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Genomic Landscape of FNAs Positive for Medullary Thyroid Cancer and Potential Impact on Systemic Therapy

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BACKGROUND

Systemic therapies targeting specific genomic alterations in advanced MTC are available or under investigation. The Afirma Genomic Sequencing Classifier (GSC) uses RNA sequencing to assess FNA specimens from cytologically indeterminate thyroid nodules, which are also tested for specific molecular aberrations associated with thyroid cancer via a suite of highly accurate malignancy classifiers (figure 1). This suite can also be applied independently to Bethesda V/VI nodules. The Afirma Xpression Atlas (XA) (figures 1 and 2) is an RNA sequencing-based add-on test that reports expressed nucleotide variants and fusions across 511 cancer-associated genes (figure 3) when added to Afirma GSC and/or malignancy classifiers.

Medullary thyroid cancer (MTC) is a rare subtype of thyroid cancer that can appear in every cytology category. Previously, the Afirma MTC classifier demonstrated 100% sensitivity and specificity among 211 FNA samples that included 21 MTCs.[1] Herein, we report the prevalence and genomic landscape of MTC classifier positive (MTC+) FNA samples in the Veracyte Clinical Laboratory.

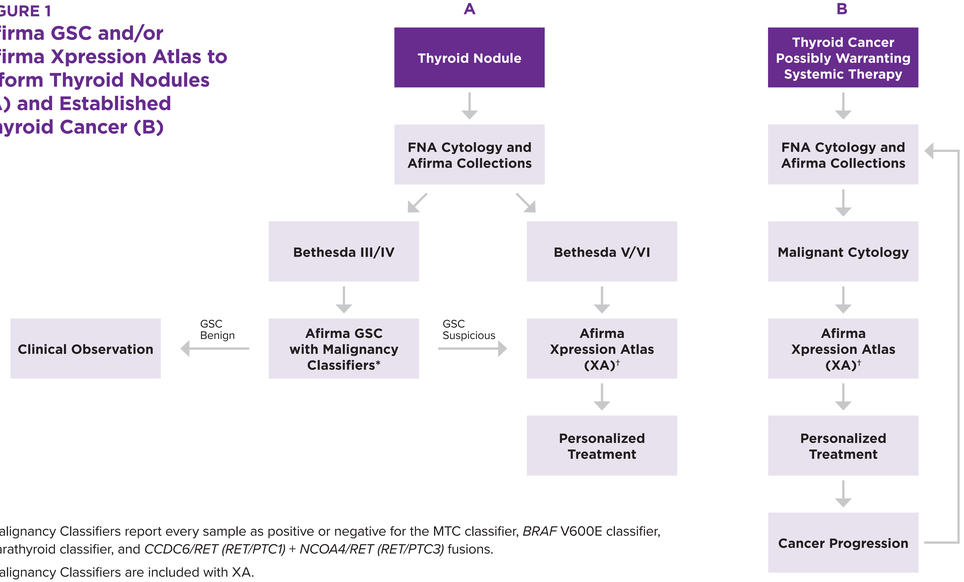
METHODS

All Afirma GSC and malignancy classifier tests run in the Veracyte Clinical Laboratory between July 2017 and January 2019 were deidentified and examined for MTC+ cases. Afirma XA was run on all MTC+ cases and all variants and fusions were tabulated.

RESULTS

Examination of 29,895 FNAs revealed 90 MTC+ cases. Among consecutive Afirma GSC tests, 32 were Bethesda III (0.14% out of 22,793) and 33 were Bethesda IV (0.60% out of 5,491). Provider-ordered Afirma testing was done on an additional 16 and 9 MTC cases from Bethesda V and VI nodules, respectively. Examining all MTC+ samples revealed that 58% harbored a *RET* variant (+/- others), 9% contained a *KRAS* variant (+/- others), 6% had an *HRAS* variant, 1% had a *BRAF* fusion, 1% had another fusion, and 26% included no variant/fusion (figure 4).

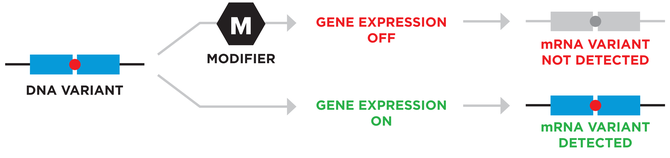
FIGURE 1
Afirma GSC and/or Afirma Xpression Atlas to Inform Thyroid Nodules (A) and Established Thyroid Cancer (B)



* Malignancy Classifiers report every sample as positive or negative for the MTC classifier, *BRAF* V600E classifier, parathyroid classifier, and *CCDC6/RET (RET/PTC1)* + *NCOA4/RET (RET/PTC3)* fusions.

† Malignancy Classifiers are included with XA.

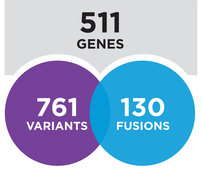
FIGURE 2
Use of RNA Sequencing in Afirma Xpression Atlas to Detect Expressed DNA Variants



Proposed mechanism: modifier turns off gene expression so the mutated gene is not active in the cell and the variant is not found in the mRNA

No modifier to turn off gene expression so variant appears in the mRNA

FIGURE 3
Afirma Xpression Atlas



VARIANT EXAMPLES

BRAF
DICER1
EIF1AX
H/K/N-RAS
RET
TG
TP53
ZFHX3

FUSION GENE EXAMPLES

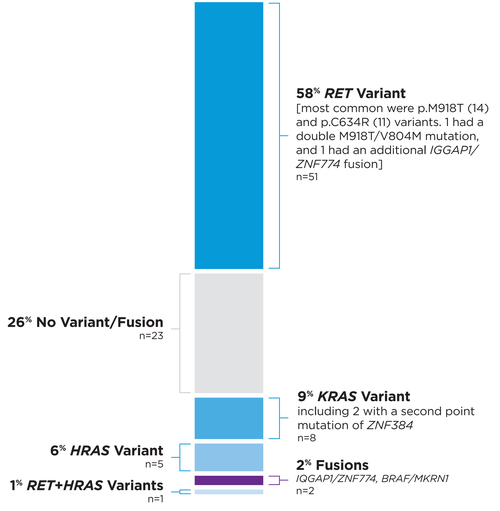
ALK
BRAF
NTRK
PAX8
RET

TARGETED THERAPY EXAMPLES

ALK	*HRAS*	*PAX8/PPAR-y*
BRAF	*MET*	*RET*
EGFR	*NTRK*	*ROS1*

Using RNA sequencing, Afirma Xpression Atlas reports expressed genomic variants and fusions among 511 genes. Therapies targeting some of these alterations are available or under investigation.

FIGURE 4
Variants and Fusions Identified in 90 MTC+ Samples Using the Afirma Xpression Atlas



CONCLUSIONS

In our cohort of Bethesda III-VI MTC+ FNAs, the Afirma XA identified a variant or fusion in 74%. Currently approved or investigational therapies exist for cancers with *RET, BRAF, HRAS,* and *KRAS* alterations, suggesting that 73% of our series might be eligible for treatment based on genomic information from FNA. In advanced MTC, noninvasive FNA sample collection at the time of diagnosis may ultimately impact on targeted therapy selection, with the option to repeat FNA testing should the disease progress (figures 1 and 3). With the emergence of new, highly effective molecularly targeted therapies for MTC, identification of driver genomic alterations will be key to optimizing therapy. Future studies may investigate how finding a genomic alteration by FNA can inform the management of MTC and, in the case of progressive disease, improve our understanding of the mechanisms of disease progression and drug resistance.

Reference

1. Randolph G, et al. Clinical Validation of the Afirma Genomic Sequencing Classifier for Medullary Thyroid Cancer (oral abstract 29). Thyroid 2017;27: A-105.

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