International Surgery Journal
Karunakaran P et al. Int Surg J. 2024 Dec;11(12):2181-2186
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20243573

Case Report

Molecular heterogeneity of clinically diverse cases of follicular thyroid carcinoma in next-generation sequencing: case report

Poongkodi Karunakaran[1-3]*, Deepak Jayakumar[4], Raj Ashok Gurunathan[5]

[1]Unit of Endocrine Surgery, Government Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India
[2]ICMR Extramural scheme, Government Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India
[3]University Online Journal, Tamilnadu Dr MGR Medical University, Chennai, Tamil Nadu, India
[4]Multidisciplinary Research Unit, Government Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India
[5]Department of General Surgery, Government Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India

Received: 18 October 2024
Accepted: 15 November 2024

***Correspondence:**
Dr. Poongkodi Karunakaran,
E-mail: poongkodithesurgeon@gmail.com

ABSTRACT

Thyroid cancer is the most common endocrine malignancy worldwide, with rising incidence. Follicular thyroid carcinoma (FTC) is the second most common thyroid cancer, accounting for 10% of thyroid cancer cases. FTC encompasses three different subtypes, with divergent clinical behavior. The encapsulated angioinvasive and minimally invasive subtypes have favorable outcomes. Whereas, the widely invasive subtype is associated with higher rates of hematogenous spread, refractoriness to radioactive iodine therapy and higher mortality rates. A better understanding of tumor biology can pave the way for targeted treatment strategies, optimizing the therapeutic outcome. To date, the molecular landscape of FTC is less well-characterized and poorly understood. Moreover, the clinical significance of the molecular characteristics of FTC remains elusive. Hence, we investigated genomic and transcriptomic profile of FTC using Next-Generation Sequencing in two patients with diverse clinical courses. This case report uncovered the molecular signatures, potentially unique to each patient, which may have clinical implications for risk stratification and personalized treatment strategies.

Keywords: Follicular thyroid cancer, Next-generation sequencing, Molecular profiling, Genomic profiling, Molecular heterogeneity, Thyroid carcinoma

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy globally and its incidence has tripled over the past 3 decades.[1-3] Follicular thyroid carcinoma (FTC) is the second most common histological type after papillary thyroid cancer (PTC) followed by medullary thyroid carcinoma (MTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC). FTC is classified into three subtypes.[4] The encapsulated angioinvasive (eaFTC) and minimally invasive (miFTC) subtypes are often associated with an excellent prognosis. Current treatment strategies with surgical extirpation of loco-regional disease, TSH suppressive thyroxine, and 131-I radioactive iodine (RAI) therapy have shown favorable outcomes. Whereas, the widely invasive (wiFTC) subtype has a propensity for distant metastases through the hematogenous spread, refractoriness to RAI therapy, and a higher morbidity and mortality rate. Thus, patients harboring FTC have clinically diverse courses. It is likely that besides histological grade, certain gene alterations could contribute to the aggressive biological behavior of the tumor. However, there is a paucity of data on the genomic characteristics of FTC. In particular, India lacks comprehensive genomic data on FTC. Moreover, the clinical relevance of genomic characteristics of FTC is insufficiently studied. The molecular mechanisms

underlying FTC cancer initiation and progression are poorly understood. Hence, it is pertinent to evaluate the molecular profile of FTC and correlate it with the diverse clinical courses to facilitate informed treatment decisions. Recent developments in molecular technology have led to a better understanding of tumor biology. Next-Generation Sequencing (NGS) is a high-throughput sequencing technology that allows thousands of genes of interest to be analyzed simultaneously. Hence, we investigated the genomic and transcriptomic landscape of follicular thyroid carcinoma using the NGS illumina Novaseq 6000 platform in two patients with diverse clinical courses.

CASE REPORT

Case 1

A 21-year-old woman presented with a progressive neck swelling of 6 months duration and occasional dysphagia. There was no high-risk feature including childhood exposure to ionizing radiation, family history of cancer, rapid increase in size, or voice change. Neck ultrasound showed a hypoechoic solid nodule about 3×2 cm in the right lobe of the thyroid gland and no significant lymphadenopathy. Cytology suggested nodular colloid goiter, Bethesda category II. Total Thyroidectomy (TT) was carried out. Surprisingly, histopathology revealed minimally invasive follicular thyroid carcinoma (Figure 1). The postoperative baseline thyroglobulin level was 12 ng/mL and she received 72 mCi of 131-I radioactive iodine therapy. 131-I post-therapy whole-body scan revealed no residual thyroid lesion nor any evidence of distant metastasis. The patient receives suppressive thyroxine therapy under regular follow-up.

Case 2

A 59-year-old man presented with multiple lytic lesions of the spine and incidental thyroid nodule. Computed Tomography-guided biopsy of the vertebral lesion revealed follicular thyroid cells suggesting distant metastasis from the thyroid primary. Neck ultrasound showed a highly vascular solid hypoechoic nodule 1×2 cm in the left lobe of the thyroid and guided-cytology revealed follicular thyroid neoplasm-Bethesda IV. A provisional diagnosis of thyroid malignancy with distant vertebral metastases was made and TT was planned in a multidisciplinary tumor board. He was a known case of systemic hypertension for the past 15 years on regular medications including two classes of antihypertensives (Tab Telmisartan 40 mg/day, tab amlodipine 5 mg/day) and anti-platelet medication-Tab. Aspirin 75 mg/day. Echocardiography revealed left ventricular hypertrophy and diffuse global hypokinesia. The ejection fraction was 58%. Given malignancy and worsening bone pain, the patient was subjected to surgery under general anesthesia ASA class III after adequate blood pressure control and withdrawing aspirin for 7 days. On induction of anesthesia, blood pressure rose from 140/90 mmHg to as high as 210/110 mmHg. Intraoperative hemodynamics were stabilized, and TT was performed. Given the absence of cervical lymphadenopathy, lymphadenectomy was not performed. The extubation and postoperative recovery were uneventful. Histopathological Examination (HPE) of the surgical specimen revealed wiFTC (Figure 2). The patient was referred to a nuclear physician for 131-I radioactive iodine therapy and 131-I post-therapy whole body scan. The patient received TSH suppressive thyroxine therapy. However, the patient developed cor-pulmonale and died of respiratory failure within 2 months after surgery.

Targeted whole exome sequencing

For DNA & RNA samples

Live thyroid tissue samples (roughly 0.5×0.5 cm) harvested during thyroid surgery were immediately immersed in RNA-protect solution, transported, and stored at -80℃ for targeted exome sequencing at MedGenome, Bengaluru, India under stringent conditions.

DNA/RNA extraction & sample QC

DNA was extracted for all samples using Qiagen DNeasy Mini Kit (Qiagen, Cat# 69504). The DNA samples were quantified using DNA Assay BR (Invitrogen, Cat# Q32853). DNA purity was checked using QIAxpert and DNA integrity was checked on 1% agarose gel. RNA was extracted by using Trizol Method from the above samples. The RNA samples were quantified using Qubit RNA BR Assay (Invitrogen, Cat# Q10211). RNA purity was checked using QIAxpert, and RNA integrity was checked using RNA Screentapes (Agilent, Cat# 5067-5576).

DNA/RNA library preparation and sequencing protocol

Custom targeted library preparation for Illumina was carried out. DNA or cDNA samples were processed and enriched using gene specific probes for final DNA library. The libraries were then checked for fragment size distribution on Tape Station using D1000 DNA Screentapes (Agilent, Cat# 5067-5582) or on Fragment Analyzer using HS NGS Fragment Kit (1-6000bp) (Agilent, Cat# DNF-474-1000) before loading on Illumina Novaseq 6000 instrument to generate ~250X, 150bp paired-end reads. Bioinformatic analyses were done and compared against reference sequence databases available at NCBI library.

QIAseq tumor mutation burden panel summary

QIAseq tumor mutation burden (TMB) panel by Qiagen is a UMI-based panel for estimating mutation load in a sample. The analysis is done using CLC Genomics. Samples are analyzed after alignment using QIAseq Tumor Mutation Burden (TMB) panel (1.3 Mb) which covers 486 genes. The panel just not targets the hotspot regions but the entire CDS for these genes in general.

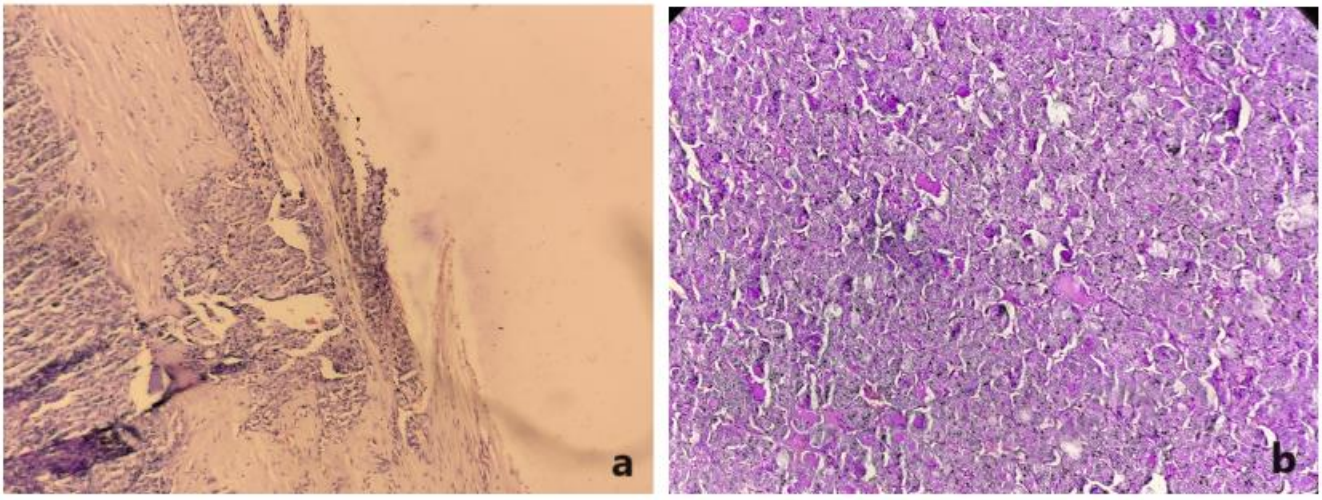

Figure 1: H&E showing minimally invasive follicular thyroid carcinoma with (a) capsular invasion (b) trabecular pattern of follicles.

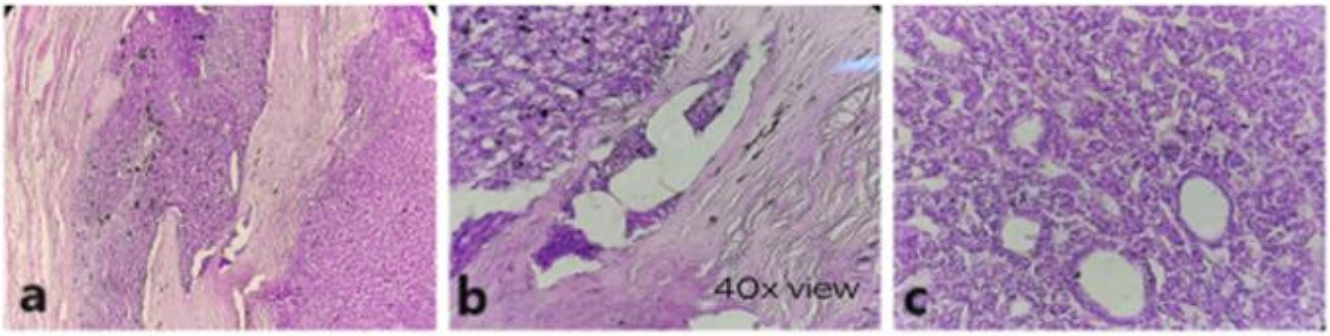

Figure 2: H&E showing widely invasive follicular thyroid carcinoma with (a) capsular invasion, (b) vascular invasion and (c) microfollicular pattern of follicles.

Table 1: Raw data summary.

Sample	Avg base quality	Total reads	GC%	%Data > Q30	Total data (Gb)	Read length (bp)
Case 1	35.68	40,429,060	47.875	92.565	6.10	151
Case 2	35.785	34,037,182	49.210	92.940	5.140	151

Table 2. Distribution of pass-on target and non-synonymous annotated variants.

Sample	Total variants	Missense	Nonsense	Startloss	Stoploss	Frameshift-del	Inframe del	Frameshift ins	Inframe ins
Case 1	5,905	2,093	80	25	3	223	141	61	6
Case 2	5,694	1,964	68	22	3	227	131	50	3
Total	11,599	4,057	148	47	6	450	272	111	9

Table 3: Overall pass-on target variant distribution.

Sample	Total variants	Total SNPs	Total In Dels	Total Heterozygous	Total Homozygous
Case 1	5,905	4,646	1,259	5,846	59
Case 2	5,694	4,510	1,184	5,602	92
	11,599	9,156	2,443	11,448	151

Table 4: Summary of next-generation sequencing showing unique mutational profile in follicular thyroid cancer patients.

Comparison results	CHROM	START	REF	ALT	GENE_NAME	VARCLASS	CDNA_CHG	AA_CHG	ZYGOSITY	ALT_DEPTH	SIFT_pred	1000G
Common in both	chr9	84955507	A	G	NTRK2	MISSENSE	c.2162A>G	p.Asp721Gly	Heterozygous	27	D	NA
Common in both	chr7	140734767	G	T	BRAF	MISSENSE	c.2131C>A	p.Leu711Ile	Heterozygous	100	D	NA
Common in both	chr7	140734754	TC	AA	BRAF	MISSENSE	c.2143_2144delinsTT	p.Glu715Leu	Heterozygous	19	D	NA
Common in both	chr7	140734767	G	C	BRAF	MISSENSE	c.2131C>G	p.Leu711Val	Heterozygous	32	D	NA
Common in both	chr7	140924644	GT	CG	BRAF	MISSENSE	c.59_60delinsCG	p.Asn20Thr	Heterozygous	32	D_lc	NA
Common in both	chr7	140924645	T	G	BRAF	MISSENSE	c.59A>C	p.Asn20Thr	Heterozygous	54	D_lc	NA
Common in both	chr7	140924689	G	C	BRAF	MISSENSE	c.15C>G	p.Ser5Arg	Heterozygous	37	D_lc	NA
Common in both	chr7	140924702	A	C	BRAF	STARTLOSS	c.2T>G	p.Met1?	Heterozygous	13	D_lc	NA
Common in both	chr7	140734754	T	A	BRAF	MISSENSE	c.2144A>T	p.Glu715Val	Heterozygous	30	D	NA
Common in both	chr7	140734770	T	A	BRAF	MISSENSE-SS-PRX	c.2128A>T	p.Ile710Phe	Heterozygous	29	D	NA
Common in both	chr7	140924644	G	C	BRAF	MISSENSE	c.60C>G	p.Asn20Lys	Heterozygous	12	D_lc	NA
Common in both	chr2	29228917	A	G	ALK	MISSENSE	c.2782T>C	p.Cys928Arg	Heterozygous	19	D	NA
Unique in Case 1	chr7	140734735	C	A	BRAF	MISSENSE	c.2163G>T	p.Leu721Phe	Heterozygous	22	D	NA
Unique in Case 1	chr7	140734753	C	A	BRAF	MISSENSE	c.2145G>T	p.Glu715Asp	Heterozygous	19	D	NA
Unique in Case 1	chr7	140734753	CTC	AAA	BRAF	MISSENSE	c.2143_2145delinsTTT	p.Glu715Phe	Heterozygous	10	D	NA
Unique in Case 1	chr7	140734760	G	T	BRAF	MISSENSE	c.2138C>A	p.Ser713Tyr	Heterozygous	42	D	NA
Unique in Case 1	chr7	140924691	T	G	BRAF	MISSENSE	c.13A>C	p.Ser5Arg	Heterozygous	17	D_lc	NA
Unique in Case 1	chr1	156879126	C	T	NTRK1	MISSENSE	c.1810C>T	p.His604Tyr	Heterozygous	380	D	0.024361
Unique in Case 1	chr2	29228936	GA	CC	ALK	MISSENSE	c.2762_2763delinsGG	p.Phe921Trp	Heterozygous	13	D	NA
Unique in Case 1	chr10	43124887	C	T	RET	MISSENSE	c.2944C>T	p.Arg982Cys	Heterozygous	416	D	0.021965
Unique in Case 2	chr7	140734758	T	A	BRAF	MISSENSE	c.2140A>T	p.Ile714Phe	Heterozygous	12	D	NA

Table 5. RNA gene fusion report of FTC case 2 patient.

ToolName	5'gene	3'gene	5'breakpoint	3'breakpoint	Spanning reads	Split reads	Read depth	Fusion Description	Exon_1_id (5' fusion partner)	Exon_2_id (3' fusion partner)	Junction sequence
FusionMap	RAF1	CHSY3	chr3:12641679:-	chr5:129240693:+	0	14	14	-	ENST00000251849,ENST00000442415, ENST00000432427,ENST00000534997, ENST00000423275,ENST00000542177, ENST00000465826	ENST00000305031	CGTGCCAGCACAAAGA GAGCGGGCACCAGT @cggcgctcagcagccgctcccccagcccca
FusionMap	TMBIM1	NOTCH2	chr2:219143244:-	chr1:120467945:-	0	12	12	-	ENST00000258412,ENST00000465082, ENST00000444881,ENST00000396809, ENST00000445635,ENST00000543441, ENST00000437694,ENST00000492966, ENST00000429501,ENST00000466012, ENST00000425694,ENST00000476429, ENST00000495113	ENST00000256646	TGAAGCCCTTACTTGCATG TCTTGCTGTTC@ccctggcag caggcaaggatcaggtaggtg
FusionCatcher	MED12	IRF2BPL	chrX:70361121:+	chr14:77493784:-	6	4	10	-	ENSG00000184634	ENSG00000119669	TCTTATAGCAGCAGCAGCAA CAGCAACAGCAGCAGCAGCAG CAGCAGCAA*TATAGCAGCAGC AGCAACAGCAACAGCAGCAGCA GCAGCAGCAGCAA

Targeted exome sequencing

The total data generated for each sample ranges from 5 Gb to 6.1 Gb. The overall alignment and the passed alignment percentage (alignment to hg38) in all the samples are above 90%, respectively. The average panel depth for each sample ranges from 391X to 2294X. The sequence read of both the FTC samples has been processed and archived in the SRA database of NCBI library with BioProject accession number PRJNA901638. Raw data analysis is summarized (Table 1). The distribution of overall pass-ontarget variants and non-synonymous annotated variants are given in Table 2 and Table 3 respectively.

DNA-based genomic analysis in 2 FTC cases revealed unique somatic mutations in BRAF, NTRK, and ALK genes (Table 4). Case 1 exhibited (i) RET mutation - Arg982Cys and (ii) NTRK1 mutation – His604Tyr which were not seen in case 2. Whereas, case 2 harbored a unique BRAF mutation ch7:140734758T>A, which was not seen in case 1. However, the classic BRAF V600E nor the rarer BRAF K601E mutants, which are associated with PTC were not detected. Mutations observed in ALK and NTRK2 genes were common in both cases. RNA-based transcriptomic analysis revealed gene rearrangements including RAF1-CHSY3, TMBIM1-NOTCH2, and MED12-IRF2BPL in Case 2 (Table 5).

DISCUSSION

Our NGS detected novel gene rearrangements including RAF1-CHSY3, TMBIM1-NOTCH2 and MED12-IRF2BPL in the lethal FTC case but none in case 1. Little information exists on these novel fusions. However, studies have shown the RAF-MEK1/2-ERK cascade is the key signal transduction pathway, dysregulated in thyroid carcinogenesis, in keeping with our observations. RAF1 (rapidly accelerated fibrosarcoma) has been shown to promote the survival of thyroid cancer cells independent of ERK pathway activation, offering new perspectives on targeted therapy.[5,6]

Oncofetal chondroitin sulfate, is exclusively expressed in the placenta, and chondroitin sulfate synthase 3 (CHYS3) overexpression is associated with poor prognosis in many solid cancers and is a promising target for immunotherapy.[7] Transmembrane Bax Inhibitor Protein Motif (TMBIM) 1 encodes for an evolutionarily conserved hydrophobic protein family which regulates calcium homeostasis and apoptosis.[8,9] Dysregulation of TMBIM protein has been implicated in cancer progression. Notch Signaling cascade regulates cell fate decision, proliferation, and differentiation of vast array of cells. Constitutive activation of NOTCH signaling by point mutations or chromosomal translocation is involved in many human cancers including T-cell leukemia, pancreatic and breast cancer.[10] Interferon Regulatory Factor 2 Binding Protein Like (IRF2BPL) gene encodes for a protein that acts as transcriptional activators.[11] Mutations of Mediator of RNA polymerase II transcription subunit 12 homolog (MED12) have been reported in 15% of PDTC patients with fatal outcomes, and are associated with tumor virulence.[12,13] It is plausible that the accumulation of these fusion genes could have contributed to the fatal outcome of FTC case 2. However, Classical RAS mutations and PAX8-PPARγ gene rearrangements common in FTC were not detected in our patients, which could possibly be attributed to ethnic and geographic variations. Previous reports have shown that PAX8-PPARγ gene rearrangements are uncommon in FTC among Asian population, corroborating with our findings.[14,15] Nevertheless, unique somatic mutations involving ALK, NTRK1 and NTRK2 genes were identified in both cases of FTC. A unique BRAF mutation, ch7:140734758T>A was identified in lethal FTC case 2, who had an advanced histopathological profile and systemic metastases. This somatic mutation has been associated with cardiomyopathy.

Likewise, our patient developed cardiomyopathy, cor-pulmonale and died of respiratory failure. Moreover, the patient harbored multiple gene fusions. Studies have shown that fusion-positive thyroid cancer exhibited heightened tumor virulence with higher rates of mortality.[16,17] Whereas, miFTC case 1 without fusion genes displayed a less aggressive course. Studies have shown that mutation burden was associated with a worse prognosis, independent of histological classification.[4] Hence, it is likely that besides the clinicopathological profile, the molecular heterogeneity of FTC could contribute to the diverse course. The genomic landscape of FTC is less well-described. Recent studies have demonstrated highly heterogenous mutations involving oncogenes (MDM2, FLI1), transcription factors and repressors (MITF, FLI1, ZNF331), epigenetic enzymes (KMT2A, NSD1, NCOA1, NCOA2), and protein kinases (JAK3, CHEK2, ALK) in FTC cases.[18,19]

A few studies have demonstrated FTC-specific driver genes including DICER1, EIF1AX, KDM5C, NF1, PRDM1, PTEN, and TP53 mutations and fusion genes involving THADA.[4] However, these mutations were not detected in our patients. Nevertheless, the unique somatic mutations present in our FTC patients have not been reported previously as pathogenic in the Cancer Genome Atlas (TCGA), Catalogue of Somatic Mutations in Cancer gene census (COSMIC), and BROCA-curated thyroid cancer susceptibility genes (tests.labmed.washington.edu/BROCA).[20,21] Thus, the molecular profile of FTC is highly heterogeneous, potentially attributing to clinicopathological and ethnic diversities. Fusion-positive FTCs are likely to have an aggressive course with a higher mortality rate. The study highlighted that NGS application can facilitate the identification of distinctive molecular signatures in the subset of patients with advanced, refractory, and progressive diseases who may benefit from newer targeted therapies.

CONCLUSION

In conclusion, our study utilizing Next-Generation Sequencing in follicular thyroid carcinoma revealed a heterogenous molecular profile, diverging from Western literature by the absence of RAS mutation and PAX-PPARG. Nevertheless, unique somatic mutations in BRAF, NTRK, and ALK genes, akin to those in other Asian populations signify the geographic and ethnic diversity. Novel gene rearrangements including RAF1-CHSY3, TMBIM1-NOTCH2, and MED12-IRF2BPL identified in the lethal FTC case, are potential drivers of aggressive disease behavior. These molecular insights highlighted the importance of NGS in identifying therapeutic targets for personalized therapies, particularly in advanced FTC cases, thus aiding prognosis and targeted therapy development. Further research is crucial to validate these observations and enhance our understanding of FTC biology and treatment strategies.

Funding: Indian Council of Medical Research extramural grant
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Miranda-Filho A, Lortet-Tieulent J, Bray F, et al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. Lancet Diabetes Endocrinol. 2021;9(4):225-34.
2. Megwalu UC, Moon PK. Thyroid Cancer Incidence and Mortality Trends in the United States: 2000–2018. Thyroid. 2022;32(5):560-70.
3. Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: A global overview. Int J Cancer. 2015;136(9):2187-95.
4. Nicolson NG, Murtha TD, Dong W, et al. Comprehensive Genetic Analysis of Follicular Thyroid Carcinoma Predicts Prognosis Independent of Histology. J Clin Endocrinol Metab. 2018;103(7):2640-50.
5. Castro L, Alves S, Chaves SR, Costa JL, Soares P, Preto A. RAF-1 promotes survival of thyroid cancer cells harboring RET/PTC1 rearrangement independently of ERK activation. Mol Cell Endocrinol. 2015;415:64-75.
6. Piscazzi A, Costantino E, Maddalena F, et al. Activation of the RAS/RAF/ERK Signaling Pathway Contributes to Resistance to Sunitinib in Thyroid Carcinoma Cell Lines. J Clin Endocrinol Metab. 2012;97(6):898-906.
7. Li X, Fan Y, Zhang Y, et al. CHSY3 can be a Poor Prognostic Biomarker and Mediates Immune Evasion in Stomach Adenocarcinoma. Front Genet. 2022;13:3389.
8. Guo G, Xu M, Chang Y, et al. Ion and pH Sensitivity of a TMBIM Ca2+ Channel. Structure. 2019;27(6):1013-8.
9. Lisak DA, Schacht T, Enders V, et al. The transmembrane Bax inhibitor motif (TMBIM) containing protein family: Tissue expression, intracellular localization and effects on the ER CA2+-filling state. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2015;1853(9):2104-14.
10. Sjölund J, Manetopoulos C, Stockhausen MT, Axelson H. The Notch pathway in cancer: Differentiation gone awry. Eur J Cancer. 2005;41(17):2620-9.
11. Marcogliese PC, Shashi V, Spillmann RC, et al. IRF2BPL Is Associated with Neurological Phenotypes. The Am J Human Gen. 2018;103(2):245-60.
12. Ibrahimpasic T, Xu B, Landa I. Genomic Alterations in Fatal Forms of Non-Anaplastic Thyroid Cancer: Identification of MED12 and RBM10 as Novel Thyroid Cancer Genes Associated with Tumor Virulence. Clinical Cancer Research. 2017;23(19):5970-80.
13. Sooraj D, Sun C, Doan A. MED12 and BRD4 cooperate to sustain cancer growth upon loss of mediator kinase. Mol Cell. 2022;82(1):123-39.
14. Mochizuki K, Kondo T, Oishi N. Low frequency of PAX8-PPARγ rearrangement in follicular thyroid carcinomas in Japanese patients. Pathol Int. 2015;65(5):250-3.
15. Song YS, Lim JA, Park YJ. Mutation Profile of Well-Differentiated Thyroid Cancer in Asians. Endocrinology and Metabolism. 2015;30(3):252.
16. Yakushina VD, Lerner L V., Lavrov A V. Gene Fusions in Thyroid Cancer. Thyroid. 2018;28(2):158-67.
17. Franco AT, Ricarte-Filho JC, Isaza A. Fusion Oncogenes Are Associated With Increased Metastatic Capacity and Persistent Disease in Pediatric Thyroid Cancers. J Clin Oncol. 2022;40(10):1081-90.
18. Swierniak M, Pfeifer A, Stokowy T. Somatic mutation profiling of follicular thyroid cancer by next generation sequencing. Mol Cell Endocrinol. 2016;433:130-7.
19. Yoo SK, Lee S, Kim S. Comprehensive Analysis of the Transcriptional and Mutational Landscape of Follicular and Papillary Thyroid Cancers. PLoS Genet. 2016;12(8):1006239.
20. Agrawal N, Akbani R, Aksoy BA. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159(3):676-90.
21. Tate JG, Bamford S, Jubb HC. COSMIC:The catalogue of somatic mutations in cancer. Nucleic Acids Res. 2019;47(1):941-7.

Cite this article as: Karunakaran P, Jayakumar D, Gurunathan R. Molecular heterogeneity of clinically diverse cases of follicular thyroid carcinoma in next-generation sequencing-case report. Int Surg J 2024;11:2181-6.