EIF1AX mutation in a patient with follicular thyroid carcinoma

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Abstract

Background The EIF1AX gene is a novel cancer gene that has previously found to be mutated in papillary thyroid carcinoma (PTC), follicular variant papillary thyroid carcinoma (FVPTC), and anaplastic thyroid carcinoma (ATC). We report a patient with follicular carcinoma found to have an EIF1AX mutation and discuss its role in tumorigenesis.

Patient Findings A 71-year-old woman presented with an enlarging right thyroid mass, which was follicular neoplasia on cytology. The fine needle aspirate of the nodule was examined with next generation sequencing (NGS) and found to harbor EIF1AX and TP53 mutations. The patient underwent right thyroid lobectomy with final pathology showing follicular carcinoma, oncocyctic-Hürthle cell type with capsular and vascular invasion. The patient returned one month later for completion thyroidectomy with the left thyroid lobe found to be negative for malignancy.

Summary The EIF1AX gene encodes a protein that mediates protein translation. Mutations in the EIF1AX gene have previously been reported in the tumorigenesis of PTC, FVPTC, and ATC. We report an EIF1AX mutation in a patient found to have follicular carcinoma.

Conclusions This is a report of an EIF1AX mutation detected in a follicular carcinoma.

Introduction

It is becoming increasingly important for the thyroid surgeon to understand the current clinical application and future potential of molecular biology for the diagnosis, management, and prognostication of differentiated thyroid cancer. Diagnostic molecular markers such as BRAF, RAS, P53, and RET-PTC have facilitated the evaluation of thyroid nodules. Molecular testing may reduce the number of unnecessary thyroid procedures and complications and may lead to a more individualized approach to thyroid surgery.

In their recent study of the genomic characterization of PTC, the Cancer Genome Atlas Research Network discovered many new driver procedures and oncogenes and may lead to a more individualized approach to thyroid surgery.

Methods

FNA sample and FFPE tumor tissue were extracted for DNA with the QIAamp DNA Micro Kit/FFPE Tissue Kit respectively. DNA was sequenced by a custom NGS panel targeting 23 genes frequently mutated in thyroid cancer on MiSeq®system. The panel contained AKT1, APC, AXIN1, BRAF, CDX2NA2, CTNNB1, DNM3A, EGFR, EIF1AX, GNAS, HRAS, IDH1, KRAS, NDUFA13, NRAS, PIK3CA, PTEN, RET, SMAD4, TERT Promoter, TP53, TSHR and VHL genes, a total of 221 amplicons that covered full regions of tumor suppressor genes and hotspot regions of oncogenes. The Illumina VariantStudio software application was used to generate VCF files and all variants/mutations were interpreted by genomic analysts for their pathogenicity.

Figure II. Identification of EIF1AX splice site mutation c.338-G>T by MiSeq. Forward (Red) and reverse (blue) sequence reads are shown in IGV. The first amino acid of exon 6 (p.A113) and the direction of transcription is indicated by the arrow. EIF1AX is coded on the complement strand of the human reference genome strand. A nucleotide change from C to T on the reference strand shown in IGV represents a G to T change for the EIF1AX c.338-G>T mutation.

Discussion

To our knowledge, this is the first documented case of follicular carcinoma with an EIF1AX mutation. Karunamurthy et al analyzed 266 thyroid tumors and nodules and detected EIF1AX mutations in 2.3% of PTC. Of the 53 follicular carcinomas analyzed, including 22 oncocyctic Hürthle cell variants, 0 harbored EIF1AX mutations. EIF1AX mutations are more prevalent in Poorly Differentiated Thyroid Cancer (PDC) and Anaplastic Thyroid Cancer (ATC). Landa et al. found EIF1AX mutations in 11% of PTC and 9% of ATC. EIF1AX mutated PTC showed significantly shorter survival and were present in larger tumors. EIF1AX mutations are clustered in two main regions, near the N-terminal domain in exon 2 or the unique splice acceptor site between exons 5 and 6 (A113_splice) where our patient’s mutation occurred. The first amino acid of exon 6 (p.A113) and the direction of transcription is indicated by the arrow. EIF1AX is coded on the complement strand of the human reference genome strand. A nucleotide change from C to T on the reference strand shown in IGV represents a G to T change for the EIF1AX c.338-G>T mutation.

Conclusions

We present the first patient with follicular carcinoma found to have an EIF1AX mutation. The EIF1AX gene encodes a protein that is a key component of the translation pre-initiation complex. Mutations in the EIF1AX gene have previously been associated with PTC, FVPTC, and ATC and further studies are necessary to better understand its role in the tumorigenesis of thyroid carcinoma.

References


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