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Original contribution

Molecular alterations in non–small cell lung carcinomas of the young☆

Christopher J. VandenBussche MD, PhD[a], Peter B. Illei MD[a], Ming-Tseh Lin MD, PhD[a], David S. Ettinger MD[b], Zahra Maleki MD[a,*]

[a]*Departments of Pathology, The Johns Hopkins Medical Institutions, Baltimore MD 21287*
[b]*Departments of Oncology, The Johns Hopkins Medical Institutions, Baltimore MD 21287*

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Summary Lung cancer is the leading cause of cancer death in the United States. Gene alterations are significant in lung tumorigenesis, with certain genes (Kristen rat sarcoma viral oncogene homolog (*KRAS*), *epidermal growth factor receptor* [*EGFR*], *anaplastic lymphoma kinase* [*ALK*], and B-Raf proto-oncogene, serine/threonine kinase (*BRAF*)) possessing alterations important in the prognosis and treatment of lung adenocarcinoma. Mutation frequencies are affected by different patient factors, such as smoking history, age, and race. Because most lung cancers occur in patients older than age of 50 years, few studies have examined molecular alterations present in these younger patients. The pathology database was searched for patients age of 50 years or younger with non–small cell lung carcinomas (NSCLCs) tested for *EGFR*, *ALK*, *KRAS*, and/or *BRAF* alterations. A total of 53 cases were identified. The mean patient age was 44.4 years old, and there were 19 men and 34 women. Of the tumors, 11.6% had *ALK* rearrangements, 25.5% had *KRAS* mutations, and 20.0% had *EGFR* mutations. No *BRAF* mutations were identified in the 28 cases tested. All but 1 (92% [12/13]) tumor with *KRAS* mutation were from women patients. A smoking history of greater than 5 pack-years was associated with *KRAS* mutations and negatively associated with *EGFR* mutations and *ALK* translocation. The frequencies of *EGFR* mutation and *ALK* translocation in the study cohort are greater than the reported frequencies among NSCLC from adults of all ages in the United States but less than the reported frequencies among NSCLC from East Asian young adults. The frequency of *KRAS* mutation is significantly greater than what was previously found in young Japanese patients.

1. Introduction

Lung cancer is the leading cause of cancer death in the United States. Non–small cell lung carcinoma (NSCLC) constitutes 85% to 90% of all lung carcinomas with a median patient age of 70 years old [1]. Mutations in *epidermal growth factor receptor* (*EGFR*), *KRAS*, *anaplastic lymphoma kinase* (*ALK*), and *BRAF* affect the prognosis and treatment of lung adenocarcinoma. The frequencies of these alterations are associated with different patient factors, such as smoking history, sex, race, and age [2-7]. However, because most lung

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* Corresponding author. Zahra Maleki, MD. Department of Pathology/Division of Cytology, 600 N Wolfe St/Carnegie 469C, Baltimore, MD 21287.
E-mail address: zmaleki1@jhmi.edu (Z. Maleki).

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cancers occur in patients older than age of 50 years, few studies have examined molecular alterations present in a younger cohort [2,3].

Malignancies affecting young adults can differ significantly from those that arise in older adults. These include differences in tumor morphology, molecular alterations, prognosis, and response to treatment [2,3,8-11]. Excluding pediatric malignancies, a significant risk factor for many cancers is age, and malignancy is rare in adults below the age of 50 years [1]. However, a cancer diagnosis in this group can be particularly devastating, often leading to a greater loss of longevity and quality of life for a given individual [12]. Although inherited genetic syndromes can result in malignancy at an earlier age, for many malignancies, it is unknown which factors contribute most to their early development.

The recently established molecular alterations in lung adenocarcinoma not only provide an understanding of tumorigenesis but are also strongly connected with patient prognosis and treatment. In this retrospective study, we examine the frequency of *ALK*, *KRAS*, *EGFR*, and *BRAF* mutations in 53 patients who developed NSCLC at or below the age of 50 years.

2. Materials and methods

2.1. Database search

Permission to conduct the study and an informed consent waiver were obtained from the institutional review board. The pathology database was searched for patients below the age of 50 years old with NSCLC who underwent testing for *EGFR*, *ALK*, *KRAS*, and/or *BRAF* gene alterations. A total of 57 cases were identified, 53 of which were ultimately diagnosed as NSCLC. The cases spanned a period of approximately 4 years, from January 2010 to 2014.

2.2. Molecular testing before February 2013

All specimens were clinical samples submitted to our hospital's Clinical Laboratory Improvement Amendments–certified molecular diagnostics and cytogenetics laboratories. Before the next-generation sequencing (NGS) platform was implemented in February 2013, mutations at codons 12 and 13 of the *KRAS* gene and codon 600 of the *BRAF* genes were examined by pyrosequencing as described previously [13,14]. If no *KRAS* mutation was identified, testing for an *EGFR* mutation within exons 18 to 21 was examined by Sanger sequencing as described previously [15]. If no mutation was identified in *KRAS* or *EGFR*, fluorescence in situ hybridization assay was performed to detect an *ALK* translocation (Fig. 1).

2.3. Molecular testing from February 2013

After its introduction in our laboratory, NGS was conducted using AmpliSeq Cancer Hotspot Panel (version 2), Life Technologies, Carlsbad, CA for targeted multigene amplification as described previously [15]. Hot spot mutations within exons 11 and 15 of the *BRAF* gene; exons 2 to 4 of the *KRAS* gene; and exons 3, 7, 15, and 18 to 21 of the *EGFR* genes were examined simultaneously. *ALK* translocation was examined if no mutation was detected in the *KRAS*, *BRAF*, and *EGFR* genes (Fig. 1).

2.4. Statistical analysis

Fisher exact test was used for statistical comparison between 2 groups.

3. Results

3.1. Description of the study population

Fifty-three cases of NSCLC in patients age of 50 years or younger were identified in the pathology database (Tables 1 and 2). There was a predominance of women (64%). The average patient age at the time of diagnosis was 44.4 years, with a range between ages of 28 and 50 years old. Most patients were white (60%) or black (28%), with only 1 Asian patient (2%) and 5 patients of another or unknown race (10%). Patients with a greater than 5 pack-year history of smoking comprised 53% of all patients. Women in this study

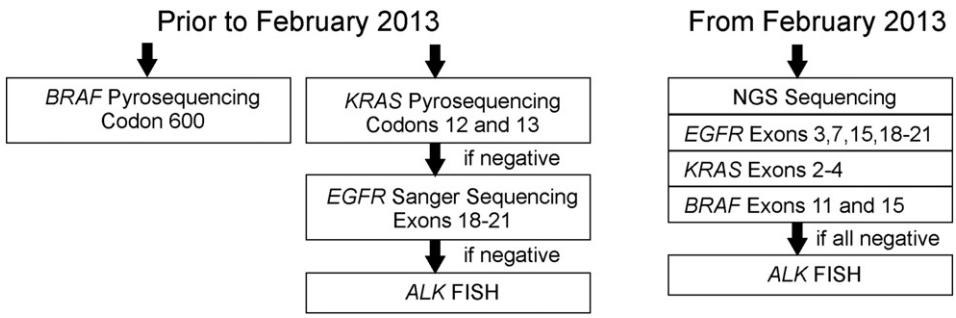

Fig. 1 Molecular testing algorithm for NSCLC specimens submitted to the molecular diagnostics and cytogenetics laboratories, both before February 2013 and after February 2013 after the introduction of NGS.