sequencing has provided valuable information to help identify variants that determine the success of chemotherapy and potentially treatable targets.⁽¹⁵⁾ Observational studies are prone to residual confounding factors, reverse causality, and bias, which can jeopardize causal inference. Drug repurposing is gaining promise as a productive approach to drug discovery⁽¹⁶⁾ as it provides a new way of reexploring available drugs. The reuse of approved drugs for new indications offers a great opportunity to accelerate the development of novel thyroid cancer therapies.⁽¹⁷⁾ Drug repurposing has several inherent advantages in the context of cancer treatment, as such medicines are usually cost-effective, proven safe, and can markedly accelerate drug development due to their established safety profile.⁽¹⁸⁾ This technique reduces the cost and time of drug innovation, but also capitalizes on the proven safety of the drug.⁽¹⁹⁾

Materials and methods

Identification of genetic variants associated with thyroid cancer

This study utilized the GWAS (<https://www.ebi.ac.uk/gwas/>) and PheWAS (<https://phewascatalog.org/>) databases to identify gene variants (SNPs) associated with thyroid cancer. GWAS data were obtained from studies specifically investigating thyroid cancer to ensure disease relevance. For PheWAS, variants associated with multiple diseases were initially collected

and subsequently filtered to retain only those relevant to thyroid cancer based on phenotype associations and literature.

SNPs derived from GWAS and PheWAS were statistically evaluated by applying genome-wide thresholds of $P < 10^{-8}$ for GWAS and $P < 4.6 \times 10^{-6}$ (FDR < 0.1) for PheWAS. Eligible variants were then analyzed using the HaploReg v4.2 tool (<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) with an $r^2 > 0.8$, with focus on identifying SNPs with missense mutations. Such mutations were prioritized because they alter amino acid sequences, potentially affecting protein structure and function and contributing to disease development; in comparison, synonymous mutations generally do not change protein function. However, other types of variants, such as regulatory or synonymous ones, may still play indirect roles and were partially captured through cis-eQTL analysis and other functional annotation criteria.

Identification of thyroid cancer risk genes

Candidate thyroid cancer risk genes were identified based on seven functional annotation criteria, and genes meeting ≥ 2 requirements (scores ≥ 2) were designated as risk genes. Each gene was evaluated based on the following annotations- 1) missense variants, in which thyroid cancer-associated SNPs annotated as missense mutations were obtained from HaploReg v4.2; 2) cis-expression quantitative trait loci (cis-eQTL), in which SNPs showing significant cis-eQTL effects in thyroid tissues were considered; 3) protein damage prediction by SIFT⁽²⁰⁾, in which missense variants predicted to be deleterious were assigned one point; 4) protein damage prediction by PolyPhen-2, in which variants probably or possibly damaging were considered; 5) genomic deleteriousness assessed by Combined Annotation Dependent Depletion scores, with high values indicating potential pathogenic impacts; 6) clinical significance from the ClinVar database⁽²¹⁾, in which variants reported as pathogenic or likely pathogenic were included; and 7) supporting evidence from PubMed-indexed literature linking the gene to thyroid cancer. Each gene was scored based on the number of criteria fulfilled, with possible scores ranging from 0 to 7. Genes with a score ≥ 2 were prioritized as thyroid cancer risk genes.^(22, 23) The overall workflow of this prioritization process is illustrated in **Figure 1**.

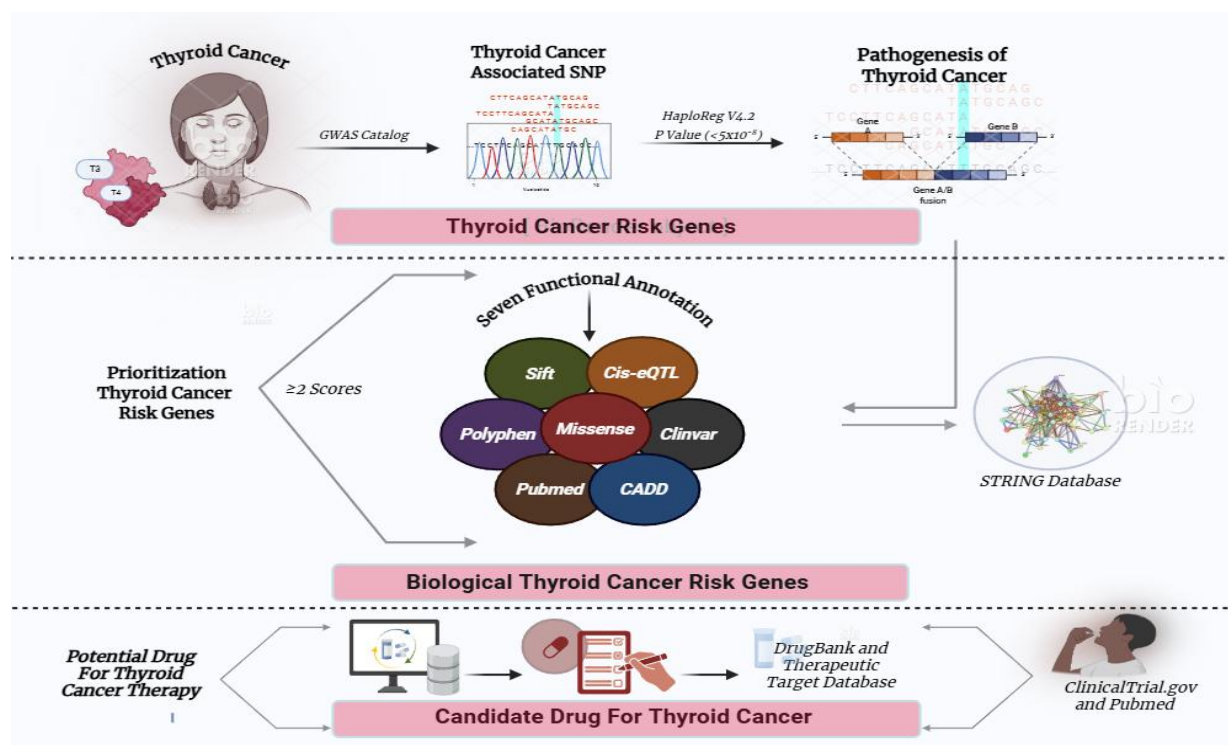


Figure 1. Bioinformatics workflow for systematic drug repurposing using genomic database in thyroid cancer.

STRING database

The STRING database (<http://string-db.org>) was used to integrate information on the functional associations of proteins expressed by organizing predicted protein–protein interaction data (**Figure 1**). Most protein networks involved in the pathogenesis of various diseases are potential therapeutic targets.⁽²⁴⁾ In thyroid cancer, risk genes were further analyzed through the STRING database to obtain additional candidate drug targets. This step reinforces the potential of thyroid cancer genomic data in elucidating risk genes involved in disease pathogenesis.⁽²⁵⁾

Drug candidates for thyroid cancer

To determine candidate therapeutic targets in thyroid cancer, the DrugBank (<https://go.drugbank.com/>) and Therapeutic Target Database (<https://db.idrblab.net/>) databases were utilized and linked to other sources, including PharmGKB (<https://www.pharmgkb.org/>). The next step was to thoroughly evaluate the identified drugs by reviewing clinical trials recorded in ClinicalTrials.gov (<https://clinicaltrials.gov/>) and PubMed (<https://pubmed.ncbi.nlm.nih.gov/>). This process not only comprehensively assessed drug candidates but also enabled an integration of relevant clinical trial data into research analysis (**Figure 1**).

Results

Identification of genetic variants associated with thyroid cancer

This study identified 121 SNPs associated with thyroid cancer through the GWAS Catalog (accessed on June 19, 2025) and PheWAS (accessed on June 20, 2025) databases. These SNPs were statistically evaluated, applying a genome-wide significance threshold of $P < 10^{-8}$ for GWAS and $P < 4.6 \times 10^{-6}$ (FDR < 0.1) for PheWAS. Then, after removing duplications⁽²⁶⁾, 47 SNPs remained for further analysis employing HaploReg v4.1.

Identification of genes associated with thyroid cancer

We applied seven functional annotations to prioritize thyroid cancer risk genes. The results were as follows– 1) genes with cis-eQTL effects ($n = 21$); 2) genes containing missense variants annotated in HaploReg ($n = 1$); 3) genes with deleterious missense variants predicted by SIFT ($n = 1$); 4) genes with missense variants recognized as probably damaging by PolyPhen ($n = 1$); 5) genes carrying variants with high CADD scores ($n = 1$); 6) genes with clinical evidence from ClinVar ($n = 2$); and 7) genes supported by PubMed-indexed literature ($n = 19$). Based on integration across all annotations, one missense gene fulfilled stringent bioinformatics requirements (**Table 1**). In total, genes with a score ≥ 2 were designated as thyroid cancer risk genes for downstream analysis.

Table 1. Biological thyroid cancer risk genes based on seven functional annotations.

Gen Code Id	Nama Gen	SNPS	P-value	Missense	Sift	PolyPhen	Pubmed	CADD	Clinvar	Cis-eQTL	Total Score
ENSG00000231672	<i>DIRC3</i>	rs6793295	3.00E-08	1	1	1	1	1	0	1	6
ENSG00000065413	<i>ANKRD44</i>	rs2289261	3.00E-09	0	0	0	1	0	1	1	3
ENSG00000236130	<i>PTCSC2</i>	rs3802160	2.00E-40	0	0	0	1	0	0	1	2
ENSG00000236130	<i>PTCSC2</i>	rs965513	6.00E-40	0	0	0	1	0	0	1	2
ENSG00000260677	<i>XPA</i>	rs925489	9.00E-35	0	0	0	1	0	0	1	2
ENSG00000129595	<i>EPB41L4A</i>	rs368187	5.00E-23	0	0	0	1	0	0	1	2
ENSG00000135749	<i>PCNX2</i>	rs56062135	5.00E-09	0	0	0	1	0	0	1	2
ENSG00000231672	<i>DIRC3</i>	rs11175834	4.00E-08	0	0	0	1	0	0	1	2
ENSG00000135749	<i>PCNX2</i>	rs4915076	7.00E-08	0	0	0	1	0	0	1	2
ENSG00000135749	<i>PCNX2</i>	rs2439302	2.00E-09	0	0	0	1	0	0	1	2
ENSG00000236130	<i>PTCSC2</i>	rs16857609	1.00E-57	0	0	0	1	0	0	0	1
ENSG00000257585	<i>LINC00609</i>	rs11693806	2.00E-24	0	0	0	1	0	0	0	1
ENSG00000157168	<i>NRG1</i>	rs7734992	4.00E-17	0	0	0	0	0	1	0	1
ENSG00000166949	<i>SMAD3</i>	rs116909374	1.00E-16	0	0	0	1	0	0	0	1
ENSG00000236130	<i>PTCSC2</i>	rs6996585	9.00E-12	0	0	0	1	0	0	0	1
ENSG00000231672	<i>DIRC3</i>	rs12129938	4.00E-11	0	0	0	1	0	0	0	1
ENSG00000151332	<i>MBIP</i>	rs7902587	5.00E-11	0	0	0	1	0	0	0	1
ENSG00000157168	<i>NRG1</i>	rs6759952	6.00E-10	0	0	0	1	0	0	0	1
ENSG00000107960	<i>STN1</i>	rs966423	1.00E-09	0	0	0	1	0	0	0	1
ENSG00000246526	<i>LINC02481</i>	rs4649295	6.00E-08	0	0	0	1	0	0	0	1
ENSG00000157168	<i>NRG1</i>	rs13290258	1.00E-47	0	0	0	0	0	0	1	1
ENSG00000257826	<i>BRMS1L</i>	rs7030280	5.00E-28	0	0	0	0	0	0	1	1
ENSG00000178919	<i>FOXE1</i>	rs8020481	6.00E-21	0	0	0	0	0	0	1	1
ENSG00000157168	<i>NRG1</i>	rs73227498	1.00E-18	0	0	0	0	0	0	1	1
ENSG00000157168	<i>NRG1</i>	rs10122541	1.00E-17	0	0	0	0	0	0	1	1
ENSG00000242268	<i>LINC02082</i>	rs7037324	1.00E-17	0	0	0	0	0	0	1	1
ENSG00000260876	<i>LINC01229</i>	rs2466076	2.00E-17	0	0	0	0	0	0	1	1
ENSG00000157168	<i>NRG1</i>	rs2466074	5.00E-11	0	0	0	0	0	0	1	1
ENSG00000236130	<i>PTCSC2</i>	rs139566210	3.00E-10	0	0	0	0	0	0	1	1
ENSG00000221706	<i>LOC100130231</i>	rs17767383	2.00E-09	0	0	0	0	0	0	1	1
ENSG00000231672	<i>DIRC3</i>	rs17767904	6.00E-09	0	0	0	0	0	0	1	1
ENSG00000171757	<i>LRRC34</i>	rs1588635	2.00E-58	0	0	0	0	0	0	0	0
ENSG00000136932	<i>TRMO</i>	rs57481445	9.00E-21	0	0	0	0	0	0	0	0
ENSG00000166949	<i>SMAD3</i>	rs9642727	4.00E-17	0	0	0	0	0	0	0	0
ENSG00000260876	<i>LINC01229</i>	rs9971770	3.00E-16	0	0	0	0	0	0	0	0
ENSG00000250748	<i>MSRB3-AS1</i>	rs13295081	3.00E-15	0	0	0	0	0	0	0	0
ENSG00000134215	<i>VAV3</i>	rs2618148	5.00E-12	0	0	0	0	0	0	0	0
ENSG00000231672	<i>DIRC3</i>	rs10786774	1.00E-11	0	0	0	0	0	0	0	0
ENSG00000231672	<i>DIRC3</i>	rs142700723	3.00E-11	0	0	0	0	0	0	0	0
ENSG00000164362	<i>TERT</i>	rs191643749	4.00E-11	0	0	0	0	0	0	0	0
ENSG00000250748	<i>MSRB3-AS1</i>	rs12130559	2.00E-10	0	0	0	0	0	0	0	0
ENSG00000231672	<i>DIRC3</i>	rs12990503	3.00E-10	0	0	0	0	0	0	0	0
ENSG00000107960	<i>STN1</i>	rs149128637	3.00E-09	0	0	0	0	0	0	0	0
ENSG00000231672	<i>DIRC3</i>	rs16857611	2.00E-08	0	0	0	0	0	0	0	0
ENSG00000166292	<i>TMEM100</i>	rs9858271	3.00E-08	0	0	0	0	0	0	0	0
ENSG00000242545	<i>FHIT</i>	rs11947482	6.00E-08	0	0	0	0	0	0	0	0
ENSG00000111058	<i>ACSS3</i>	rs78752938	7.00E-08	0	0	0	0	0	0	0	0

Identification of thyroid cancer biological risk genes was performed using seven predefined functional annotations. Genes with an accumulated score ≥ 2 were categorized as risk genes potentially involved in the pathogenesis of thyroid cancer. Based on the results, ten thyroid cancer risk genes were obtained, with scores of 2 (n = 8), 3 (n = 1), and 6 (n = 1). The scoring reflects the biosignificance level of each gene. The higher the score, the stronger the bioinformatic and clinical evidence supporting the gene's involvement in thyroid cancer. Thus, genes with the maximum scores can be prioritized as prime candidates for further study, as diagnostic biomarkers and potential therapeutic targets in new drug development.⁽²⁷⁾

Risk expansion analysis of thyroid cancer biology through the STRING database

Using the STRING database, we expanded the list of thyroid cancer risk genes to enhance the likelihood of identifying potential drug targets. This analysis recognized 47 genes (**Table 1**), which were subsequently prioritized as candidate drug targets for further investigation.

Therapeutic candidates for thyroid cancer

At this stage, we searched for therapeutic target genes and candidate drugs interacting with them using

DrugBank and TTD. We identified two compounds, amphetamine and methamphetamine, from drug databases as interacting with thyroid cancer-related pathways; however, they are not clinically approved or validated as therapeutic agents for thyroid cancer (**Figure 2**). Based on the research findings of Fleischer LM, *et al.* (2018), the role of trace amine-associated receptor 1 (TAAR1) receptors is activated by amphetamine.⁽²⁸⁾ They noted that long-term amphetamine use is associated with an increased risk of several cancers (e.g., lymphoma).⁽²⁹⁾ In contrast, the endogenous ligand of TAAR1, namely T1AM, shows antiproliferative activity against cancer cells: *in vitro* incubation of T1AM with MCF7 or HepG2 cells reduces cell proliferation.⁽²⁹⁾ In other words, while amphetamine (TAAR1 agonist) can be a potential cancer-promoting ligand, a similar ligand (T1AM) derived from thyroid hormone was active against cancerous cell models.

Thus, the identified risk genes can be more appropriately regarded as potential biomarkers or novel therapeutic targets, requiring further validation through experimental studies and clinical trials. These findings also underscore the importance of exploring innovative therapeutic strategies targeting key molecular pathways of thyroid cancer to advance the development of precision therapies.

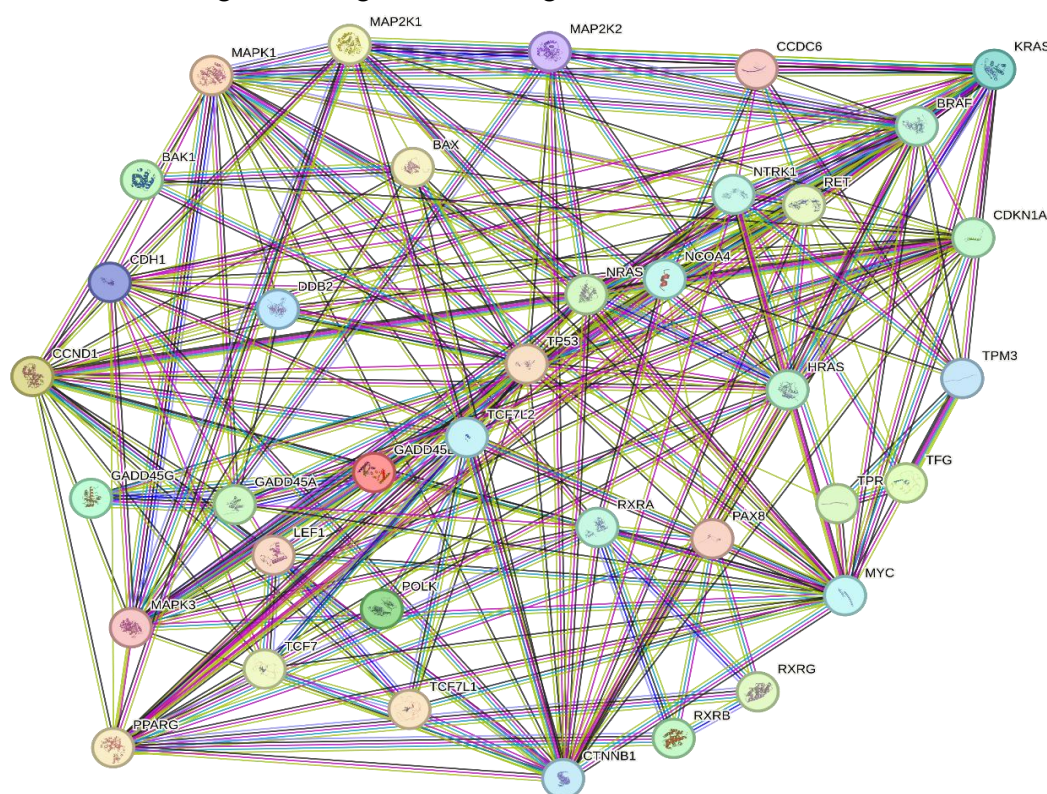


Figure 2. Network illustrating interactions between thyroid cancer risk genes and candidate drug compounds

Discussion

Drug repurposing in oncology offers great potential, as already approved drugs can be more quickly and economically adapted for new indications. Repurposed drugs are safe and can speed up the drug development process, as their toxicity profile is known.⁽³⁰⁾ Thyroid cancer was explored using this approach; for example, several studies have highlighted the anticancer impacts of antidiabetic drugs on thyroid cancer. Greco, *et al.* reported that biguanides (e.g., metformin), DPP-4 inhibitors, and thiazolidinediones exhibited multifaceted antithyroid cancer effects. These findings suggest that antidiabetic drugs may provide novel therapeutic opportunities by promoting apoptosis, inhibiting metastasis, and modulating the tumor microenvironment. This approach is relevant to the finding that thyroid cancer cells are often metabolically disrupted (Warburg effect); thus, inhibiting metabolic pathways by using antidiabetic drugs *via* AMPK activation or *via* glucose uptake can trigger cancer cell death and decrease tumor aggressiveness.⁽³¹⁾

Identifying drug candidates through a specific protein target approach offers several advantages. It enables a clearer understanding of the pharmacological mechanism of action, pharmacokinetic profile, metabolic pathways, and potential side effects. Novel drug discovery strategies can be directed towards three main aspects: drug-, disease-, and therapy-oriented. In this study, the focus was on a disease-oriented approach, utilizing the mechanisms of specific genes as the main targets for developing new drug candidates.⁽³²⁾

The main systemic therapy for radioiodine-resistant (RAI-refractory) differentiated thyroid cancer (DTC) is multitargeted tyrosine kinase inhibitors. The drugs lenvatinib and sorafenib, which prolong progression-free survival in RAI-refractory DTC, were selected.⁽³³⁾ We ensured the sensitivity of the results by setting a biological score threshold of ≥ 2 , to screen more genes as thyroid cancer genes, and thus can be considered as drug target candidates. Amphetamine and methamphetamine were identified from drug databases as interacting with thyroid cancer-related pathways; however, there is no clinical or preclinical evidence supporting their use as therapeutic agents in thyroid cancer. Importantly, their identification reflects the potential involvement of the TAAR1 signaling pathway rather than a direct therapeutic applicability. Therefore, future studies should focus on identifying safer and more selective modulators targeting this pathway. Existing studies

provide evidence of the adverse effects and potential cancer-promoting properties of amphetamine. Some bioinformatics and molecular evidence (TAAR1 pathway) suggests a link between amphetamine-like ligands (e.g., 3-iodothyronamine) and suppression of cancer cell growth; however, this effect is associated with thyroid hormone derivatives rather than amphetamine itself.⁽³⁴⁾ Thus, amphetamine/methamphetamine are not currently considered a therapeutic candidate for thyroid cancer, and further studies are needed to explore similar molecules that may have anticancer impacts. Methamphetamine hydrochloride is an FDA-approved drug for the long-term treatment of attention deficit hyperactivity disorder (ADHD) and the short-term treatment of exogenous obesity; however, its use for obesity is extremely restricted due to prominent risks and safety concerns. During a 15-month randomized controlled trial, amphetamine demonstrated marked reductions in non-attentiveness, hyperactivity, and disruptive behaviors compared with placebo. Furthermore, a meta-analysis of several randomized controlled trials in adults with ADHD confirmed that amphetamines improved ADHD symptoms in the short term compared with placebo.⁽³⁴⁾

Certain genetic mutations have long been associated with thyroid cancer. The BRAF V600E mutation in papillary thyroid carcinoma (PTC) has a prevalence of 29.0%–69.0%. In addition, RAS mutations—especially in 10.0%–20.0% of follicular variant PTC cases—and PAX8–PPAR γ fusions frequently found in follicular thyroid carcinoma also suggest a vital role in thyroid tumorigenesis.⁽³⁵⁾ To uncover additional potentially undetectable risk genes through conventional analyses, integrative bioinformatics approaches are being widely used. Yu, *et al.* (2024) utilized gene expression data from patients with thyroiditis and thyroid cancer and combined it with bioinformatics-based functional annotation.⁽³⁶⁾ Using a six-category annotation scoring system—including knockout mouse phenotype data, KEGG pathway analysis, and Gene Ontology classification—they prioritized candidate genes and identified four key genes—*CXCR4*, *IL6ST*, *PPARG*, and *TP53*—with robust evidence of a role in thyroid cancer pathogenesis.⁽³⁶⁾

Overall, although drug repositioning strategies in thyroid cancer are still at an early stage of innovation, integrated approaches based on genomic data and AI play a crucial role in uncovering hidden targets. The combination of evidence from population, molecular biology, and computational studies allows mapping of

indirectly connected pathways to thyroid cancer risk genes. This ability, along with the exploration of antidiabetic and other non-oncology drugs, opens up new therapeutic opportunities. However, each repurposed candidate still needs to undergo thorough pre-clinical and clinical validation, given the pharmacological and regulatory challenges. Additionally, not all identified genes are targetable or exhibit pharmacological activity with a profile suitable for clinical use. Therefore, some of the identified genes may lose their potential druggability for certain diseases. With continued research efforts, repositioning strategies may complement the therapeutic arsenal of thyroid cancer, especially for patients with advanced disease or who are resistant to standard therapies. Preclinical and clinical validation is crucial to ascertain whether these drug candidates produce the desired interactions, cause unexpected side effects, or even provide suboptimal effects. The relationship between thyroid cancer risk genes and currently used drugs is illustrated in **Figure 3**. This network underscores the lack of direct interactions between identified genes and existing therapies, supporting the presence of a therapeutic gap (**Figure 3**).

Conclusion

This study identified ten thyroid cancer risk-associated genes that may play a role in pathogenesis, with *DIRC3*

emerging as the top candidate. STRING network expansion further revealed additional genes with such potential. However, no clinically validated drugs directly targeted these genes, highlighting a therapeutic gap. These genes can therefore be considered potential biomarkers and novel therapeutic targets, requiring further validation through preclinical and clinical studies. Integrative genomics and drug repurposing approaches remain promising pathways for advancing precision therapy in thyroid cancer.

Author contributions

DR and LMI contributed substantially to data acquisition, literature review, and analysis and interpretation of data. DR, PPSA, RY, SW, WA, BCW, RDS, DD, BHR, RC, IA, and PTP contributed substantially to data acquisition. DR, LMI, and WA contributed to drafting the manuscript. LMI and WA critically revised the manuscript for scientific content. All authors approved the final version submitted for publication and take responsibility for statements made in the published article.

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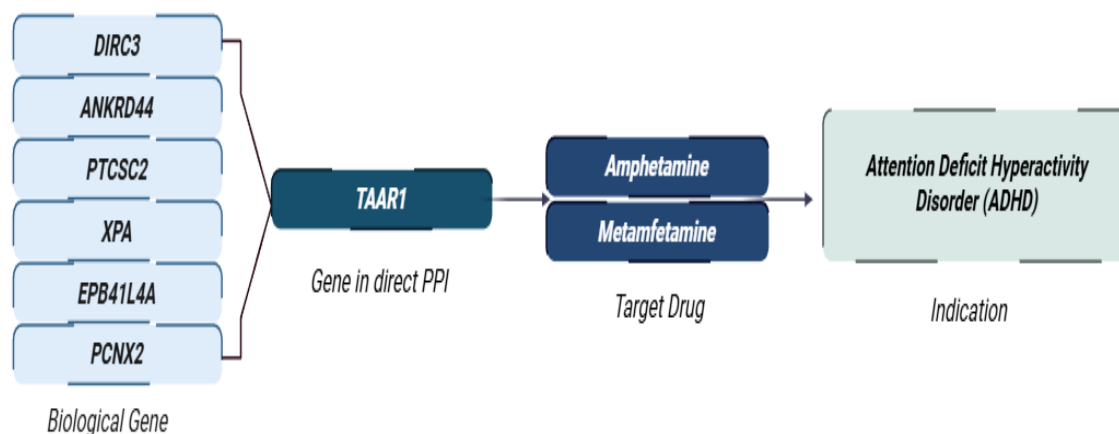


Figure 3. Linkage of thyroid cancer risk genes with drugs used in thyroid cancer clinical therapy.

Conflict of interest statement

All authors declare no conflicts of interest.

Data sharing statement

All data generated or analyzed during the study are included in the article. For non-commercial purposes, further details can be provided by the corresponding author on reasonable request.

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