

Clinicopathological and molecular features of DICER1-altered follicular-patterned differentiated high-grade thyroid carcinoma: a case series

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Abstract

Background

Differentiated high-grade thyroid carcinoma (DHGTC) is a recently recognized entity within high-grade follicular cell-derived non-anaplastic thyroid carcinoma. The molecular features of DHGTC remain incompletely characterized. We investigated the clinicopathological and molecular features of DICER1-altered tumors in a WHO 5th edition-based high-grade thyroid carcinoma series.

Methods

Ten high-grade follicular cell-derived non-anaplastic thyroid carcinomas were reclassified as DHGTC or poorly differentiated thyroid carcinoma (PDTC). Targeted next-generation sequencing was performed on primary tumors and one paired lymph-node metastasis. Clinicopathological and molecular findings were compared descriptively.

Results

The cohort comprised eight DHGTCs and two PDTCs. DICER1 alterations were detected in four DHGTCs (4/8, 50.0%) and in no PDTCs. All DICER1-altered tumors had follicular morphology and lacked canonical BRAF/RAS driver alterations and reportable TERT promoter alterations. Two tumors harbored candidate truncating-plus-RNase IIIb-domain DICER1 two-hit configurations. In a paired primary tumor and lymph-node metastasis, p.R624* was shared, whereas p.D1810Y was restricted to the primary tumor. DICER1-altered tumors were smaller than DICER1-wild-type tumors (median, 2.15 vs 5.0 cm; $P = 0.010$).

Conclusions

DICER1 alterations identify a candidate follicular-patterned molecular subgroup of DHGTC characterized by RNase IIIb-associated variants, absence of canonical MAPK drivers, and a distinct clinicopathological profile. The data support a potential DICER1-related route of high-grade thyroid tumor evolution.

Introduction

The fifth edition of the World Health Organization (WHO) Classification of Thyroid Tumours recognizes high-grade follicular cell-derived non-anaplastic thyroid carcinoma as a category comprising PDTC and DHGTC [1–3]. PDTC is defined by the Turin criteria, whereas DHGTC retains differentiated thyroid carcinoma morphology but shows tumor necrosis and/or a mitotic count of at least 5 per 2 mm² [2, 3]. This distinction has immediate diagnostic and prognostic relevance, yet the molecular basis of DHGTC remains incompletely defined [4, 5].

DICER1 encodes an RNase III endoribonuclease essential for microRNA maturation. DICER1-associated tumorigenesis commonly involves a loss-of-function event and a somatic hotspot variant in the RNase IIIb domain, resulting in abnormal 5p microRNA processing [6, 7]. In the thyroid, DICER1 alterations occur in a spectrum of follicular-patterned lesions, including follicular nodular disease, follicular adenoma, follicular thyroid carcinoma, follicular-patterned papillary thyroid carcinoma, and selected high-grade tumors [8–14]. Adult high-grade thyroid carcinomas with somatic DICER1 alterations have been reported, but their morphology and relationship to DHGTC require further clarification [10, 11].

We therefore characterized DICER1 alterations in a WHO 5th edition-based series of high-grade follicular cell-derived non-anaplastic thyroid carcinomas, with emphasis on morphology, co-mutation patterns, clinicopathological features, and spatial heterogeneity in a paired primary–metastatic case.

Materials and methods

Case selection and histological review

This retrospective study included thyroid carcinomas diagnosed at the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine (JSATCM) between 2018 and 2026. All available hematoxylin-eosin slides were independently reviewed by two pathologists using WHO 5th edition criteria. PDTC was diagnosed according to the Turin algorithm. DHGTC was diagnosed as an invasive differentiated follicular cell-derived carcinoma with tumor necrosis and/or ≥ 5 mitoses per 2 mm², without anaplastic morphology. Anaplastic thyroid carcinoma and intrathyroid thymic carcinoma were excluded. The institutional review board approved this study; the requirement for informed consent was waived because of the retrospective use of de-identified archival material. The study was approved by the JSATCM Institutional Review Board.

Molecular analysis

Tumor-rich areas were selected by pathologists and macrodissected from formalin-fixed paraffin-embedded tissue sections. Genomic DNA and total RNA were extracted using a DNA/RNA Extraction Kit (RuiJing Biotech, Shanghai, China). Molecular profiling was performed using the Thyroscan® Human Thyroid Cancer Gene Detection Kit (amplicon sequencing method; RuiJing Biotech, Shanghai, China), a multiplex polymerase chain reaction-based next-generation sequencing assay designed to detect single-nucleotide variants, insertions/deletions, and gene fusions involving 177 thyroid cancer-related genes. Total RNA was reverse-transcribed into complementary DNA. Target regions in genomic DNA and complementary DNA were amplified by multiplex PCR. Unique index adapters and universal sequencing adapters were added by PCR amplification. Following purification, library concentrations were determined using a Qubit Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). Qualified libraries underwent 150-bp paired-end sequencing on a next-generation sequencing platform. Raw sequencing reads were processed using Cutadapt (v1.18) to remove adapter sequences and low-quality bases.

Processed reads were aligned to the human reference genome (hg19) using BWA (v0.7.17). Single-nucleotide variants and insertions/deletions were identified using VarScan2 (v2.4.4) and annotated using the Ensembl Variant Effect Predictor. Gene fusions were detected using customized scripts and reference sequences. Variants were interpreted with consideration of sequencing quality, variant allele frequency, population frequency, predicted functional effect, and published evidence.

Statistical analysis

Continuous variables were compared with the Mann–Whitney U test and categorical variables with Fisher’s exact test. Analyses were exploratory. Two-sided P values < 0.05 were considered statistically significant.

Results

Cohort characteristics

After exclusion of one anaplastic thyroid carcinoma and one intrathyroid thymic carcinoma, 10 tumors were included: eight DHGTCs and two PDTCs. Patients ranged from 16 to 79 years of age; eight were female. All tumors showed a mitotic count of ≥ 5 per 2 mm². Detailed clinicopathological data are summarized in Table 1.

On histological review, all four DICER1-altered DHGTCs showed predominantly follicular differentiation. Case 1 displayed a follicular growth pattern with brisk mitotic activity (Fig. 1A,B). In case 2, the primary tumor contained a cellular nested component, and the lymph-node metastasis retained follicular-patterned architecture (Fig. 1C,D). By comparison, the DICER1-wild-type DHGTC with a papillary thyroid carcinoma background and the PDTc with solid architecture illustrate the morphologic distinction between these diagnostic categories (Fig. 1E,F).

Table 1
Clinicopathological characteristics of 10 case Follicular-Patterned Differentiated High-Grade Thyroid Carcinoma.

Case	Diagnosis	Age/sex	Size (cm)	Necrosis / VI / ETE	LN met.	Follow-up(month)	DICER1
1	DHGTC	36/F	1.0	- / - / -	-	1/A	Altered
2	DHGTC	57/F	2.3	+ / - / -	+	Lost	Altered
3	DHGTC	20/F	2.0	- / - / -	-	Lost	Altered
4	DHGTC	74/F	4.5	- / - / -	-	60/A	Altered
5	DHGTC	52/F	3.0	- / - / -	-	Lost	Wild-type
6	DHGTC in PTC	29/F	5.0	- / - / -	-	20/A	Wild-type
7	PDTC	59/M	7.0	- / + / +	-	43/A	Wild-type
8	PDTC	79/F	5.0	- / + / -	-	Lost	Wild-type
9	DHGTC	16/F	5.0	- / + / +	-	15/A	Wild-type
10	DHGTC	69/M	7.5	- / + / +	-	24/D	Wild-type

VI, vascular invasion; ETE, extrathyroidal extension; LN, lymph node; FU, follow-up in months/status; A, alive; D, dead; ND, not documented.

DICER1 mutation spectrum and co-mutations

DICER1 alterations were identified in four tumors, all of which were DHGTCs with follicular morphology. Case 1 harbored p.R656* and p.D1709N; case 2 harbored p.R624* and p.D1810Y in the primary tumor. Cases 3 and 4 carried p.E1705K and p.E1813Q, respectively. The truncating-plus-RNase IIIb combinations were compatible with candidate two-hit DICER1 configurations. No DICER1-altered tumor carried BRAF or RAS driver alterations or a reportable TERT promoter alteration. In contrast, RAS Q61R alterations were detected in two DICER1-wild-type tumors and BRAF p.V600E in one (Figure 2, Supplementary data).

Paired primary–metastatic analysis

In case 2, p.R624* was detected in the primary tumor (VAF, 65.96%) and lymph-node metastasis (VAF, 49.79%). p.D1810Y was detected in the primary tumor (VAF, 31.05%) but was not detected in the lymph-

node metastasis. These findings are consistent with spatial subclonal heterogeneity.

Clinicopathological comparison

DICER1-altered tumors ranged from 1.0 to 4.5 cm (median, 2.15 cm), compared with 3.0 to 7.5 cm in DICER1-wild-type tumors (median, 5.0 cm; $P = 0.010$). Vascular invasion and extrathyroidal extension were documented only in DICER1-wild-type tumors. One DICER1-altered tumor had lymph-node metastasis. Follow-up information was available for two DICER1-altered tumors, both of which were alive at 1 and 60 months, respectively. In the DICER1-wild-type group, three patients were alive at 15–43 months and one patient died 24 months after surgery; the remaining patients were lost to follow-up.

Discussion

In the WHO 5th edition classification, high-grade follicular cell-derived non-anaplastic thyroid carcinoma includes PDTC and DHGTC [1–3]. The distinction is morphologic. PDTC is diagnosed using the Turin algorithm, whereas DHGTC retains differentiated thyroid carcinoma architecture and/or cytology while showing tumor necrosis and/or a mitotic count of ≥ 5 per 2 mm². “Follicular-patterned” is an architectural descriptor and not an independent WHO entity. In the present series, all DICER1-altered tumors retained follicular differentiation and fulfilled the criteria for DHGTC. None met the morphologic requirements for PDTC.

DICER1 alterations were identified in 4 of 8 DHGTCs and in none of the 2 PDTCs. Although the number of PDTCs was limited, the distribution is of interest because the molecular profile of DHGTC more commonly follows the BRAF-like/RAS-like dichotomy of differentiated thyroid carcinoma. BRAF V600E is particularly frequent in high-grade papillary thyroid carcinoma, whereas RAS mutations are enriched in tumors with a follicular phenotype; TERT promoter mutation and alterations in TP53, EIF1AX, PI3K/AKT-pathway genes or chromatin-remodeling genes may accompany high-grade progression [4, 5, 15]. In contrast, the four DICER1-altered tumors lacked canonical BRAF/RAS drivers and reportable TERT promoter alterations. This pattern suggests that DICER1-altered follicular-patterned DHGTC may represent a molecular subset that differs from the usual MAPK-driven high-grade tumors.

Two tumors carried a truncating DICER1 variant together with an RNase IIIb hotspot variant. The RNase IIIb domain contains metal-binding residues required for cleavage of the 5p arm of precursor microRNAs. Hotspot mutations at this domain produce a characteristic 5p microRNA-processing defect and altered 3p/5p microRNA balance [6, 7]. In DICER1-mutated thyroid tumors, loss of thyroid-abundant microRNA families, including let-7 and miR-30, has been associated with altered MAPK-related transcriptional programs [14]. The p.R656* plus p.D1709N and p.R624* plus p.D1810Y combinations are consistent with this model. However, because allelic phasing and loss-of-heterozygosity analysis were not performed, biallelic involvement cannot be confirmed in these tumors.

The association with follicular morphology is concordant with the established thyroid spectrum of DICER1 alterations. Somatic DICER1 hotspots have been reported in nodular thyroid disease, follicular adenoma, follicular thyroid carcinoma and follicular-patterned papillary thyroid carcinoma [8–14, 16, 17, 21]. Thus, DICER1 alteration is neither a marker of malignancy nor a marker of high-grade transformation. Our findings extend this spectrum to DHGTCs that retain follicular morphology. The shared morphology across benign, differentiated and high-grade tumors raises the possibility that DICER1 is an early event in a subset of follicular-patterned thyroid neoplasms, with additional events required for the acquisition of high-grade features. The present data do not demonstrate progression from conventional follicular thyroid carcinoma to DHGTC. Such a relationship would require identification of conventional and high-grade components within the same tumor and component-specific molecular analysis showing a shared early DICER1 alteration. This hypothesis-generating model is summarized in Fig. 3.

The absence of DICER1 alterations in the two PDTCs should not be interpreted as a molecular criterion for separating PDTC from DHGTC. The two diagnoses remain dependent on morphology. DICER1 testing may be informative in a follicular-patterned DHGTC without a conventional BRAF or RAS driver, but it does not replace the Turin criteria or the WHO definition of DHGTC.

The paired primary tumor and lymph-node metastasis from case 2 showed p.R624* in both sites, whereas p.D1810Y was detected only in the primary tumor. This finding is compatible with intratumoral heterogeneity, with p.R624* present in a shared clone and p.D1810Y restricted to a subclone. Regional sampling and a metastatic allele fraction below the assay threshold remain alternative explanations. Since the pair was not orthogonally validated and only one region from each site was tested, no inference can be made regarding the role of p.D1810Y in metastatic dissemination. The case nevertheless illustrates that a molecular result obtained from a single block may not represent all tumor regions or metastases [18–20].

In this cohort, DICER1-altered tumors were smaller than DICER1-wild-type tumors; vascular invasion and extrathyroidal extension were observed only in the DICER1-wild-type group. These are merely descriptive observations. Given incomplete follow-up data and the small sample size of the present study, tumor recurrence risk, metastatic behavior and patient survival outcomes cannot be attributed to DICER1 genetic status. Further investigations with larger sample sizes are warranted.

Conclusions

DICER1 alterations were identified in a subset of DHGTCs with follicular morphology, RNase IIIb-associated variants, and absence of canonical BRAF/RAS driver alterations. These findings support DICER1-altered DHGTC as a candidate molecular-pathological subgroup and suggest a follicular-patterned route of high-grade tumor evolution.

Declarations

Conflict of interes

The authors declare that they have no conflict of interest.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine (Nanjing, China). Informed consent was waived due to the retrospective design of the study. All procedures performed in this study were in strict accordance with the principles of the Declaration of Helsinki and the institutional ethical guidelines and regulations.

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Author Contribution

S.Y. conceived and designed the study, acquired and analyzed the experimental data, interpreted the results, and drafted the manuscript. Y.W. and Z.S. performed and interpreted the molecular genetic analyses. S.Y., R.L. and Z.Z. collected clinical cases, critically reviewed and revised the manuscript for important intellectual content, and ensured the scientific integrity of this work. All authors have read and approved the final version of the manuscript.

Data Availability

The sequencing data generated in this study have been deposited in the Genome Variation Map (GVM) of the National Genomics Data Center, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences, under accession number GVM001582. The data are publicly available at:<https://ngdc.cncb.ac.cn/gvm/getProjectFile?t=90553405>.

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Figures

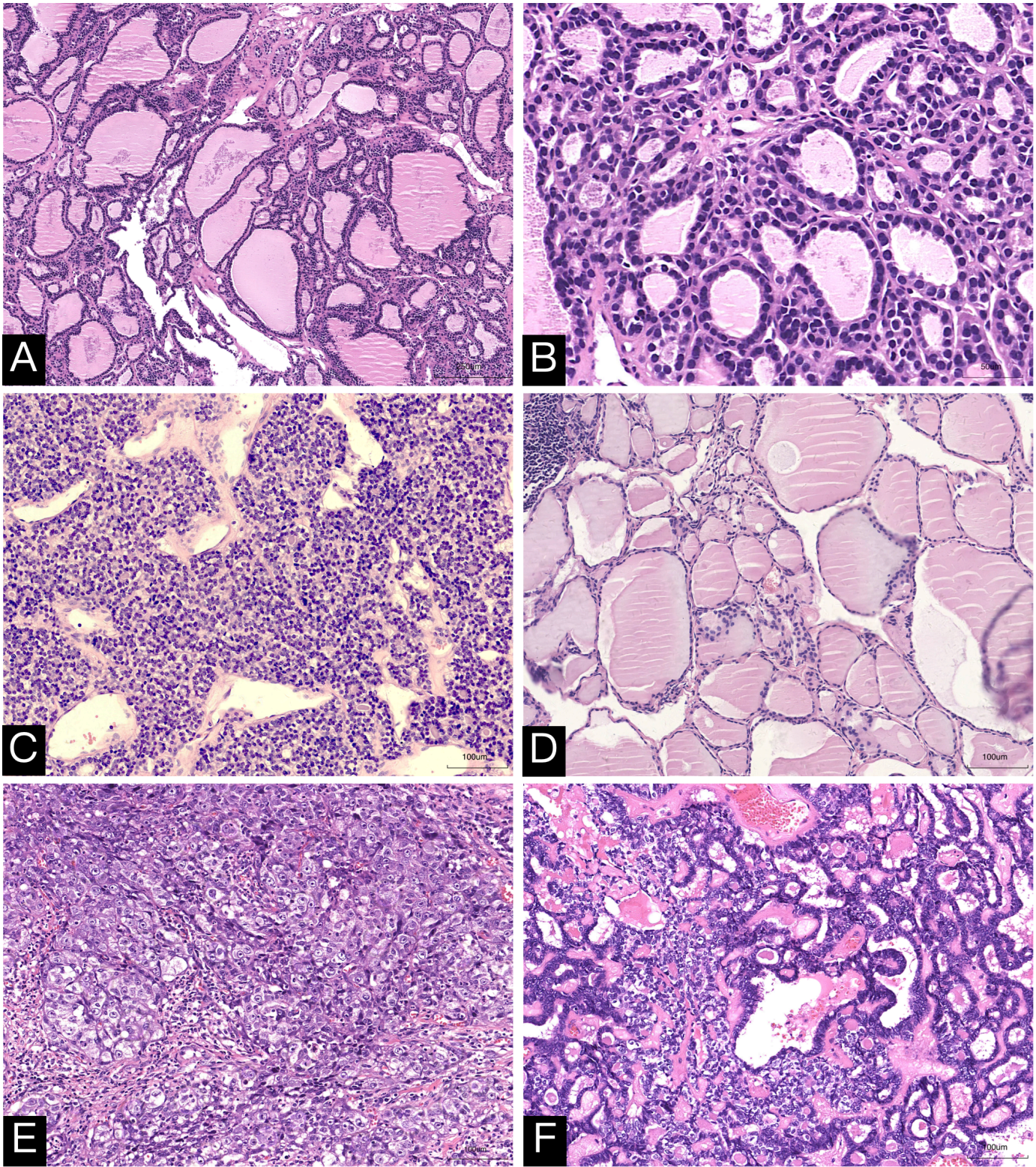


Figure 1

Histological spectrum of high-grade follicular cell-derived thyroid carcinomas.

(A,B) Case 1, DICER1-altered DHGTC, showing a predominantly follicular growth pattern (A) and mitotic activity at high power (B). (C) Case 2, DICER1-altered DHGTC, primary tumor with a cellular nested/solid component. (D) Lymph-node metastasis from case 2. (E) DICER1-wild-type DHGTC with a papillary

thyroid carcinoma background (case 6). (F) PDTC with a solid/trabecular growth pattern (case 7). Hematoxylin and eosin stain; scale bars as indicated.

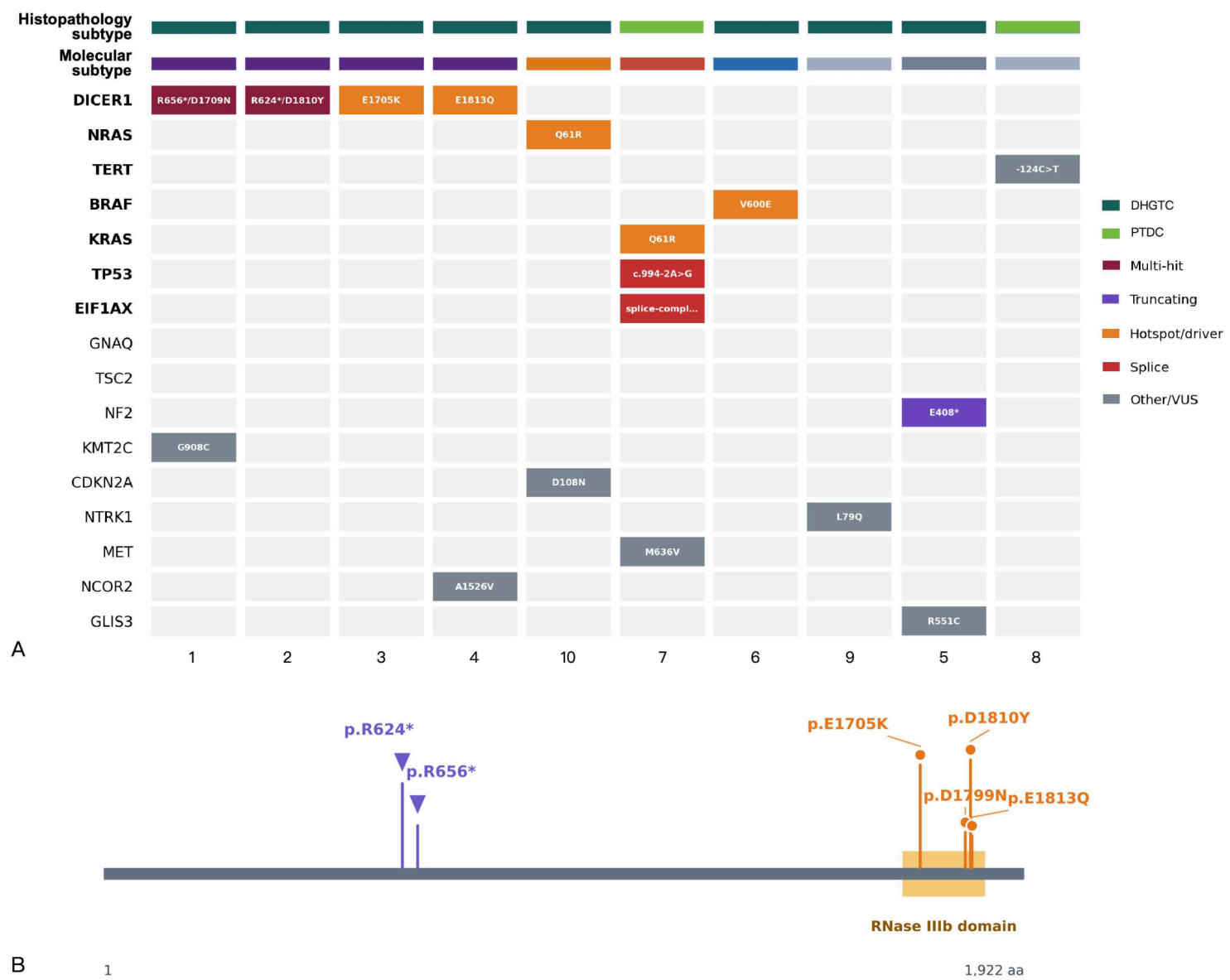


Figure 2

(A) Clinical-Pathological-Molecular Integrative Profiling of 10 Cases of High-Grade Thyroid Carcinoma. Patient-level molecular landscape of the preliminary high-grade thyroid carcinoma series, showing the distribution of recurrent driver and additional genetic alterations. (B) Distribution of DICER1 alterations across the protein. Truncating variants and RNase IIIb-domain variants are shown; two tumors harbored a truncating variant together with an RNase IIIb-domain variant, compatible with a candidate two-hit pattern.

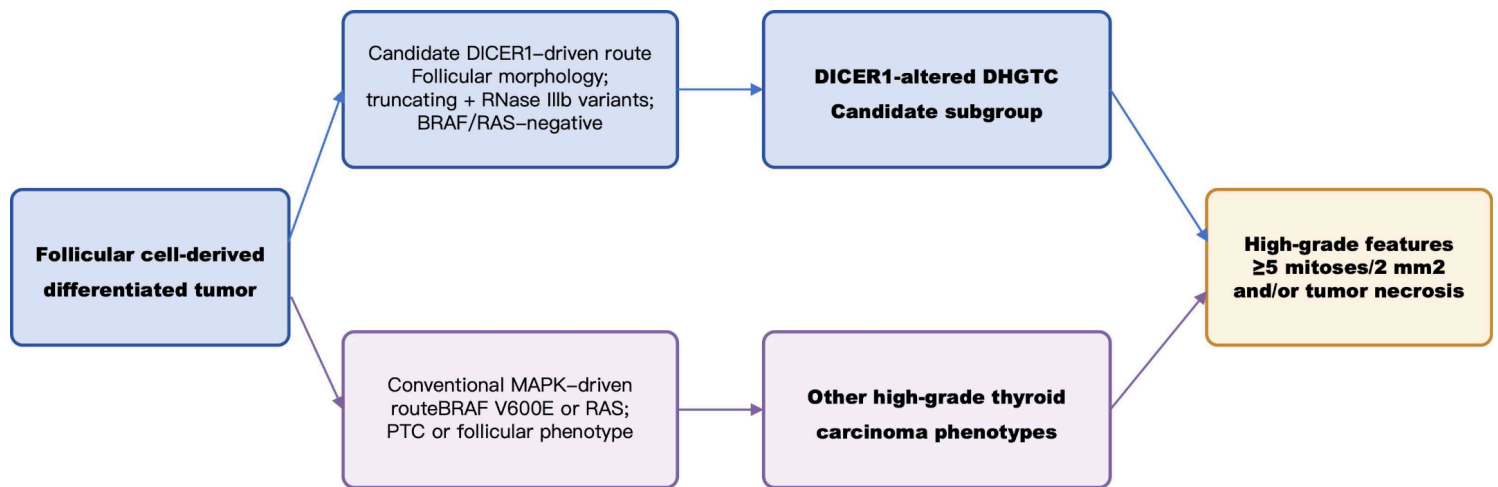


Figure 3

Proposed molecular-pathological routes to high-grade follicular cell-derived thyroid carcinoma. The DICER1-associated route is presented as a hypothesis-generating model and does not establish direct progression from conventional FTC to DHGTC.

Supplementary Files

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