

# Molecular Pathology of Differentiated Thyroid Cancer



Yuri E. Nikiforov, MD, PhD

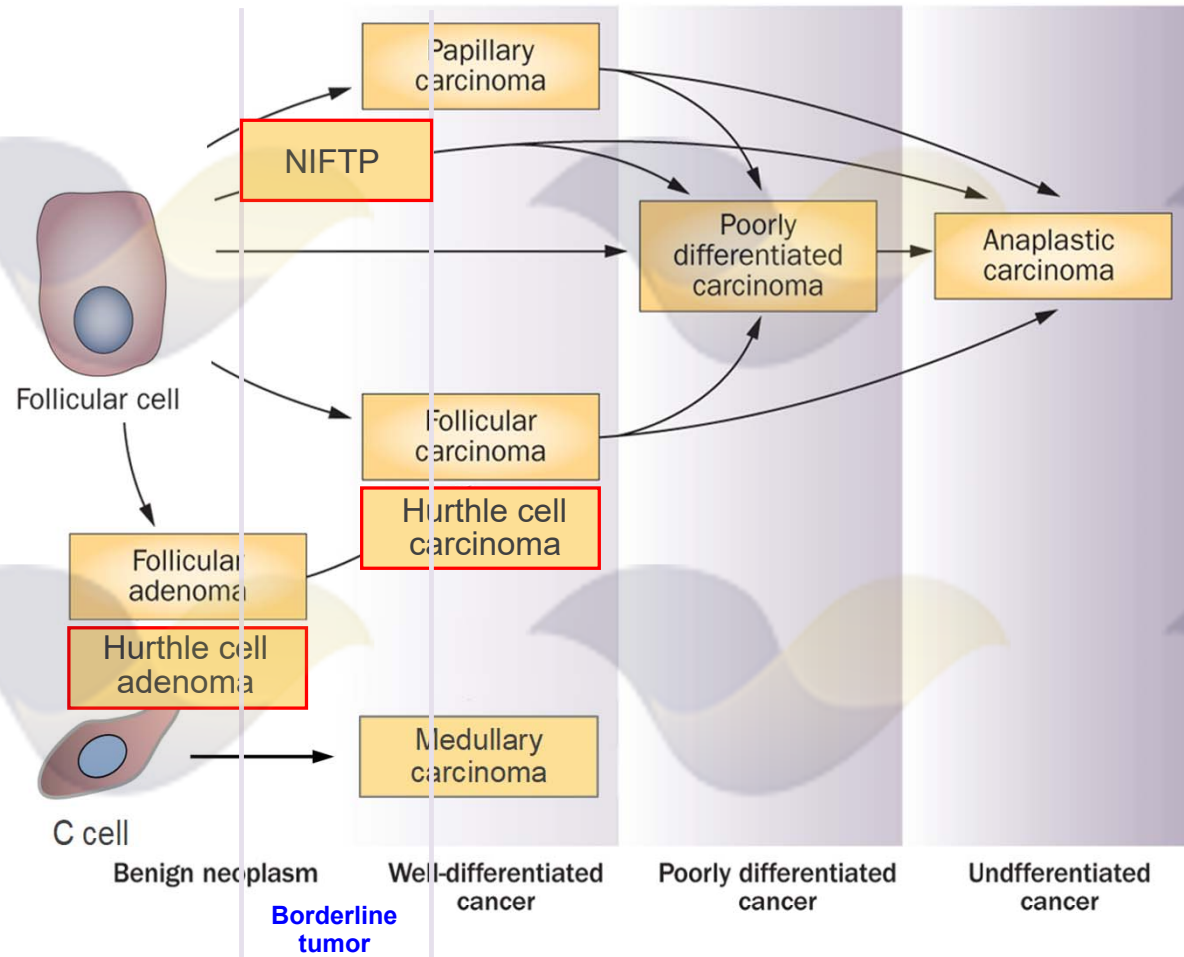
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Director, Division of Molecular & Genomic Pathology  
Co-Director, Multidisciplinary Thyroid Center  
University of Pittsburgh Medical Center

**UPMC** LIFE  
CHANGING  
MEDICINE

# Disclosures

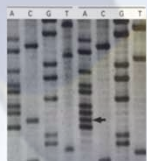
- Own IP related to ThyroSeq through University of Pittsburgh (royalties)
- Consultant to Sonic Healthcare USA (consultant fees)

# Thyroid Tumors



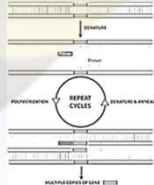
# Progress in Technology and Understanding Thyroid Cancer Genetics

▶ 1953  
DNA structure discovered



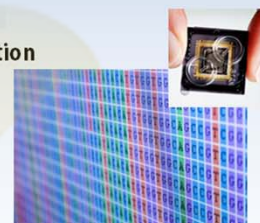
▶ 1977  
Sanger sequencing

▶ 1983  
Polymerase chain reaction

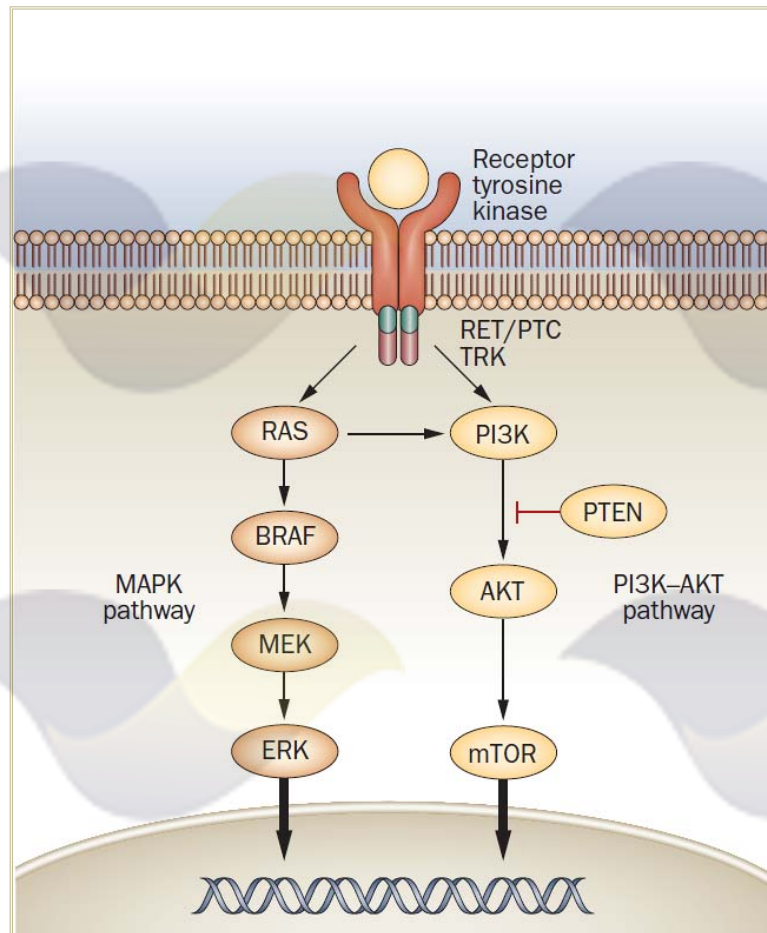


▶ 2001  
Working draft of human genome published

▶ 2004  
Next Generation Sequencing



# Molecular Pathogenesis of Thyroid Cancer



## Types of driver alterations in thyroid cancer:

- **Point mutations**
- **Gene fusions**
- **Copy number alterations (CNAs)**

# Genetics of Papillary Thyroid Carcinoma

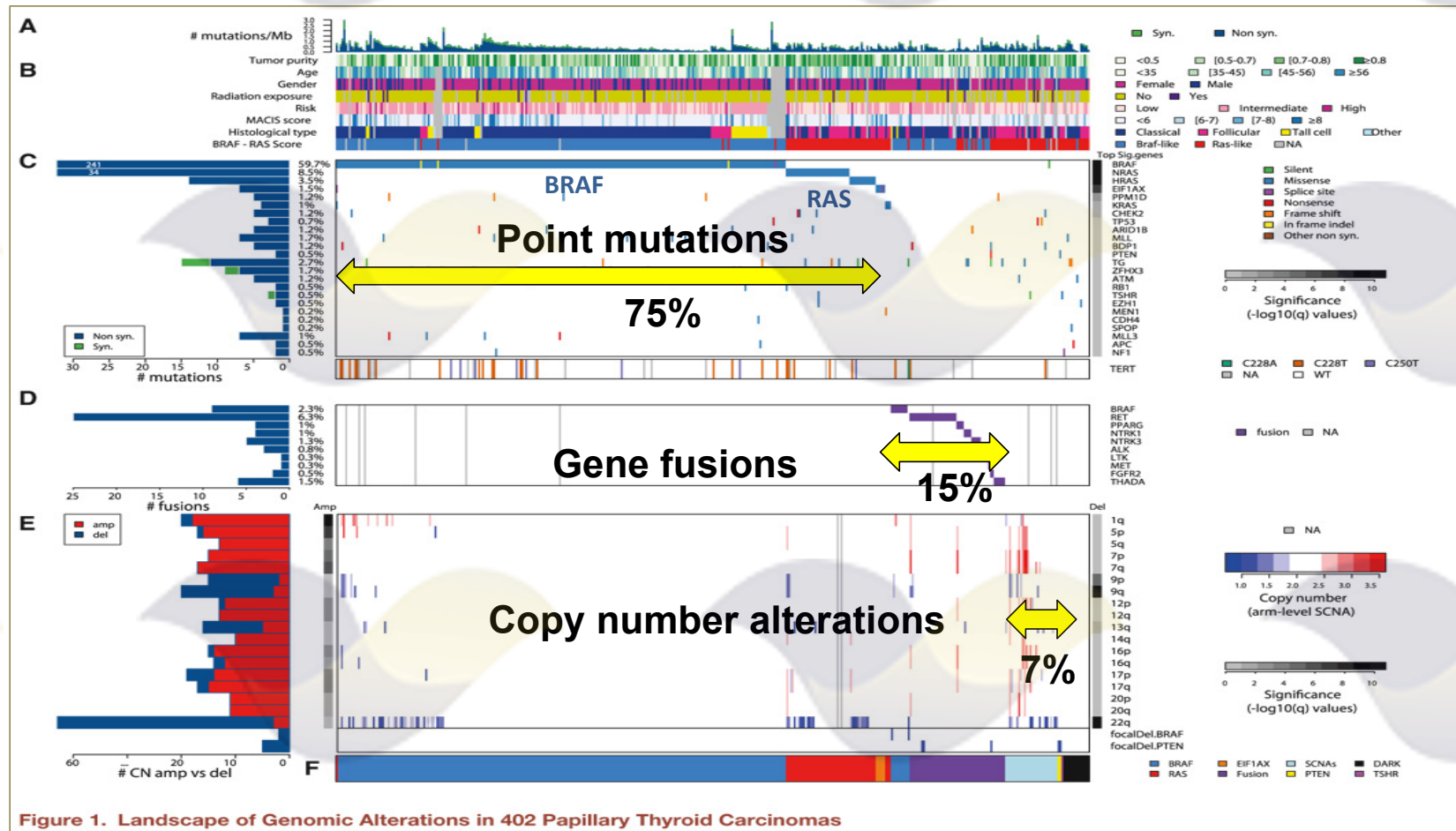
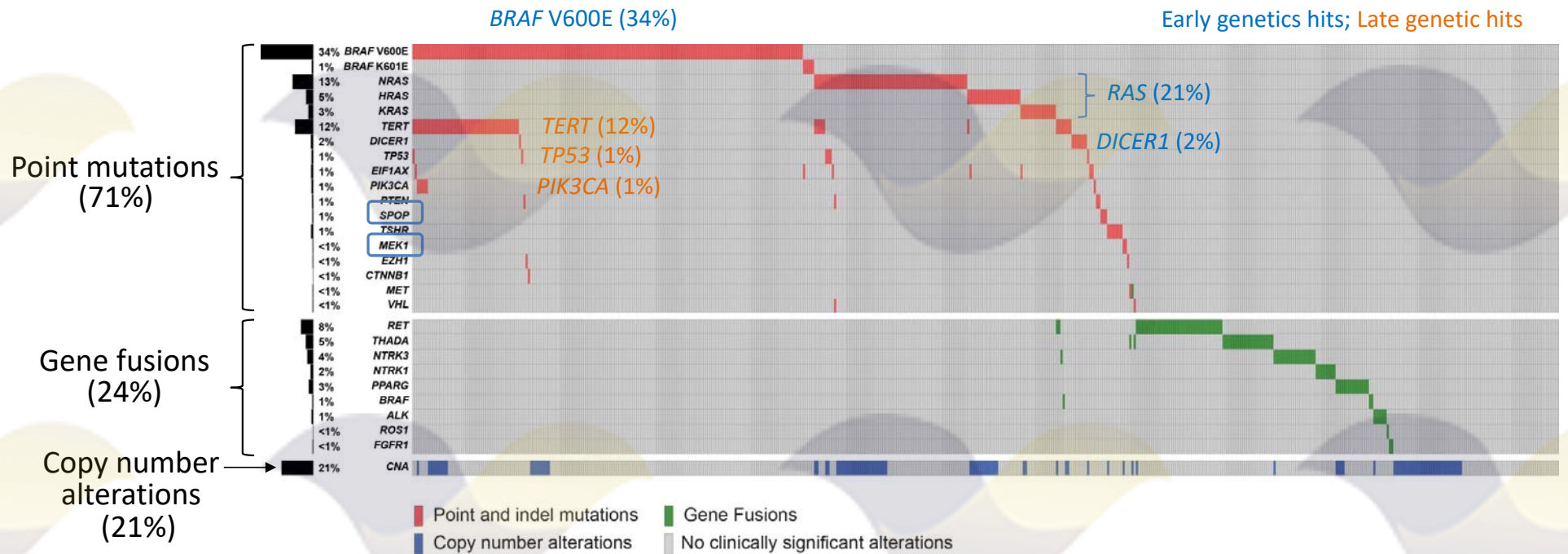


Figure 1. Landscape of Genomic Alterations in 402 Papillary Thyroid Carcinomas

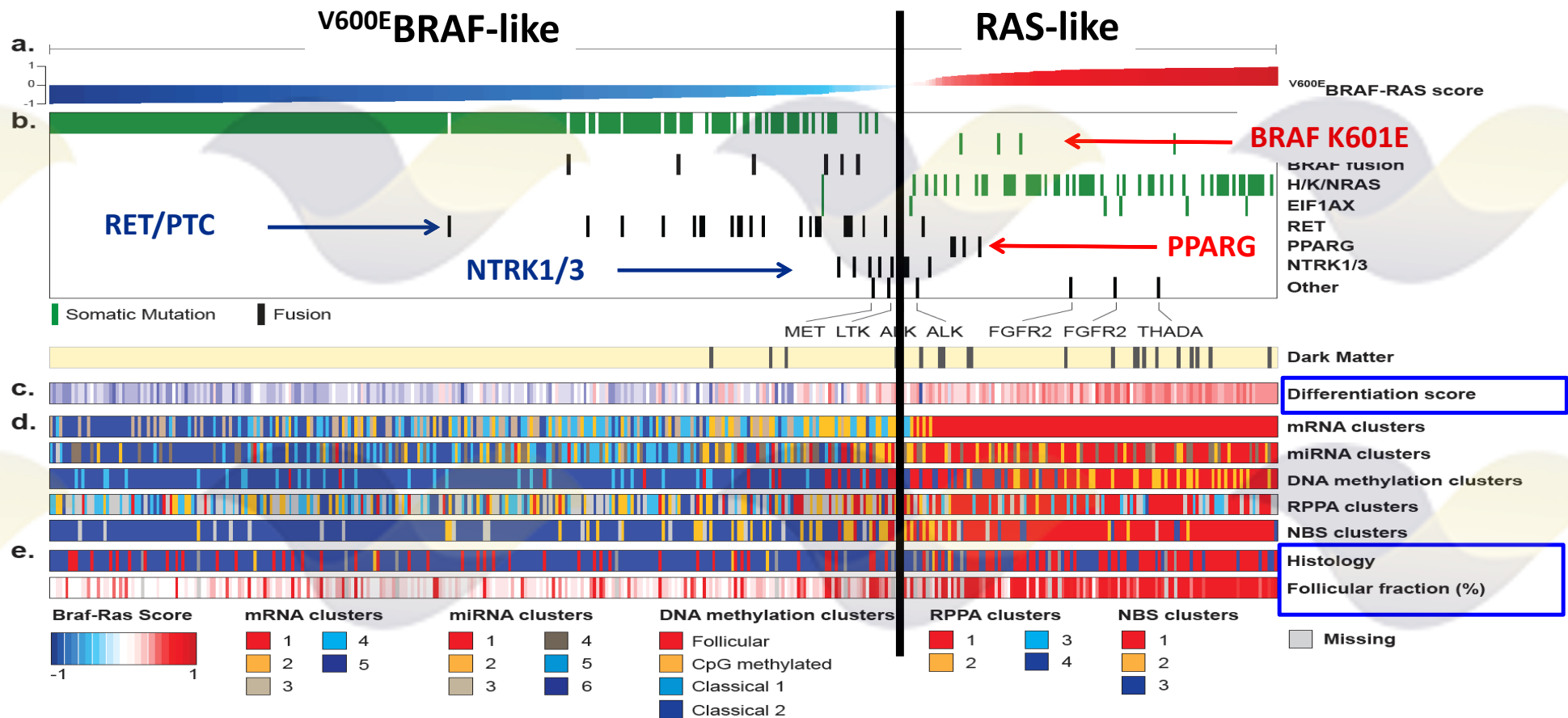
# Genetics of Papillary Thyroid Carcinoma

(single institution, consecutive series, n=512)



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# BRAF-like and RAS-like Papillary Carcinomas

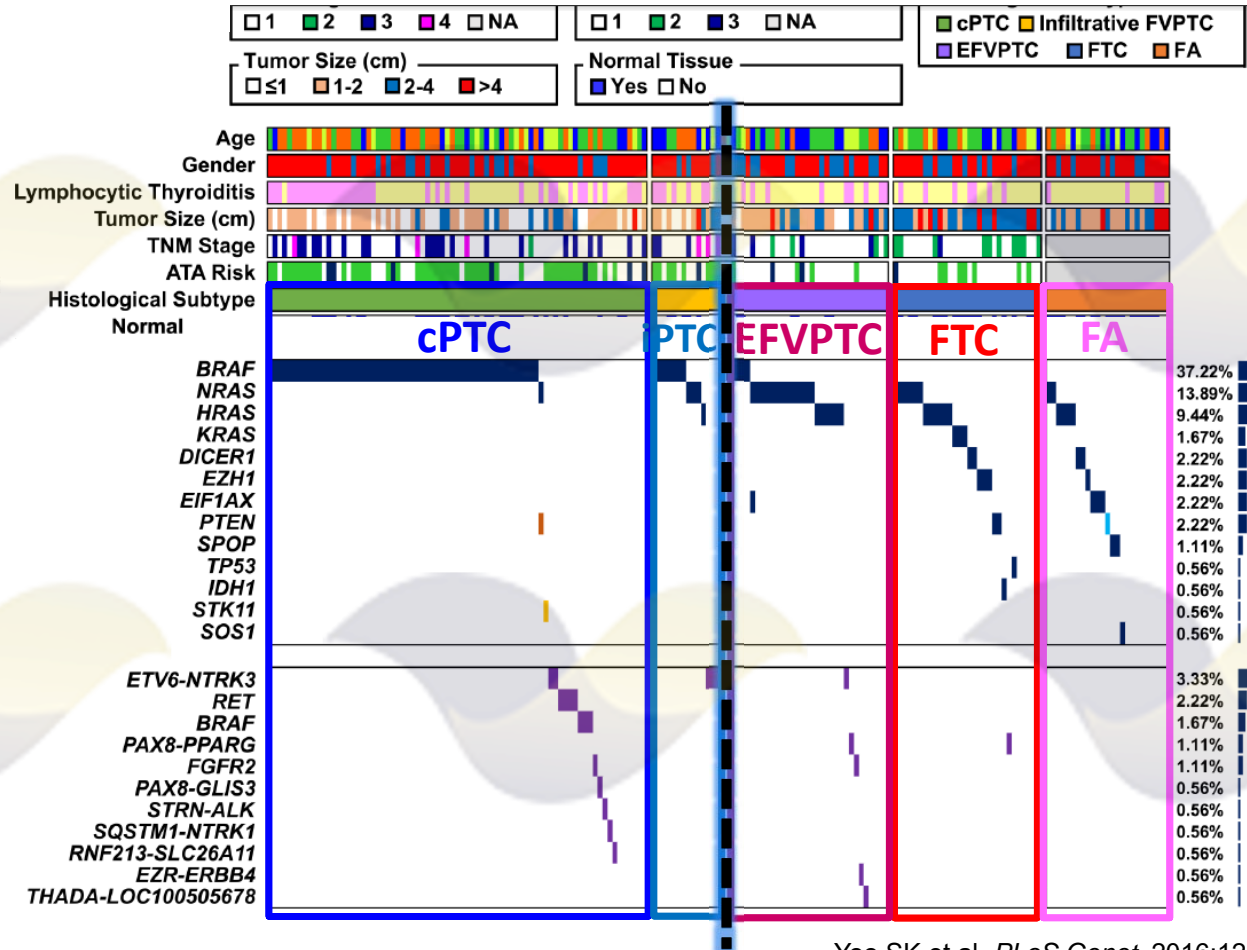
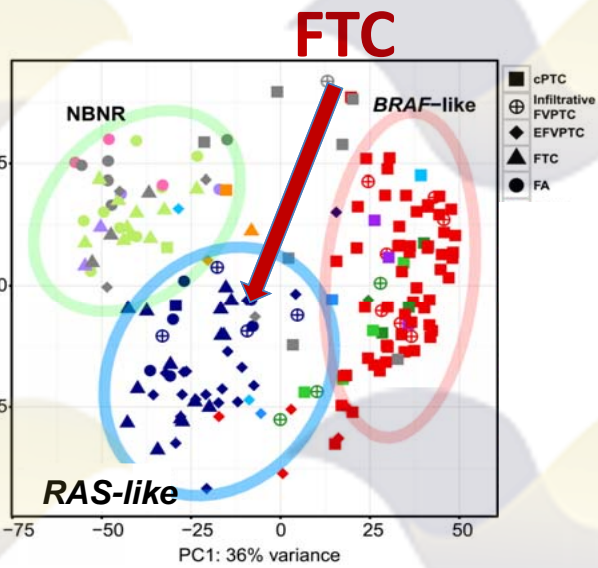


The Cancer Genome Atlas Research Network. *Cell* 159:676-690 (2014)



# Follicular Thyroid Carcinoma

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# NIFTP

## Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

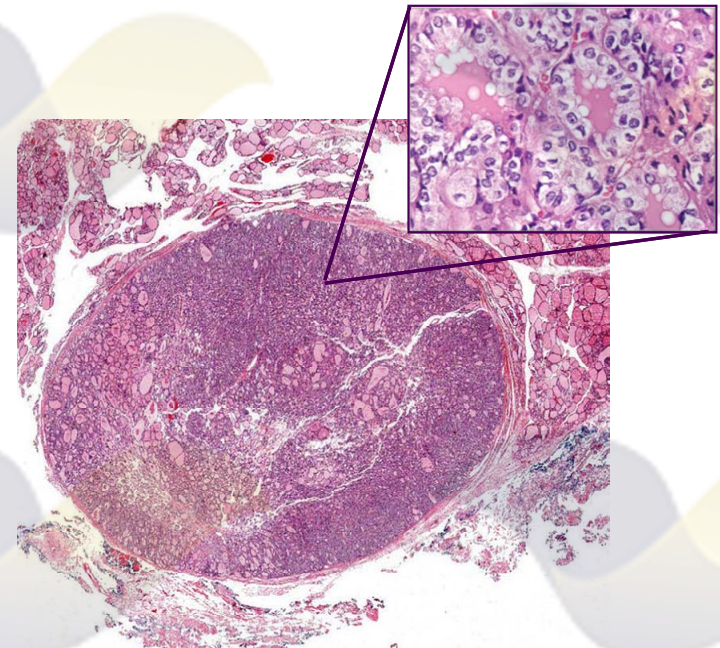
**JAMA Oncology**

Research

Original Investigation

### Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

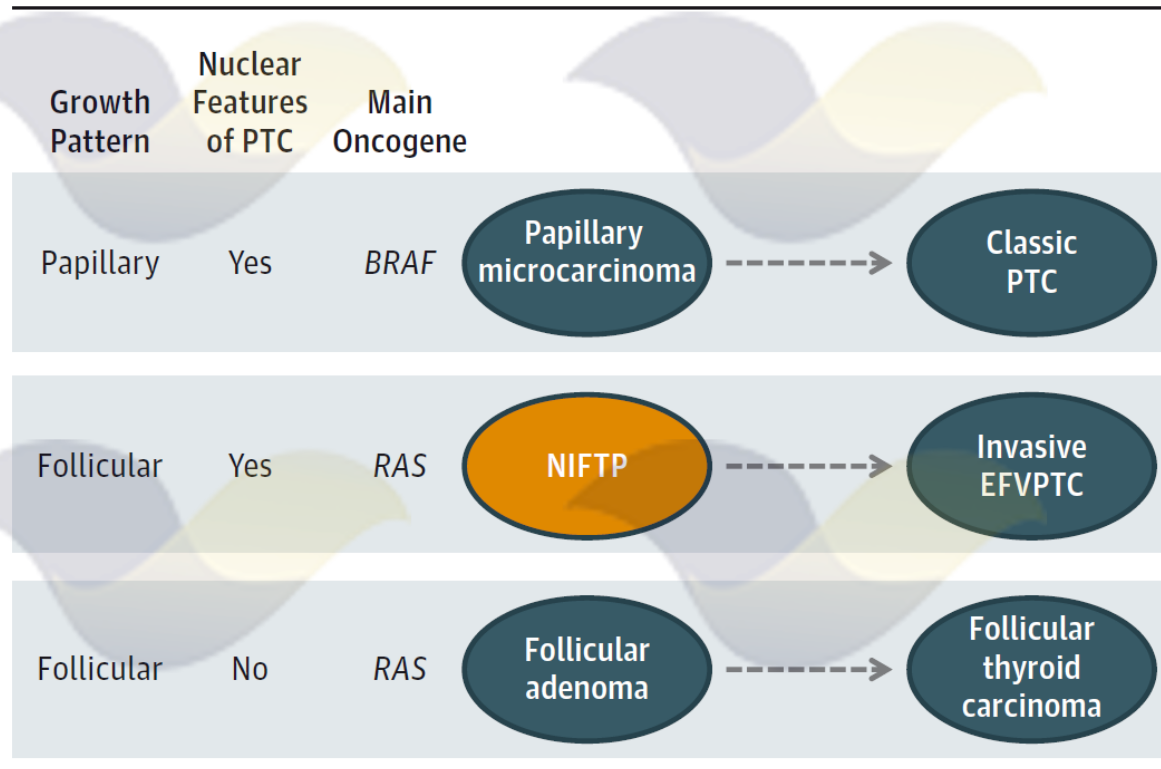
Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD;  
Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD;  
Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD;  
Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS;  
Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD;  
Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD;  
Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. Livolsi, MD; Gregory W. Randolph, MD; Ronald A. Gosselin, MD



Nikiforov et al. *JAMA Oncology* (2016)

# Multistep Cancer Progression and Existence of Borderline Tumors: NIFTP

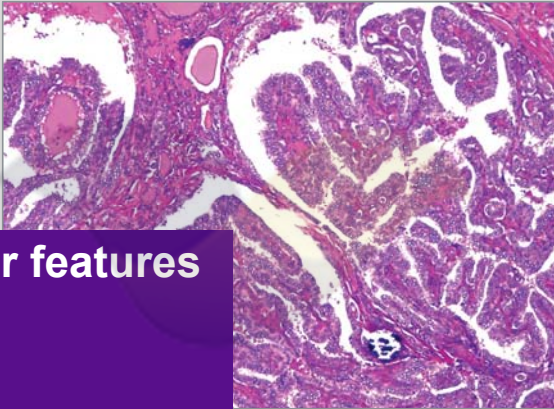
Figure 2. Putative Scheme of Thyroid Carcinogenesis



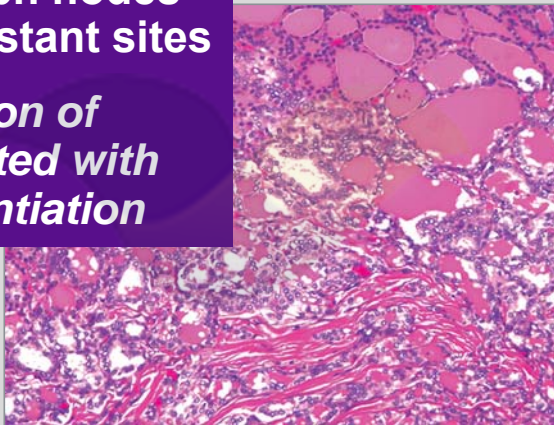
Nikiforov et al. *JAMA Oncology* 2016; 2:1023-9.

## BRAF-like tumors

cPTC



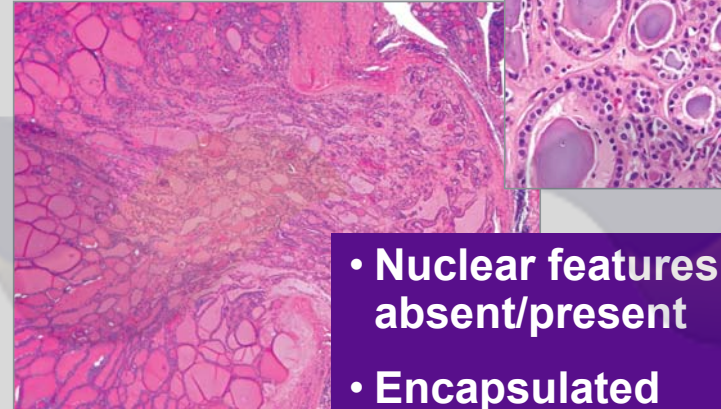
VPTC



- Classic nuclear features of PTC
- Infiltrative
- Spread to lymph nodes first, later to distant sites
- *Lose expression of genes associated with thyroid differentiation*

## RAS-like tumors

FTA/FTC



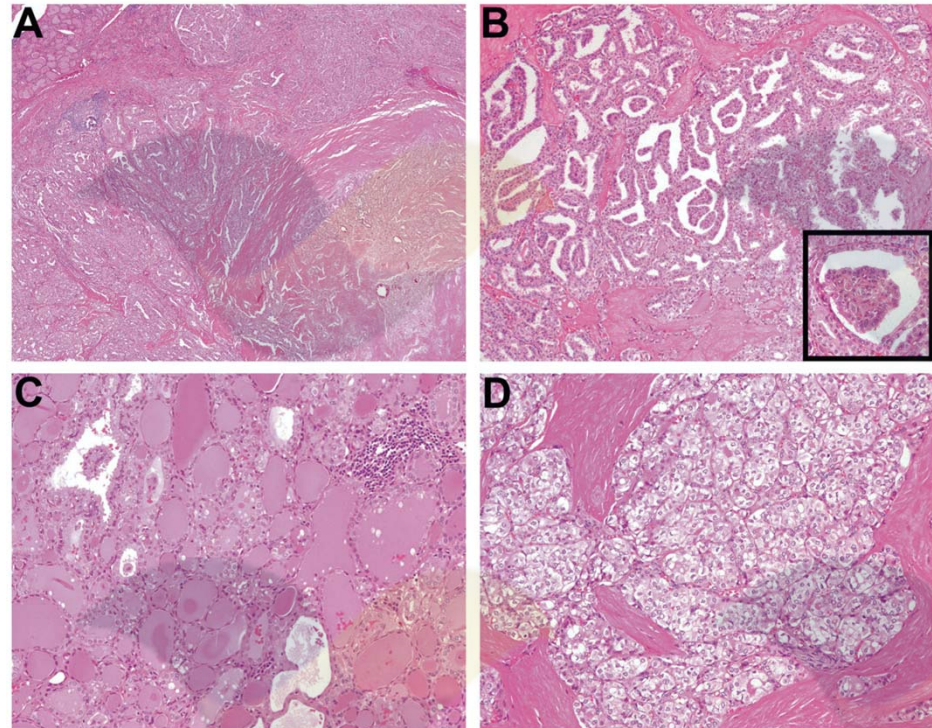
NIFTP Invasive



- Nuclear features of PTC absent/present
- Encapsulated
- Spread to distant sites, rarely to lymph nodes
- *Retain expression of genes associated with thyroid differentiation*

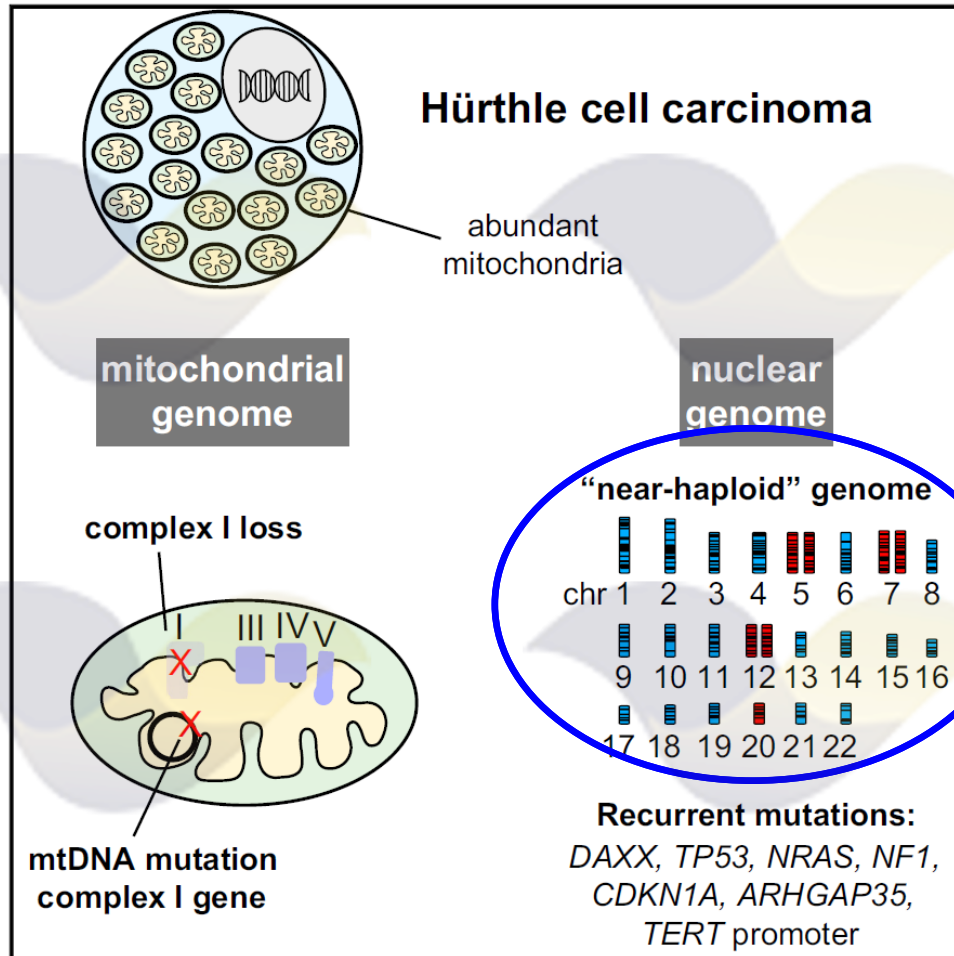
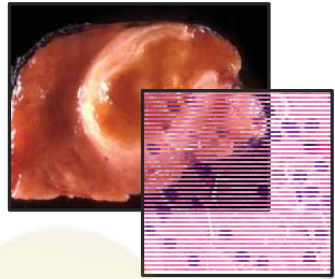
# Morphology of kinase fusion-positive thyroid carcinomas

- Multinodular growth
- Prominent fibrosis
- Extensive lymphovascular spread
- Mixed papillary/follicular/solid architecture



*IRF2BP2-NTRK1* fusion-positive PTC

# Genetics of Hurthle cell carcinoma



Mitochondrial DNA mutations

Chromosomal copy number alterations (CNA)

Nuclear DNA mutations

Gopal et al. Cancer Cell 2018

# Genetics of Hurthle cell carcinoma

Endocrine-Related Cancer | W R Doerfler et al. | Molecular alterations in Hurthle cell tumors | 283 | 301-309

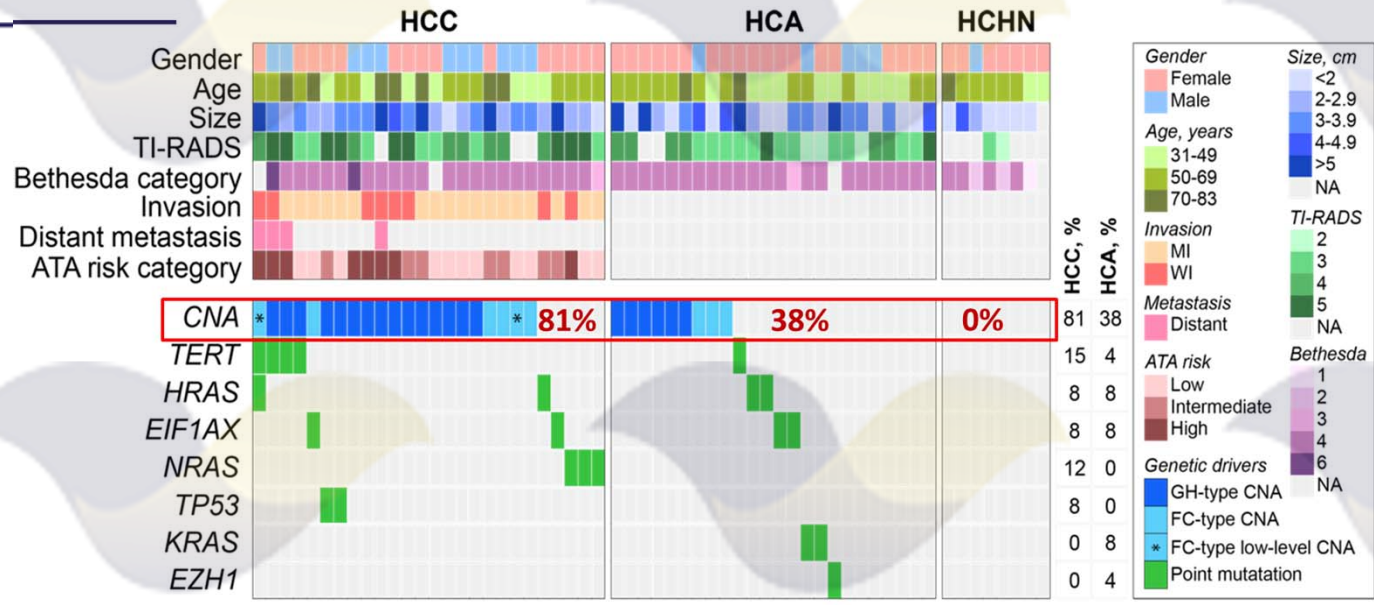
RESEARCH

## Molecular alterations in Hurthle cell nodules and preoperative cancer risk

William R Doerfler<sup>1</sup>, Alyaksandr V Nikitski<sup>1</sup>, Elena M Morariu<sup>1</sup>, N Paul Othori<sup>2</sup>, Simion I Chiosea<sup>3</sup>, Michael S Landau<sup>4</sup>, Marina N Nikiforova<sup>5</sup>, Yuri E Nikiforov<sup>5</sup>, Linwah Yip<sup>3</sup> and Pooja Manroa<sup>1\*</sup>

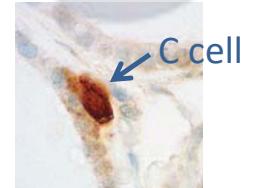
<sup>1</sup>Division of Endocrinology and Metabolism, University of Pittsburgh, Pittsburgh, Pennsylvania, USA  
<sup>2</sup>Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA  
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\*Correspondence should be addressed to P Manroa: [pomanroa@utmb.edu](mailto:pomanroa@utmb.edu)

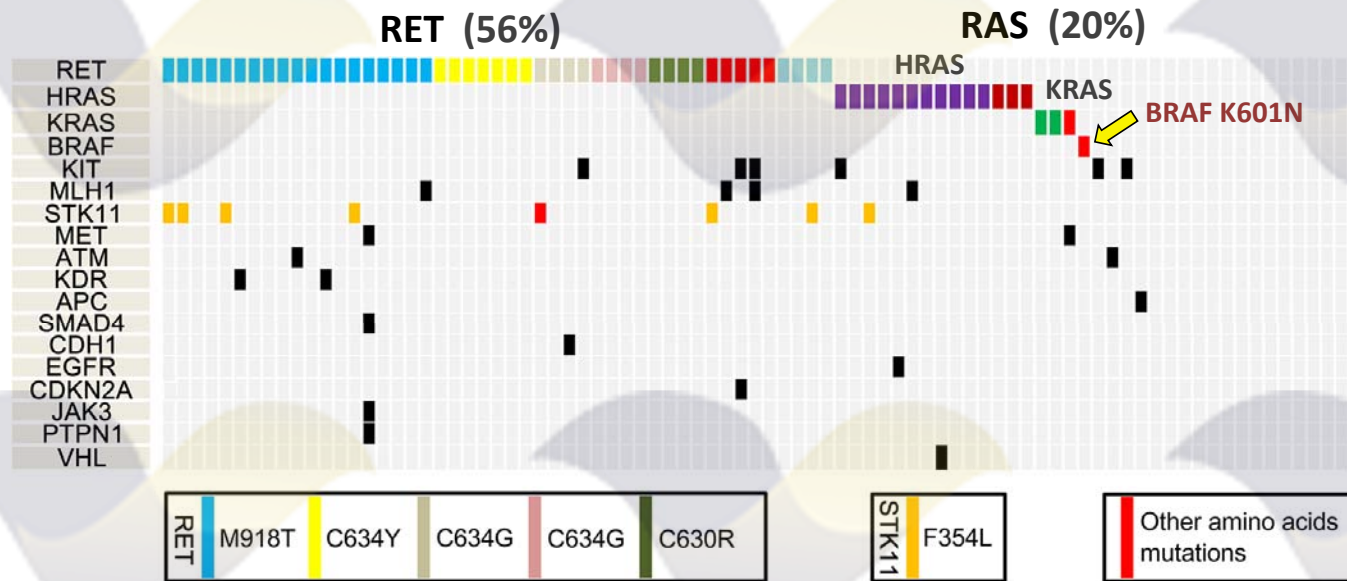


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# Genetic alterations in medullary carcinomas



- Familial MTC >95% RET mutations
- Sporadic MTC



- Singler cases described with ALK, RET, BRAF fusions
- All MTC strongly express calcitonin and other neuroendocrine genes



# Genetic alterations in thyroid cancer: *Summary*

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## Point mutations

	NIFTP	PTC	FTC	HCC	MTC	PDTC	ATC
<i>BRAF</i> V600E, %		40-45			<5	5-30	10-45
<i>RAS</i> , %	30-40	20	40-50	10-20	10-15	20-40	20-40
<i>EIF1AX</i> , %	5-10	<5	10-15	10-15		10	10
<i>PTEN</i> , %	~5	<3	10-15	10-15		5-20	10-15
<i>DICER1</i> , %	~5	<5	10-15				
<i>TP53</i> , %		<5	<10	15-20	<5	10-30	50-70
<i>TERT</i> , %		5-10	15	10-20		30-50	70
<i>PIK3CA</i> , %		<5	<5			5-20	5-18
<i>AKT1</i> , %						<5	<5
<i>RET</i> , %					40-50		

## Gene fusions

<i>RET/PTC</i> , %		5-10				<5	<1
<i>PPARG</i> , %	20-30	<5	10-20			5-7	<1
<i>NTRK1/3</i> , %		<5				1-5	
<i>ALK</i> , %		<5			2	5-10	<5
<i>THADA</i> , %	20-30	5	<5				

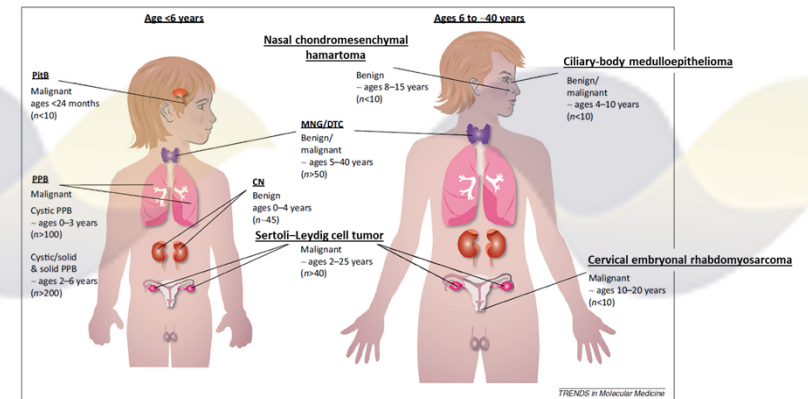
## Copy number alterations

CNA %	20	5-10	40-50	70	20	50	90
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# DICER1 mutations in thyroid nodules and cancer

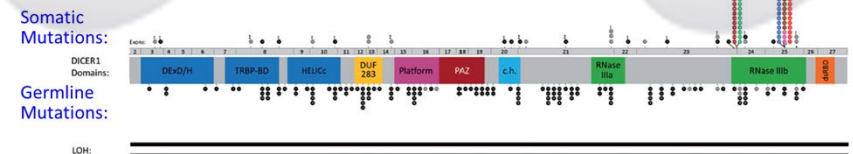
- DICER1 gene involved in production of miRNA that regulates gene expression
- Germline mutations can cause DICER1 syndrome
- Hotspot *DICER1* mutations found in ~1.4% of thyroid nodules (Chong et al. JCEM 2021;106:968)
- Most are somatic, but some co-exist with germline mutations
- DICER1-driven thyroid nodules: colloid-rich histologically hyperplastic nodules; low-risk follicular variant PTC; poorly differentiated cancer of childhood and adolescence

## DICER1 syndrome



Choong CS et al. Trends Mol Med. 2012;18:503

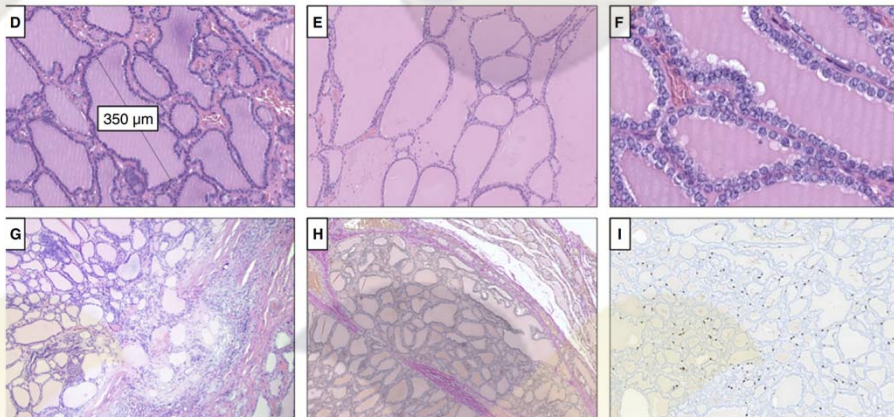
## Location of somatic and germline mutations in DICER1 gene



Foulkes et al. Nature Reviews Cancer 2014

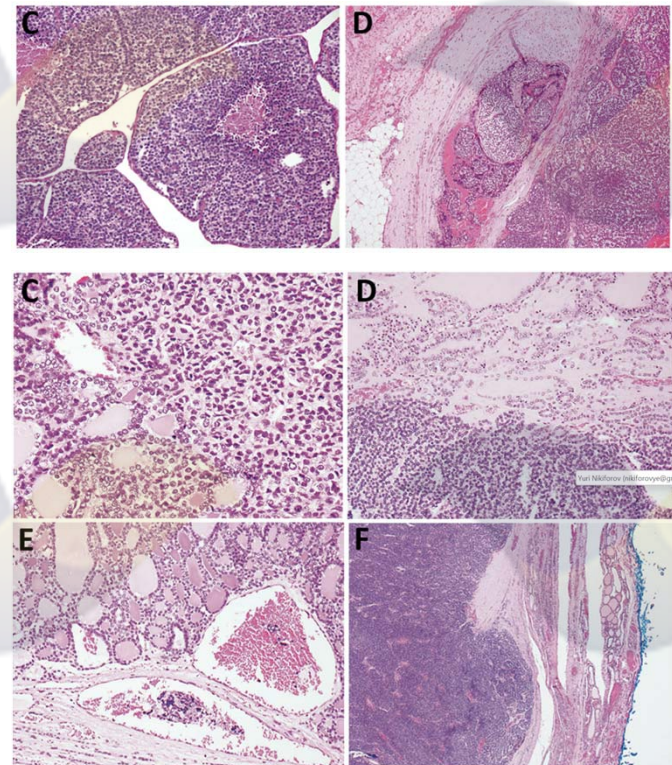
# Spectrum of DICER1-driven thyroid cancers

## Low-risk macrofollicular variants of PTC or FTC



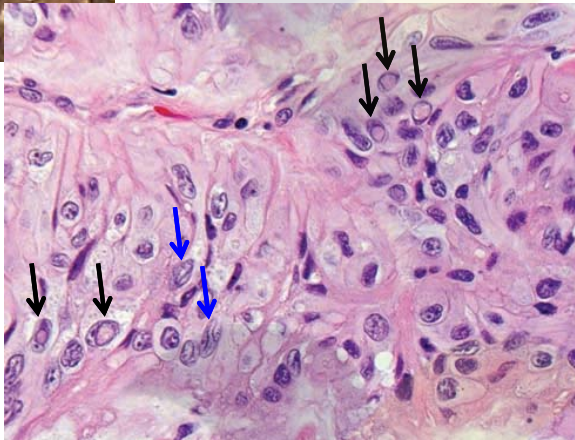
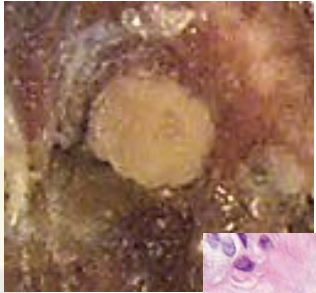
Juhlin CC et al. *Histopathology* 2021;79:661

## Poorly differentiated cancer of childhood and adolescence



Chernock RD et al. *Mod Pathol.* 2020;33:1264

# Hyalinizing trabecular tumor: PTC or not?



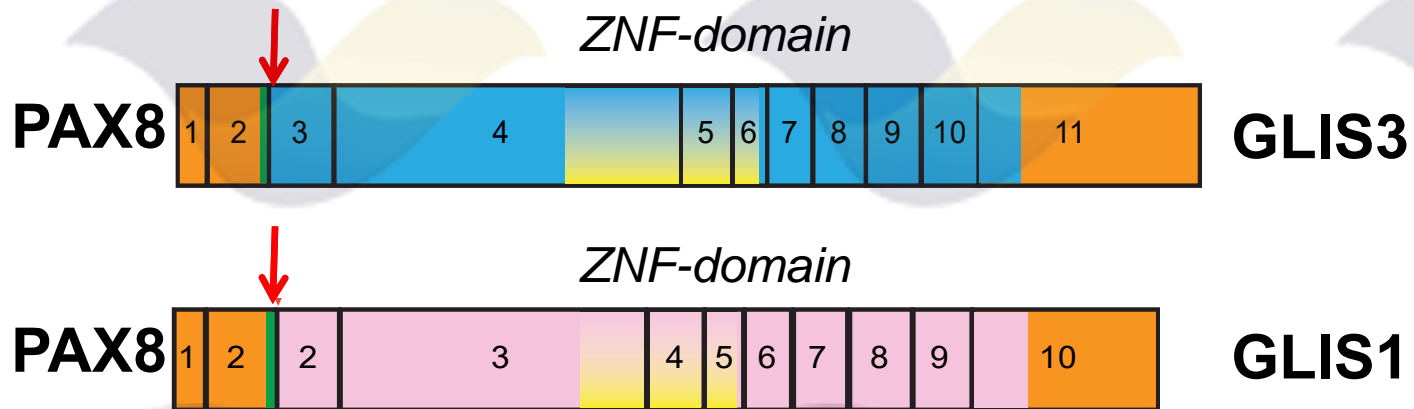
Multiple grooves and pseudoinclusions frequently seen mimicking PTC

## HTT Diagnosis on FNA Cytology

Study	HTT	Follicular neoplasm	Other suspicious	Suspicious for PTC or PTC
Carney et al. (n=55)	4 (7%)	7 (13%)	5 (9%)	33 (60%)
Casey et al. (n=25)	0	5 (20%)	2 (8%)	18 (72%)

Carney JA et al. GLIS. *AJSP* (2008); Casey MB et al. *AJSP* (2004)

# PAX8-GLIS fusions are a hallmark of HTT



*Nikiforova et al. Thyroid (2019)*

# Prevalence of PAX8-GLIS fusions in HTT and PTC

## Prevalence of GLIS Fusions in Thyroid Surgical Samples

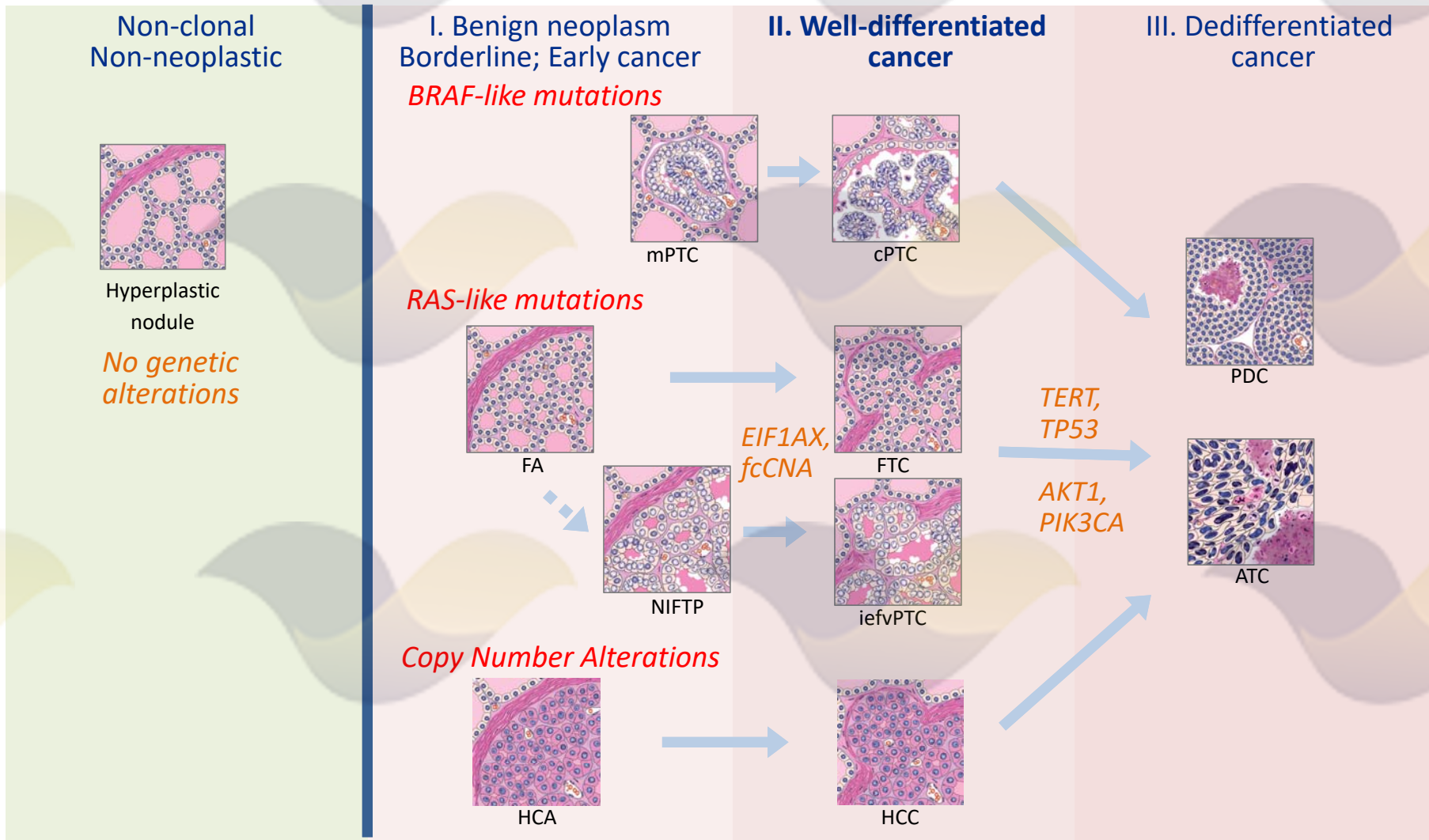
	<i>PAX8-GLIS3</i>	<i>PAX8-GLIS1</i>	Total
HTT (n=14) <sup>1</sup>	13/14 ( <b>93%</b> )	1/14 ( <b>7%</b> )	14/14 ( <b>100%</b> )
PTC (n=704) <sup>2</sup>	0/704 ( <b>0%</b> )	1/704 ( <b>0.1%</b> )	1/704 ( <b>0.1%</b> )

<sup>1</sup>Nikiforova et al. *Thyroid* (2019); <sup>2</sup> Combined Nikiforova et al. *Thyroid* (2018) (n=220) and TCGA *Cell* (2014) (n=484)

- HTT and PTC have different genetic origin
- HTT is a distinct type of thyroid tumors

*Nikiforova et al. Thyroid (2019)*

# Summary: Molecular Classification of Follicular Cell-Derived Thyroid Cancer



# Conclusions

- Genetic drivers for the majority of thyroid cancers have been uncovered
- Driver genetic alterations determine cancer phenotypical features, biological and clinical properties
- Molecular classification of thyroid cancer



# Thank you!

