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Unique mutation patterns in anaplastic thyroid cancer identified by comprehensive genomic profiling

Saad A. Khan, MD¹, Bo Ci, BS², Yang Xie, PhD², David E. Gerber, MD^{1,2}, Muhammad S. Beg, MD¹, Steven I. Sherman, MD³, Maria E. Cabanillas, MD³, Naifa L. Busaidy, MD³, Barbara A. Burtress, MD⁴, Andreas M. Heilmann, PhD⁵, Mark Bailey, MS⁵, Jeffrey S. Ross, MD⁵, David J. Sher, MD⁶, and Siraj M. Ali, MD, PhD⁵

¹Division of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, Texas

²Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas

³Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, Texas

⁴Department of Internal Medicine, Yale School of Medicine; Developmental Therapeutics Program, Yale Cancer Center, New Haven, Connecticut

⁵Foundation Medicine, Inc., Cambridge, Massachusetts

⁶Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas

Abstract

Introduction: Anaplastic thyroid cancer (ATC) is a highly aggressive thyroid cancer. Those ATC with genomic alterations (GAs) in TSC2, ALK, and BRAF may respond to targeted therapies.

Methods: Comprehensive genomic profiling on 90 ATC specimens identified base substitutions, short insertions and deletions, amplifications, copy number alterations, and genomic rearrangements in up to 315 cancer-related genes and 28 genes commonly rearranged in cancer.

Results: Median patient age was 65 (range, 33–86) years, 50 patients were male. There was a mean of 4.2 GA per case, range 1–11. The most common GA were TP53 (66%), BRAF (34%), TERT (32%), CDKN2A (32%), and NRAS (26%). BRAF V600E and NRAS/HRAS/KRAS alteration were mutually exclusive. BRAF, CDKN2A, PIK3CA, and JAK2 were more frequent in patients >70 years of age; while myc, PTEN, and NRAS were more common in those ≤50 years.

Conclusion: ATC shows many GA with potential therapeutic significance and suggesting different molecular pathways can lead to ATC.

Correspondence Saad A. Khan, Division of Hematology and Oncology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. saad.khan@utsouthwestern.edu.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Keywords

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1 | INTRODUCTION

Anaplastic thyroid cancer (ATC) is a rare and lethal malignancy that is clinically distinct from differentiated thyroid cancer (DTC). Fewer than 1000 ATC patients are diagnosed annually in the United States, compared to DTC which affected more than 55 000 patients in 2017.¹ The genetics of ATC are ill-defined, its optimal treatments are uncertain, and patients have a median survival of only 5 months with a 1-year survival of approximately 20%,^{1,2} while DTC has well-understood genetics,² clear treatment recommendations, and excellent patient outcomes.^{3,4} Conventional chemotherapy does not provide any improvement in overall survival.¹ For patients with locally advanced ATC, external beam radiation therapy is administered to palliate local symptoms, and systemic therapy typically has trivial efficacy. Even clinical trials are rarely recommended in this disease due to the fatalism and expected futility.

Although the genomic landscape of DTCs such as papillary thyroid cancer (PTC) is well described,³ the biology and oncogenic drivers of ATC are poorly understood. Identifying the true prevalence of genetic abnormalities is challenging, as few cancer centers see enough cases to perform a comprehensive analysis on more than a handful of cases. As in DTC, many ATC demonstrate BRAF and RAS abnormalities, but ATC lacks a pathognomonic genomic marker. Comprehensive genomic profiling (CGP) can provide insight into the pathogenesis of ATC as well as the possibility of enhancing diagnosis.^{4–7} Landa and colleagues analyzed 33 ATC cases from one institution using the MSK-IMPACT testing platform and identified a mechanism whereby ATCs arise from differentiated tumors as they accumulate genetic abnormalities. Recently, Pozdeyev and colleagues⁵ analyzed reported the genetic abnormalities in 583 DTC and 196 ATC, identifying many novel genetic events. Our current study focused on 90 of those ATC patient samples using FoundationOne results, providing a comprehensive analysis as well as focusing on patient age variation and mutations of therapeutic relevance.

Indeed, molecularly targeted therapies administered to patients with ATC harboring TSC1/2,⁶ ALK,⁷ or BRAF^{8,9} genomic alterations (GAs) have yielded exceptional responses. By accurately describing the prevalence of genetic abnormalities present in ATC, clinical trials targeting GA can be designed. Ongoing ATC-specific trials targeting mutations include those targeting the cell cycle as well as ALK¹³ abnormalities. To achieve the promise of these and other therapies for this challenging disease, full characterization of molecular abnormalities is needed.

On the basis of altered clinical outcomes, we hypothesized that GA patterns would vary by patient age and divided them into three groups: <50, 50–70, and >70 years. In ATC patients, age less than 50 was previously reported to be an independent prognostic variable favoring better survival, with an odds ratio of 0.68, confidence interval of 0.49–0.95.¹⁰ Similarly, ATC patients that were 71 years or older had a risk ratio of 1.54 (P = .001) for shorter

survival.¹¹ Although poorer survival in the elderly may relate to increased comorbidities and reduced functional reserve, we hypothesized that these differences in outcome may also have a biologic basis. The traditional theory of origin of ATC is from long-standing PTC that eventually accumulates enough genetic mutations, such as p53, to trans-form into a much more aggressive malignancy.^{12,13} Up to 80% of ATC may arise from a preexisting DTC.¹⁴ However, that the origin of ATC is more complex. Older patients may thus have a greater prevalence of PTC transforming into ATC, while younger patients may present more commonly with ATC that arose without such an intermediate step. Patients that were between 50 and 70 years of age may demonstrate an intermediate pattern.

To provide key information regarding the etiology, natural history, and potential treatment of ATC, we performed CGP on 90 ATC cases. This series represents comprehensive genomic analysis of ATC using a platform that is readily available to clinicians at any location. The resulting data on alteration types and frequency may inform future diagnostic tests and guide development of clinical trials of targeted therapies. It also compares how ATC and PTC overlap in their genetic abnormalities as well as how they differ. These genetic differences may explain why ATC behaves so much more aggressively than DTC.

2 | SUBJECTS AND METHODS

Tumor biopsy specimens from 90 patients with a diagnosis of ATC were submitted to Foundation Medicine for CGP during the course of clinical care from October 2012 to July 2015. These samples were collected from patients at multiple different centers across the United States, including both academic and community sites. Details about stage of the disease, site of biopsy, geographic location of patient, prior or subsequent treatments, and outcomes were not available for this analysis. Samples underwent hematoxylineosin review to ensure a minimum of 20% DNA derived from tumor cells.

The methods employed for this analysis have been previously described.¹⁵ In brief, formalin-fixed paraffin-embedded slides or blocks from tumor samples were subjected to CGP at the reference laboratory (Foundation Medicine, Inc., Cambridge, Massachusetts). At least 50 ng of DNA per specimen was extracted and next-generation sequencing was performed on hybridization-captured adaptor ligation-based libraries to high uniform coverage (>500×) for all coding exons of 182–315 cancer-related genes and 14–28 genes commonly rearranged in cancer.

Base substitutions, short insertions and deletions, copy number changes, gene fusions, and rearrangements were identified and reported for each patient sample. To maximize mutation detection sensitivity in heterogeneous tumor biopsies and resections, the test was validated to detect base substitutions at 10% mutant allele frequency with 99% sensitivity and indels at 20% mutant allele frequency with 95% sensitivity, with a false discovery rate of <1%.¹⁵ Approval for this study, including a waiver of informed consent and a HIPAA waiver of authorization, was obtained from the Western Institutional Review Board (Protocol No. 20152817).

2.1 | Statistical analysis of previously identified actionable and other mutations

GAs were defined as those that were previously described in databases such as COSMIC, or those with known targeted therapy available commercially or as part of a trial. Non-reportable genomic variants were identified by the same methodology and have the same degree of confidence, but differed in that they had not been previously identified or lacked obvious targeted therapy.

When calculating the gene mutation frequency, if one gene had multiple alterations in the same patient, it was counted as one. Based on the prognostic and proposed biologic differences, patients were divided into three age groups as follows: 50, >50 to 70, and >70 years of age for comparison of GA. Fisher's exact test was used to test whether the age group has an effect on the mutation pattern of selected genes. Fisher's exact test was used to test whether the gender has an effect on the mutation pattern of selected genes. All the P-values were adjusted by Bonferroni methods (significant level $P < .05$). All computations were conducted in the R environment.

3 | RESULTS

GAs that had previously been reported were identified in all the ATC samples; the types of abnormalities included point mutations, deletions, rearrangements, and amplifications and their distribution is described in Table 1. All samples had at least one GA with an average of 4.2 per sample (range, 1–11). The most common GAs are shown in Figure 1. A small number of genes, PTEN, TET2, TP53, and CDKN2A showed multiple GA mutations in the same patient.

The most common GA was TP53 at 65.6%. Others that were commonly seen included BRAF V600E, CDKN2A, and TERT (each 32%). All TERT alterations were in the promoter region; –124C>T accounted for 29 of 31 while –146C>T was found in the remainder. Alterations in NRAS (26%), CDKN2B (20%), NF2 (14.4%), PTEN (13.3%), PIK3CA (12.2%), and NF1 (12.2%) were also seen. The most common NRAS alterations were Q61R in 15 of 23, while the remainders were Q61K and one patient also had NRAS amplification. No ALK fusions were identified in this series, and two patients had RET-CCDC6 fusion, while two cases harbored RET point mutations at E511K and M1109L.

3.1 | Comparison of ATC genomic pattern with papillary thyroid cancer

We compared the alterations observed in The Cancer TP53 mutations were highly prevalent in ATC at 65.6%, compared to less than 1% in PTC. In ATC, BRAF and NRAS were detected in 34% and 26% of samples, while in TCGA, PTC specimens mutations were found in BRAF (59.7%) and NRAS (8.5%). Out of the 20 most frequent alterations in ATC and PTC, only BRAF and NRAS were seen in both while the remainder differed. TP53 and TERT promoter mutations were present in 65% and 32.2% of our ATC tumor set, respectively, whereas these were found at very low frequencies in the TCGA PTC specimens (0.7% and 9.4%, respectively).

3.2 | Association of ATC genomic pattern with age

In our series, the frequency of TP53 alterations was similar among all age groups at 65%, but other genes were altered in correlation with the patient age in ATC's. CDKN2B, NF2, JAK2, ARID1A, PIK3CA, and RB mutations were not seen in patients <50 years but were more common in those that were older. GAs with variation by age are shown in Figure 2. When all GAs were included in the analysis, BRAF, CDKN2A, and MLL2 were much more common in those above 70 years of age and NRAS, ARID1A, PTEN, and others were more common in those <50 years.

3.3 | Identification of GAs with clinically actionable potential

GAs that are associated with response to targeted therapy in ATC or other cancer types were described as those with clinically actionable potential. The full lists of GA that includes those that may attain clinically actionable potential in the future are listed in Supporting Information Figure S1. BRAF V600E (32.2%) was the most common form of BRAF abnormality (29 of 90). Other mutations that are potentially predictive of response to targeted therapy include PTEN (12 of 90), PIK3CA (11 of 90), JAK2 amplification (5 of 90), RET (4 of 90), MYC (3 of 90), AKT (3 of 90), and mTOR (1 of 90). TERT promoter -124C>T mutations were seen in 29 of 90, 8 of which also had a concurrent BRAF mutation. Comparing the 50 males with 40 females, there was no differences in mutation pattern by gender. When expanded out to include non-reportable genomic variants of undetermined significance (VUS), mutations were found in TSC1 (12.2%), FGFR (7.8%), PARP (12.2%), NTRK (7.8%), EGFR (3.3%), and ALK (2.2%), but by definition these GAs have unclear functional impact.

4 | DISCUSSION

Understanding the GAs that drive ATC has led to promising treatments such as BRAF inhibitors that may finally improve patient outcomes, as well as enhanced our understanding of how this disease develops. We identified genomic abnormalities in all 90 cases of ATC with an average of 4.2 per each sample. The most frequently seen type of abnormality included substitutions and loss/amplifications. Our analysis also suggested that patients greater than 70 years of age have a distinct genomic profile compared to younger ATC patients, including a higher prevalence of BRAF mutations. This result suggests that there may be distinct pathways to the development of ATC in older vs younger patients. ATC in older individuals may represent cancer that arises or transforms from long-standing BRAF-mutated DTC that then dedifferentiated, whereas in younger patients there may have been de novo development of ATC without the concurrent presence of DTC with its high rates of BRAF mutation. In addition to the lower rates of BRAF in those younger than 50 years of age, CDKN2b, Rb, and NF2 mutations were also not seen, while they had higher rates of myc. We also found that genomic profiles varied by patient age and included GA that can be associated with dramatic responses to targeted therapies, but did not vary by sex. These age-related differences did not reach statistical significance with adjusted P-values >.05 using the Bonferroni method. These genomic differences by age are hypothesis generating and indicate that extra attention should be paid to the age distribution of patients enrolled on to

ATC clinical trials. They do suggest that biologic differences, in addition to better functional status, may explain the better outcomes for ATC patients under the age of 50 years.

Our results are consistent with prior studies that analyzed the genomic landscape of ATC. Landa and colleagues reported¹⁶ the genomic profiling of 33 ATC and found that 73% showed TP53 alterations and 73% TERT promoter mutations. BRAF was mutated in 45% of ATC, with NRAS 18%, and HRAS 6%. Alterations in BRAF and NRAS or HRAS were mutually exclusive. Other clinically relevant alterations included ALK, seen in 4% of ATC, and TSC $\frac{1}{2}$ in 3% of ATC. The authors concluded their data supported the tumor model of ATC having greater mortality due to differing GAs as compared to DTC.

Identifying genomic differences between ATC and other thyroid cancers may help in early and accurate diagnosis. As such, we compared the genomic profiles of PTC and ATC and identified clear differences between the two. From the TCGA analysis, TP53 abnormalities were identified in <1% (3 of 402) PTC compared to 65.6% of our ATC samples. TERT promoter mutations were identified in 36 of 384 (9.4%) of PTC and in 32.2% of ATC.² We also identified that ATC had either RAS or BRAF abnormal in 59 of 90 samples. Patients either had a BRAF V600E abnormality (n = 29) or a NRAS/HRAS/KRAS (n = 27), thus they were entirely mutually exclusive. Two patient samples did have both BRAF non-V600E and RAS mutations; BRAF D594G with HRAS and BRAF amplification with NRAS Q61K. Although rare, co-occurrence of RAS and BRAF has been previously described in thyroid cancer.¹⁷ RAS mutations may represent the development of resistance to anti-BRAF therapy, but that cannot be determined to be the case in this dataset. As larger scale genomic studies are performed, it may be possible to rapidly differentiate ATC from DTC with a high degree of confidence by using specific GA signature unique to each malignancy.⁵

Combination therapy with BRAF and MEK inhibitors has been tested in BRAF V600E-mutated ATC.^{8,9} The combination of dabrafenib and trametinib thus represents the first approved targeted therapy option for ATC patients in the United States. BRAF V600E was seen in one-third of all our ATC patients and nearly half of all patients over the 70 years. The high prevalence of BRAF abnormalities and the promising initial results provide further confirmation that all metastatic ATC patients should have BRAF testing done, either as a single test or as part of a comprehensive genomic panel. With poor rates of cure even with locally advanced disease, BRAF testing should be considered at diagnosis so that combination targeted therapy can be rapidly initiated at the time of progression.

We identified GAs in patients with ATC that may respond to targeted therapy. In addition to BRAF V600E, promising targets identified included CDKN2A mutations were seen in 32.3% of ATC patients, suggesting a role for agents that interfere with cell cycle progression such as CDK4/6 inhibitors.¹⁸ myc is another target that was mutated in 13.3% of young patients and may hold therapeutic promise, albeit more remotely.¹⁹ The VUS included TSC $\frac{1}{2}$ mutations in 12.2% of cases and ALK point mutations in 2.2% but no fusions of the ALK gene. Although these are not currently considered clinically actionable, there are reported responses in ATC patients with everolimus⁶ and with the ALK-inhibitor crizotinib.⁷ Although ALK fusions²⁰ or rearrangements⁷ have previously been identified in ATC and potentially associated with responses to ALK-inhibitors, point mutations may also hold

clinical significance. Murugan et al²¹ identified ATC with novel ALK mutations in L1198F and G1201E, and mutated cells had increased tyrosine kinase activity as well as oncogenic behavior. This suggests that future analyses of ATC samples and outcomes should focus on genes with targeted therapy options available. RET and NTRK inhibitors have shown promise in early clinical trials,²² despite their low prevalence of these GA in our dataset, thyroid cancers with fusions involving ALK, RET, or NTRK may respond to targeted therapy. RET genomic abnormalities have special therapeutic significance, as novel RET inhibitors show promising results. RET E511K is specifically associated with increased oncogenic potential in thyroid cancer and is considered an activating mutation permitting enrollment onto ongoing clinical trials of RET inhibitors (NCT03157128). We also identified a fusion of RET-CCD6 that has previously been identified in lung cancer,²⁵ as well as an M1109I mutation,²⁶ both of which have uncertain impact on behavior but may also permit enrollment onto RET inhibitor trials. One patient harbored an NTRK-TPM3 fusion of the type associated with a dramatic response.²⁷ NTRK point mutations that were only found in VUS may not have qualified these patients for clinical trials and must be interpreted with caution.

Currently the American Thyroid Association guide-lines²⁸ do not recommend comprehensive genomic sequencing of all ATC at diagnosis or at the time of metastasis and the NCCN guidelines for thyroid cancer recommend molecular testing for actionable mutations such as ALK and BRAF. When genomic sequencing is done, the increasing number of targeted therapy drugs that are now available may provide patients with options that were previously unavailable. When performed in conjunction with a clinical trial, genomic analysis can be effective in pairing mutations with targeted therapy drugs while simultaneously adding to our knowledge of the genomic abnormalities seen in ATC.

Immune checkpoint inhibitors have recently shown promising results in ATC.²⁹ Spaltalizumab was reported to show an overall response rate of 20% in 26 patients with metastatic ATC, including 77% who had previously been treated. There are additionally ongoing trials using check- point inhibitors in ATC (NCT02688608, NCT03181100, NCT03122496, NCT03211117, and NCT03246958). Analogous to oncogenedriven lung cancer (such as those with activating EGFR mutations) which has an attenuated response to immune checkpoint inhibitors,³⁰ it is possible that BRAF V600E mutated ATC may not robustly respond to anti-PD1 immune therapy. Compared to cancers with high tumor mutation burden such as melanoma and lung cancer, there were fewer mutations identified in our analysis. Including all GA and other non-reportable variants, the average total number of genomic abnormalities seen per sample averaged 12.9, with a range of 5–27, suggesting that single agent immunotherapy may not be effective in a relatively low mutation burden tumor such as ATC. However, emerging data suggest that in ATC a high tumor mutation burden is not required for responses to immune checkpoint inhibitor therapy.³¹

One of the strengths of this work is that it is the correlation of genomic data with the available patient demographic data. This permitted us to propose the GA differences between younger and older patients as a possible explanation for why younger patients have better outcomes. The CGP platform we used is validated for matching mutations to targeted therapy and entry into national clinical trials, such as NCI-MATCH, EA3132, SWOG 1400,

and ASCO TAPUR. This analysis offers an opportunity to rationally design targeted therapy ATC clinical trials knowing the frequency of the actionable mutation. This analysis benefits from being derived from a well-tested real-world platform so is highly reflective of the results delivered to the clinicians who treat the majority of ATC. The limitations of this type of study include the inability to correlate genomic profile findings with clinical outcomes as individual patient information was not available. The mutations identified in this dataset should be prospectively evaluated to determine their impact on patient outcomes.

Future directions after this work include validation of this genomic analysis in a larger number of ATC samples using whole genome or exome techniques to supplement our targeted panel approach. It would also be useful to compare the genetic abnormalities seen in ATC with those of follicular thyroid cancer to supplement our comparison between ATC and PTC. Future ATC genomic analyses should consider comparing the genomic patterns in patients at the extremes of age, as well as evaluating the impact of GA on prognosis.³² Future clinical trials could identify patients with GA associated with worse prognosis and intensify therapy while those with markers of better prognosis could get treatment deintensification.

In conclusion, genomic abnormalities are highly prevalent in ATC and are distinct from those seen in PTC. GAs vary by patient age and may identify subsets of ATC patient that could be offered targeted therapies. As greater numbers of ATC undergo genomic sequencing, there are benefits in enhanced diagnosis and increased therapeutic options. Genomic sequencing may help identify those ATC-subpopulations that arise from existing DTC or those which have oncogenic drivers for which targeted therapies are available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Genomic alterations were found in every patient sample with a mean of 4.2 per sample (range, 1–11). TP53 was the most common (65.6%), followed by BRAF and TERT in a third of patients. Genomic alterations that occurred in >3% of patients are shown [Color figure can be viewed at wileyonlinelibrary.com]

Clinically Relevant ATC Genomic Alterations Showed Variation by Patient Age (%)

FIGURE 2.

Anaplastic thyroid cancer (ATC) clinical observations suggest better outcomes for patients <50 years of age compared to those who are >70 years. Distinct genomic patterns were seen between the youngest and oldest age groups, with intermediate genomic findings in those between 50 and 70 years of age [Color figure can be viewed at wileyonlinelibrary.com]

Frequency of each category of genetic alterations detected in 90 samples of anaplastic thyroid cancer (ATC). All samples showed at least one genetic abnormality. Genomic alterations are those that are previously described in databases such as COSMIC, or those with established targeted therapy implications. Other variants are non-reportable variants identified by the same methodology and degree of confidence but have not previously been reported

TABLE 1

Type of mutation	Substitution	Amplification	Deletion	Loss	Insertion	Rearrangement	Indel	Total
Genomic alterations	221	44	36	53	12	13	1	380
Other variants	651	51	37	8	26	10	0	783
Total	872	95	73	61	38	23	1	1163

Abbreviation: Indel, insertion and deletion.