ATA 2018
ThyroSeq®
Short Call
Poster 79

Prevalence and Outcome of Thyroid Nodules Carrying DICER1 Mutations in Adult Patients: Study of 6,732 Thyroid Nodules

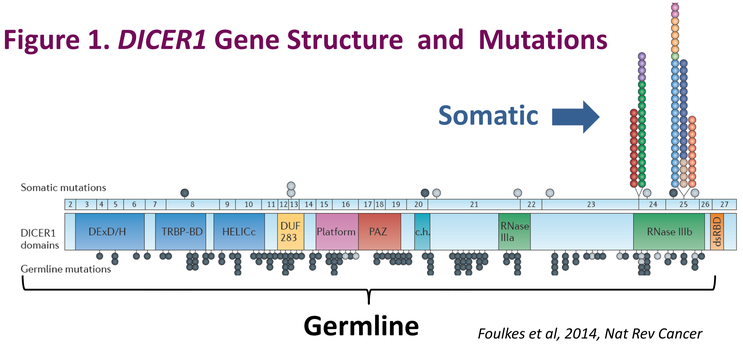
Yuri E. Nikiforov [1], Dev Abraham [2], Zubair Baloch [3], Victor Bernet [4], Sally E. Carty [1], Steven Hodak [5], Sophia Hu [6], Darren Lackan [7], Susan Mandel [3], Mira Milas [8], Marina N Nikiforova [1], Achilles Paparsenos [9], Kepal N. Patel [5], Snehal Patel [10], Barbara Rivera [11], Linwah Yip [1], William D. Foulkes [11,12]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA [2]University of Utah, Salt Lake City, UT [3]University of Pennsylvania, Philadelphia, PA [4]Mayo Clinic, Jacksonville, FL [5]NYU Langone Medical Center, New York, NY [6]Mt Sinai Health System, New York, NY [7]Diabetes and Thyroid Center of Fort Worth, Ft. Worth, TX [8]Banner-University Medical Center, Phoenix, AZ [9]Bucks Thyroid & Endocrine Care LLC, Yardley, PA [10] Emory University, Atlanta, GA [11]McGill University, Montreal, QC, [12]Research Institute of the McGill University Health Centre, Montreal, QC, Canada

INTRODUCTION

DICER1 encodes an endoribonuclease involved in microRNA maturation and therefore has an important role in gene transcript regulation. Germline mutations scattered along *DICER1* are associated with DICER1 syndrome which prominently features thyroid nodules (Figure 1). The tumors typically carry a second somatic mutation in the RNase IIIb catalytic domain, referred to as "hotspot." These hotspot *DICER1* mutations are found in ~1-2% of thyroid papillary carcinomas (PTC). The incidence of the hotspot mutations in thyroid nodules in adults, their association with malignancy and with other, germline *DICER1* mutations remain largely unknown.

Figure 1. *DICER1* Gene Structure and Mutations



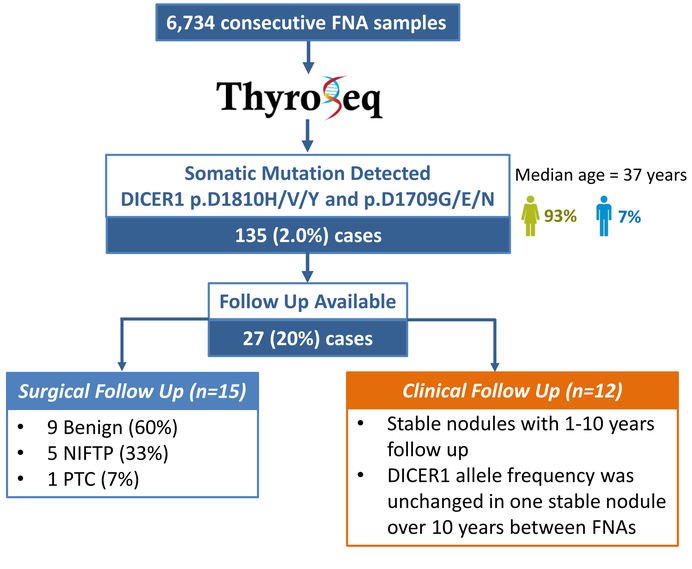
Foulkes et al, 2014, Nat Rev Cancer

METHODS

- 6,734 consecutive clinical FNA samples from indeterminate cytology thyroid nodules were analyzed for hotspot *DICER1* mutations using ThyroSeq v3 targeted next generation sequencing (NGS) assay from 11/2017-05/2018
- Follow-up was collected for 27patients
- A subgroup of cases underwent full *DICER1* coding region and exon-intron boundaries analysis using a custom Fluidigm Access Array followed by NGS on Illumina MiSeq

RESULTS

Somatic *DICER1* hotspot mutations were identified in 135 (2.0%) of nodules, with D1810H/V/Y and D1709G/E/N being most common. Median patient age was 37 years (range 19-79 y), 93% were females. Follow-up was available for 27 patients: 15 underwent surgery with benign diagnoses in 9 cases, NIFTP in 5 and follicular variant PTC in 1. Twelve patients were managed non-surgically, including one with a stable nodule harboring *DICER1* mutation at an allele frequency unchanged over 10 years between FNA procedures.



A subset of 11 positive cases was tested for alterations in the entire *DICER1* gene, which confirmed the hotspot mutations in 10 cases and detected additional alterations in 9 (90%) samples, including non-hotspot mutations in 8 and LOH in 1 case (Table 1).

TABLE 1. DICER1 Sequencing of Coding Region and Exon-Intron Boundaries (n=11 cases)

Case #	Somatic Hot Spot Mutations		Truncating Mutations or LOH
Case 1	c.5126A>G	p. D1709G	c.3993_3994insT;p. C1333Lfs*5
Case 2	c.5114A>T	p.E1705V	c.734+3A>G
Case 3	c.5437G>C	p.E1813Q	c.5603+2T>C
Case 4	c.5437G>A	p.E1813K	Loss of Heterozygosity (LOH)
Case 5	c.5429A>T	p.D1810V	c.4005C>A;p.Y1335X
Case 6	c.5437G>C	p.E1813Q	None
Case 7	None	None	None
Case 8	c.5428G>T	p.D1810Y	c.2257-2A>G
Case 9	c.5428G>T	p.D1810Y	c.566delT:p.M190fs*
Case 10	c.5437G>C	p.E1813Q	c.488_491delCTTA;p.L164Hfs*17
Case 11	c.5113G>A	p.E1705K	c.996C>A;p.Y332X

CONCLUSIONS

- We report for the first time that likely somatic hotspot *DICER1* mutations are relatively common and found in ~2% of thyroid nodules in adults, who are typically middle-age women.
- At surgery, most of these nodules are found to be benign, with ~33% risk of NIFTP and ~7% risk of follicular variant PTC.
- Our analysis also shows that somatic hotspot mutations are usually accompanied by a second, loss of function *DICER1* mutation, which may in some cases be germline in nature.

REFERENCES

1. Foulkes et al. DICER1: mutations, microRNAs and mechanisms. 2014, Nat Rev Cancer 14(10):662-72
2. de Kock L et al. Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. 2014 Acta neuropathologica 128(1): 111-22