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Unveiling the molecular landscape: Advanced gene expression analysis identifies novel biomarkers for thyroid cancer

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Abstract

Thyroid cancer cases increased rapidly in the past years. Treatments and clinical management depend on the full understanding of the cancer staging, types, histology, along with possible causes. Presently, public data sources including NCBI GEO provide high-throughput datasets that highlights various aspects of certain diseases and health conditions. Therefore, computational analysis of public gene expression datasets became of high importance where gene expression studies can suggest novel biomarkers. Methods: In this work, we analyzed 6 human NCBI gene expression datasets that covers different aspects of thyroid cancer aiming to identify gene expression signatures associated with thyroid cancer prognosis. Initially, we analyzed 3 thyroid cancer datasets focusing on radiation exposure with samples acquired from the Chernobyl Tissues Bank. Next, we analyzed advanced datasets that labels tumor samples according to gender, tumor stage, and malignancy potential. Finally, we incorporated the uncovered differentially expressed genes in intensive enrichment analysis of biological processes and pathways. Results: We identified many signatures associated with the radiation-exposure samples in terms of differential gene expression and perturbed biological processes. Similarly, we reported a set of tumor class characterizations consider tumor stages or patient gender. Finally, we presented conditions that require further attention malignancy analysis of thyroid cancer. Conclusion: This work presents an advanced gene expression analysis of various aspects of thyroid cancer. We uncovered a set of novel biomarkers along with the biological processes and pathways they are involved in. Additionally, we performed literature validation for a wide fraction of our findings. Our findings present a good guidance to differentiate between thyroid cancer types, stages, malignancy potential, and gender related conditions aiming to facilitate drug discovery and patient personalized therapies.

Keywords: Thyroid cancer, Differential expression, Gene Ontology, Gene set enrichment, Biological pathways, Chernobyl Tissues Bank, Good health and well-being.

1. Introduction

Thyroid cancer cases increased rapidly in the past 5 years becoming the most diagnosed endocrine malignancy. In 2020, thyroid cancer had around half a million reported cases with around 43000 deaths and was ranked 11 among other cancers in terms of new cases [1]. Surprisingly, WHO recently reported that thyroid cancer elevated to rank 7 in terms of new cases with more than 800000 cases and rank 24 in terms of mortality with more than 47000 deaths [2]. Moreover, the thyroid cancer reported female cases are about 3 times more than reported cases in males [3] and more than 60% of the reported cases are in Asia [2]. Ionizing radiation is one of the thyroid cancer lead causes where thyroid cancer increased exponentially after Chernobyl (1986) and Fukushima (2011) incidents in the affected areas. Generally, thyroid cancer patients might suffer from neck lump, neck swelling, voice change, persistent cough, along with neck or throat pain.

Thyroid cancer had many classification schemes but presently tumor cell of origin and molecular profile are widely used to in the classification process [4]. The term "thyroid follicular nodular disease" is currently used to label the heterogeneous group of non-neoplastic and benign neoplastic lesions [5]. Most of the thyroid neoplasms are Follicular cell–derived tumors and can be labelled as benign, low-risk, and malignant neoplasms [6]. Benign thyroid tumor category includes follicular adenoma with papillary architecture and the oncocytic adenoma. The Low-risk neoplasms category are expected to have an excellent prognosis characterization and still cannot be categorized as benign such as thyroid tumors of uncertain malignant potential. Malignant neoplasms have many different sub-categories including Papillary thyroid carcinoma (PTC) accounting for nearly 90% of the cases [7], [8], Oncocytic thyroid carcinoma, High-grade follicular-

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derived thyroid carcinoma, or the Squamous cell carcinoma [9]. However, in terms of differentiation, thyroid cancer can be classified into high differentiation as in PTC and follicular thyroid carcinoma or Anaplastic Thyroid carcinoma (ATC) with poorly differentiation status or undifferentiation.

Diagnosis procedures start with physical examination followed by an ultrasound radiology study or any imaging test [10], [11]. If the thyroid nodule is greater than 1cm, a fine-needle-aspiration (FNA) can be performed [12]. FNA findings leads the following diagnosis procedures including several molecular tests to complete a transcriptomic analysis or a gene specific mutational panel [13]. Consequently, Therapeutic approaches will be considered. PTC is mainly treated by Thyroidectomy with radical lymphadenectomy. Moreover, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved several kinase inhibitors such as lenvatinib and sorafenib as part of the PTC clinical treatment [14], [15]. Patients with thyroid nodules greater than 4cm are advised to undergo surgical treatment as it has a greater disease-free survival chance [16].

Thyroid cancer is generally overlooked as it is considered stable with high mortality rate. However, recent studies reported frequent aggressive characteristics [7], unexpected prognostic significance leading to death in many cases [17], or even cancer recurrence[18]. Therefore, thyroid cancer should have increased attention and targeted projects including computational projects similar to the recent work of Hu et.al. [19,58].

Computational projects will have a great impact considering that availability of public data sources. For instance, NCBI GEO currently has around 97 thyroid cancer expression profiling datasets for human. However, the amount of expression analysis projects targeting thyroid cancer are fewer than expected. Therefore, we present in this work an intensive analysis of 6 NCBI GEO gene expression datasets aiming to present a broad idea about the characteristics of thyroid cancer and to suggest novel biomarkers for future studies.

2. Methods

2.1 Datasets

To have a broad idea about Thyroid cancer statistics, we intensively analyzed 6 NCBI GEO datasets with different experimental conditions. GSE29265 compares expression profiles of a cohort of papillary thyroid tumors from the Chernobyl Tissues Bank (CTB) along with French patients with no history of exposure to radiations, and their patient-matched healthy adjacent thyroid. Similarly, GSE35570 discusses Gene signature of the post-Chernobyl papillary thyroid cancer along with no radiation exposure patient samples and a cohort of healthy samples [20]. Moreover, GSE33630 dataset compares gene expression of anaplastic thyroid carcinomas from France and Belgium hospitals, papillary thyroid carcinomas from the CTB, along with and normal thyroids [21], [22]. Datasets GSE29265, GSE35570, and GSE33630 studied post-Chernobyl thyroid cancer samples and we analyzed their unique and common features in this work. To complete this task, we created pairs of classes prior the differential expression analysis that are Radiation Vs. Control, No Radiation Vs. Control, and Radiation Vs. No Radiation. Common features include common differentially expression genes (DEGs) in the 3 datasets and common perturbed biological processes or pathway. Later in this work, only common DEGs from the three datasets where further studied to understand the biological processes and pathways they effect using advanced gene set analysis.

Additionally, we analyzed in this work GSE65074 dataset which discusses metastatic potential by measuring RNA expression in the primary tumor at the time of cancer surgery [23]. This dataset presents gene expression data combined with gender and tumor stage information. We performed two different analyses for this dataset. The first analysis considered classes Female and Male where regardless of the tumor stage. The second analysis considered classes T1-T2 and T3-T4 regardless of the gender. For uncovered the DEGs for each of the classes in both analyses. For instance, to find the DEGs of the female class, we consider only the female sub-classes Female T1-T2 and Female T-3T4.

Finally, we analyzed the GSE82208 and GSE27155 datasets considering the malignant follicular thyroid cancer and benign follicular thyroid adenoma [24], [25], [26]. Differential results in these datasets indicates that DEGs and perturbed processes did not act the same in malignant and benign classes and it worth further attention. In this analysis, we accepted the DEGs only if found commonly in both datasets.

2.2 Differential expression analysis module

In this work, we check for DEGs using Kolmogorov–Smirnov (KS) test followed by analysis of the biological representations of the resulted DEGs using enriched GO biological processes and perturbed pathways. The basis of analysis method in this work was used in previous cancer studies [27], [28], [29] . We started by calculating the KS test in Python environment through the scipy.stats package [30] to find the top 500 differentially expressed genes for each dataset along with their perturbed biological processes and pathways. To discover the enriched biological processes, we employed Gene Ontology enrichment analysis using gseapy library, which is widely used for analyzing RNA-seq, ChIP-seq, and Microarray data [31]. Moreover, the perturbed pathways are found using Kyoto Encyclopedia of Genes and Genomes (KEGG) database, accessed using bioservices package [32,59]. Later, we visualized the enriched GO biological processes via the Bioconductor packages GOSim [33], clusterProfiler [34], [35], [36], [37], and ggplot2 [38]. Moreover, the enriched pathways are detected using ShinyGo0.82 [39] or NIH DAVID [40,60]. Finally, we analyzed the differential expression up or down expression behaviors using log2 fold change in case the tested classes appeared in multiple datasets. In this analysis, we tested the up or down regulation status of early defined DEGs considering the same classes in different datasets. To the end, we applied a strict selection method where only genes with the same status in majority of the datasets where considered.

This multi-layer analysis system is proven to suggest promising biomarkers. We expect to discover some literature validated DEGs and a set of promising DEGs for future work. Moreover, this analysis system facilitated basic homogeneity tests between different datasets in terms of reported perturbed GO biological processes and pathways where increased similar findings between datasets with the same classes increases the trustworthiness of the findings.

3. Results

In this section we report our findings when we applied our gene expression module to the chosen datasets along with the enriched biological processes and perturbed pathways. The following sub-sections correspond to the experimental environments as reported in NCBI GEO.

3.1 Radiation exposure

Here we report the common findings of the analysis performed to the GSE29265, GSE35570, and GSE33630 datasets as those datasets have post-Chernobyl samples along with no radiation exposure samples in addition to the control samples.

To check the homogeneity of the perturbed processes considering the three datasets, we checked for common perturbed pathways and biological processes in the three datasets. We found 235 commonly perturbed pathways (on average, ~67% of all perturbed pathways in each dataset) and around 1800 common biological processes (on average, ~65% of all enriched Processes in each dataset) which indicates a great match between the three datasets. To have abroad idea about such findings, we checked the common differentially expressed genes underlying these perturbed processes in the three datasets. Surprisingly, we found that only the Radiation Vs. Control class in the three datasets shared DEGs while other classes (Radian Vs. No Radiation, No Radiation Vs. Normal) shared none. The 96 common DEGs where further analyzed for the enriched biological processes they represent as presented in Figure 1 where the dot size indicates the number of genes involved, and color reflects the adjusted p-value. The common DEGs are reported in Supplementary table S1.

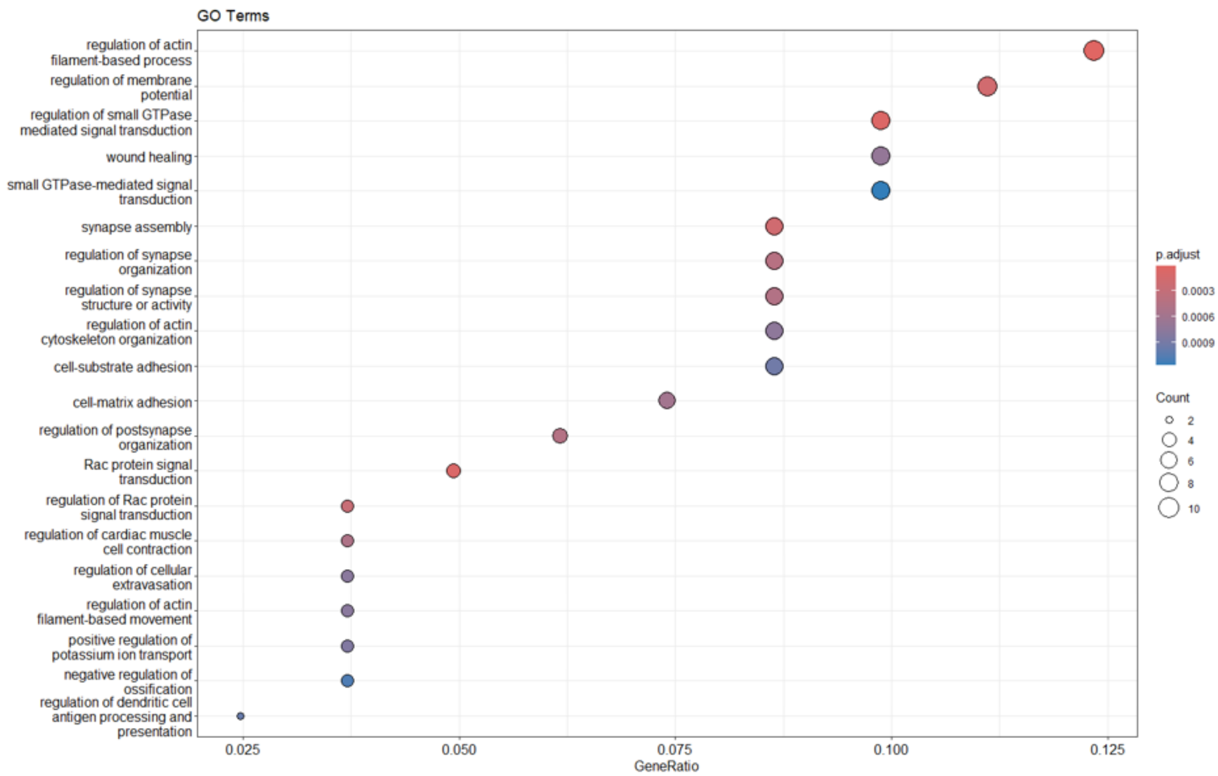

Figure 1: Enriched biological processes considering the radiation vs. control DEGs

Moreover, the top enriched processes where further analyzed to present the commonly participating genes in each of them as presented in Figure 2.

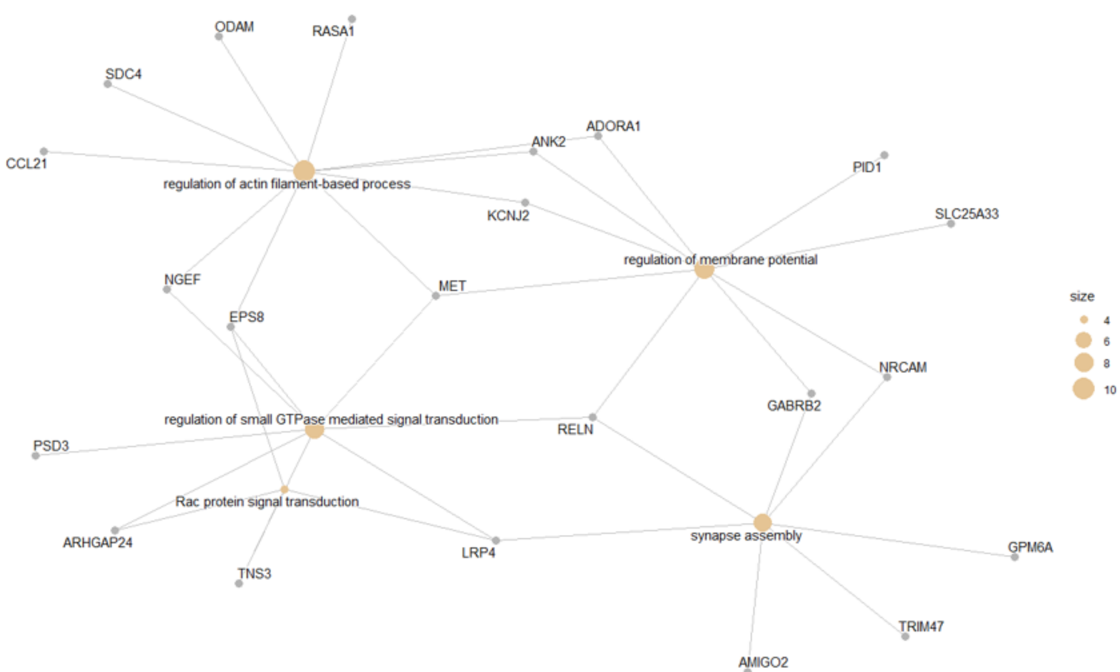

Figure 2: Top radiation vs. control enriched processes along with participating DEGs

Later, we checked the enrichment of the perturbed pathways related considering the common Radiation Vs. Normal DEGs, and we found that the top enriched pathways are the Proteoglycans in cancer, ECM-receptor interaction, Axon guidance, Renin secretion, and Morphine addiction. Finally, we checked expression behavior of the DEGs and noticed that AMIGO2, NRCAM, GABRB2, LRP4, PSD3, NGEF, KCNJ2, and ADORA1were commonly up regulated in tumor samples while GPM6A, RELN, ARHGAP24, CCL21, ODAM, and ANK2 where constantly down regulated. Figure 3 presents the top up and down regulated genes in selected datasets.

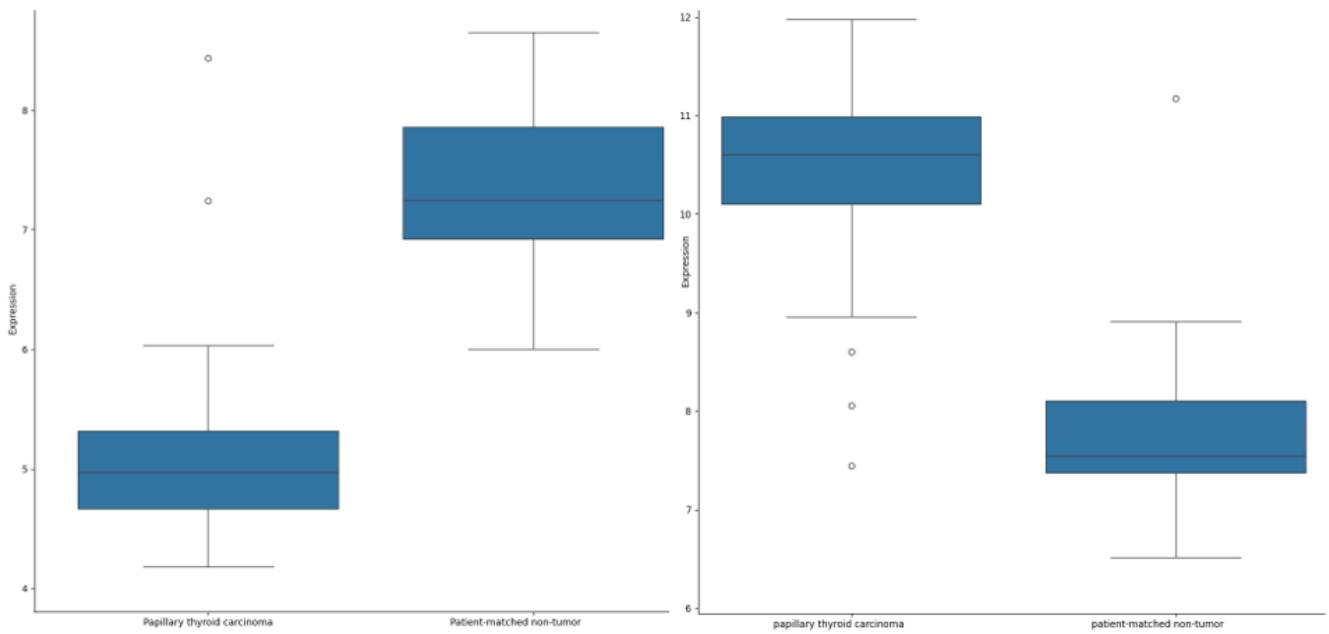

Figure 3: (left) Down-regulated CCL2 as in GSE29265. (right) up-regulated AMIGO2 as in GSE33630

3.2 Gender and tumor stages

In this section we report the findings of our analysis when we considered the dataset GSE65074. This dataset facilitated wide comparisons considering the gender and tumor stages T1-T2 and T3-T4.

Our analysis reported 22 common DEGs characterizing the female class that are not differentially expressed within in the male class (Supplementary table S1). Next, we analyzed the enriched biological processes of the DEGs and we found only three main perturbed GO biological processes controlling the sensory perception of pain, stimulus detections, and mRNA pseudouridine synthesis. Moreover, the DEGs were involved two biosynthesis pathways specialized in Glycosylphosphatidylinositol (GPI)-anchor or Ubiquinone and other terpenoid-quinone in addition to two amino acid metabolism pathways related to tyrosine and phenylalanine. On the other hand, we

found 28 common DEGs characterizing the male class that are not differentially expressed in the female class and were associated with biological processes distinct from those observed in the female class (Supplementary table S1). The enriched biological processes include protein transport or localization along with non-canonical NF-kappaB signal transduction but with no detected enriched pathways.

Later, we worked on the characterization of tumor stages using DEGs and perturbed processes. We found 76 DEGs that were characterizing the T1-T2 tumor stage class that are not differentially expressed in the T2-T3 class (Supplementary table S1). The DEGs especially the Immunoglobulin Heavy Constant gene family have major roles in the enriched GO biological processes as presented in Figure 4. However, no enriched pathways were reported for this set of DEGs.

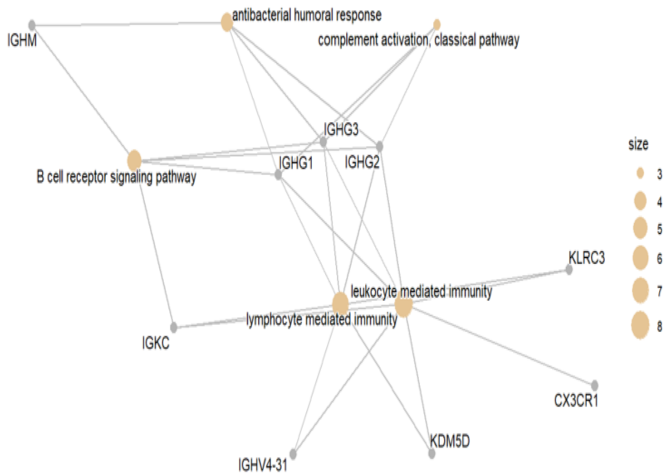

Figure 4: Top T1-T2 tumor stage enriched processes and participating DEGs

Similarly, we analyzed the T3-T4 class and found 134 special DEGs that are not differentially expressed in the T1-T2 class (Supplementary table S1). The enriched biological processes involved the inclusion body assembly, protein sumoylation, and negative regulation of protein binding. Additionally, we found three enriched pathways considering the DEGs that are the Chemical carcinogenesis - DNA adducts, Drug metabolism – cytochrome, and the Metabolism of xenobiotics by cytochrome.

3.3 Malignancy potential

In this section we analyzed GSE27155 and GSE82208 datasets to label the processes that act differently between the malignant and benign classes of thyroid cancer. We started by measuring the homogeneity of the findings considering the results of the two datasets. We found that ~61% of the enriched GO biological processes and ~85% of all perturbed pathways were common in the results of both datasets. Next, we checked for the common DEGs and found that only 34 DEGs were common (Supplementary table S1). While only the small cell lung cancer pathway was enriched considering the common DEGs, multiple enriched biological processes were uncovered involving mainly the tube formation and closure as in Figure 5. However, none of the uncovered genes were constantly up or down regulated considering both datasets.

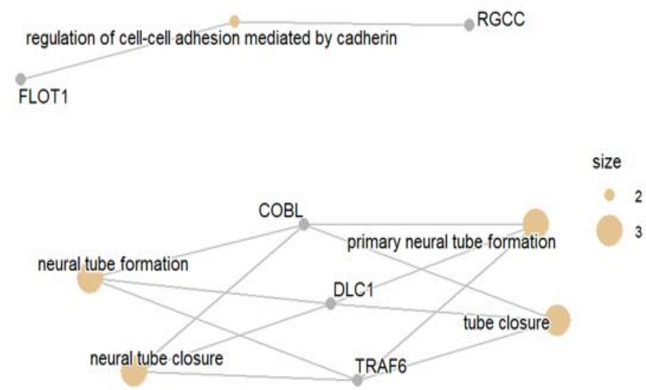

Figure 5: Top malignant Vs. benign enriched processes along with participating DEGs

4. Discussion

In this section we discuss our findings and provide literature validations. The validated findings of our computational approach indicate that the yet unvalidated findings should get extra attention in wet-lab analysis in thyroid cancer related experiments. We found Noticeable Homogeneity between the three datasets especially in the Radiation Vs Control class considering the shared pathways and GO terms. Moreover, the most of top common DEGs (Figure 2) have known roles in thyroid cancer such as CCL21 which is known for its roles in promoting the invasion, proliferation, and metastasis in thyroid cancer via CCR7/ERK [41], [42], [43]. Moreover, our analysis reported that CCL21 had constantly down-regulated expression behavior in most analyzed datasets. PSD3 has a similar effect promoting proliferation, migration, invasion, and G1/S transition while inhibiting apoptotic in papillary thyroid cancer [44]. KCNJ2 is frequently upregulated in papillary thyroid carcinoma cells and recent studies suggest that interfering with KCNJ2 expression can inhibit the proliferation, invasion and migration of PTC cells [45]. NrCAM expression could be implicated in the pathogenesis and behavior of PTC as it has persistently high mRNA and protein levels in different tumor stages [46]. Similarly, MET is frequently overexpressed in thyroid carcinoma samples and is associated with adverse outcomes [47] including high risk of metastatic dissemination in PTC [48]. Therefore, MET protein has known roles in approved thyroid cancer treatment medicines [49]. On the other hand, the expression of GPM6A decreases in thyroid cancer as the tumor progresses, and it can inhibit the progression of malignant tumors by inhibiting some signaling pathways, suggesting that it may be a tumor suppressor gene [50].

Next, we analyzed the GSE65074 dataset which facilitated the gender and tumor stage specific analyses. We created 4 classes that are Male, Female, T1-T2, and T3-T4. We made intensive pairwise comparisons and found that gender classes as well as the stage classes can be characterized using the DEGs and perturbed processes. Supplementary table S1 presents the differences in the reported DEGs. It is noticed that many of is the reported DEGs were already intensively studied in literature for thyroid cancer. For example, the female class DEGs had ANO1 and FOXE1. Suppressing ANO1 activity noticeably reduced migration and invasion of anaplastic thyroid carcinoma [51]. Similarly, genetic variants and SNPs in the FOXE1 have a significant risk factor for developing thyroid cancer [52]. Similarly, the male class DEGs involved FOXO4, UBQLN3, and *CLPTM1L*. FOXO4 is noticeably upregulated in follicular thyroid carcinomas suggesting potentially tumor-promoting roles [53]. A mutation in the *UBQLN3* gene (*UBQLN3*_R624Q), encoding a ubiquitin-like protein, is detected in a classical subtype PTC [54]. Additionally, the chromosome 5p15.33 *TERT-CLPTM1L* region have a significant association with PTC [55].

Finally, we analyzed the GSE27155 and GSE82208 datasets which highlights the malignant and benign classes. Initially, we checked how similar were the findings between the two datasets and we found that the resulted homogeneity was very high considering perturbed biological processes and pathways. The cross-datasets highly similar results promote the trustworthiness of the findings. Moreover, we found low amount of DEGs indicating low amount of differentially acting processes in both cancer types. Surprisingly, the top enriched biological processes were the neural tube formation and closure supporting that thyroid cells (specifically C cells) exhibit features common in neuroendocrine cells [56], [57].

5. Conclusions

Our multi-layer gene expression analysis model revealed novel thyroid cancer biomarker genes supported by the perturbed biological processes. Our overall findings are of great help to understand cancer possible causes and prognosis aiming to facilitate drug discovery and patient personalized therapies. Initially, we reported a set of common DEGs between datasets with radiation exposure data indicating the possibility of identifying such cancer types using certain DEGs and biological processes. Next, we reported a set of DEGs and perturbed processes that help understanding the tumor stage differences. Moreover, our findings pointed at possible gender specific perturbed biological processes. Finally, we reported a set of DEGs and biological processes that should be considered when discussing the malignancy potential of thyroid cancer. The main limitation of this study is the low number of specialized datasets and the change experimental conditions in the past years.

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Abbreviations

The following abbreviations are used in this manuscript:

NCBI	National Center for Biotechnology Information
GEO	Gene Expression Omnibus
DEG	Differentially Expressed Gene
PTC	Papillary thyroid carcinoma
GO	Gene Ontology
WHO	World Health Organization
ATC	Anaplastic Thyroid carcinoma
FNA	fine-needle-aspiration
FDA	Food and Drug Administration
EMA	European Medicines Agency

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