Germline Mutations in Driver Oncogenes and Inherited Lung Cancer Risk Independent of Smoking History

Geoffrey R. Oxnard, Kim-Son H. Nguyen, Daniel B. Costa

Correspondence to: Daniel B. Costa, MD, PhD, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215 (e-mail: dbcosta@bidmc.harvard.edu).

Although the single most important risk factor for developing lung cancer is a personal history of cigarette smoking, it is well documented that there also exists inherited lung cancer risk that cannot entirely be accounted for by smoking patterns alone (1). Genome-wide association studies of patients with lung cancer have provided strong evidence for a susceptibility region in chromosome 15q25.1 (Table 1), a region containing three genes (CHRNA3, CHRNA5, and CHRNB4) that encode for nicotinic acetylcholine receptors (2). Genetic variation in this gene cluster is associated with increased tobacco dependence and increased risk of smoking-related morbidity such as lung cancer, head-neck cancer, chronic obstructive pulmonary disease, and peripheral arterial disease (1). In addition, rare germline mutations in the tumor suppressor genes tumor protein 53 (TP53) and retinoblastoma 1 (RB1) are associated with a high lifetime relative risk of lung cancer in smokers (Table 1) (3).

However, 10% to 20% of lung cancers in the United States occur in never-smokers (4), defined as persons who have smoked less than 100 cigarettes in a lifetime. Indeed, non–small cell lung cancer (NSCLC) in never-smokers is independently the seventh most common cancer worldwide (4). This is a disease with a distinct biology marked by an increased incidence of targetable mutations in oncogenes (Table 1) such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), and human epidermal growth factor receptor 2 (HER2) (5,6). The risk factors for lung cancer in never-smokers, both environmental and inherited, are poorly understood, and genome-wide association studies have been relatively unrevealing of a unifying genetic basis. To illustrate the latter, in the largest cohorts, even the most statistically significantly linked variants at 13q31.3 (which alters the expression of the glypican 5 [GPC5] gene that has putative effects on oncogenic signaling pathways) (7) or susceptibility loci in 3q28, 6p21.32, 6q22.2, 10q25.2, and 17q24.3 (8) were associated with a low relative risk ratio and were unable to account for the majority of cases of NSCLC. Our ability to study inherited lung cancer risk in never-smokers is limited by the challenge of identifying relatives of never-smokers with lung cancer (9). Note that most mechanisms for documenting family history do not ask about family smoking history, such that an individual with a family history of lung cancer in smokers (a common occurrence) is not studied any differently than one with a family history of lung cancer in nonsmokers (which is far more rare).

The discovery of germline EGFR mutations in 2005 has heightened interest in identifying germline alleles carrying a high risk of lung cancer, independent of smoking exposure (10). Several case reports have now identified relatives with multigenerational EGFR mutated NSCLCs, each harboring an activating EGFR mutation in combination with germline EGFR-T790M (10–13). However, germline EGFR-T790M has been found to be a rare allele in all-comers with lung cancer (12). One study screened blood from 369 never-smokers with lung cancer and found only two cases (0.5%) of germline T790M (13). As a somatic mutation, EGFR-T790M is commonly identified in lung cancer as a mechanism of acquired resistance after treatment with EGFR kinase inhibitors (14–16), but it is found in only 1% to 4% of treatment-naive EGFR mutated tumors (9,11,12). A second germline EGFR mutation, V843I, has also been described to be associated with familial lung cancer (17), but this mutation is even rarer than EGFR-T790M in lung cancers.

In this issue of the Journal, Yamamoto et al. (18) describe a novel germline HER2-G660D mutation identified in relatives with multigenerational lung adenocarcinoma in never-smokers (18). This germline mutation is an HER2 point mutation located in the transmembrane domain. No additional cases were identified through HER2 sequencing of 315 sporadic NSCLCs, highlighting the rarity of this allele. Although HER2 kinase mutations are known to occur in 2% to 4% of lung adenocarcinomas, the vast majority are in-frame insertions within exon 20 (5,19), which have been shown to be oncogenic in preclinical model systems (20). Low frequency HER2 transmembrane V659E mutations have been described as somatic events in NSCLC (18,21). No HER2 comutations occurred with G660D in the familial lung cancers studied (18), as have been seen in lung cancers from patients with germline EGFR mutations (11), and therefore the oncogenic alteration occurring with the germline risk allele remains unclear. The presented data add support for the hypothesis that germline mutations in proto-oncogenes, such as EGFR and HER2, can mediate inherited risk of lung cancer that is independent of smoking exposure (Table 1).

The methods used to identify the HER2 G660D mutation should be highlighted because their use is increasingly common (18). The investigators, with appropriate approvals, performed whole-exome sequencing of paired tumor and germline DNA from the affected proband, whole-exome sequencing of tumor from her affected mother (deceased), and whole-exome sequencing of germline DNA from her unaffected sister and father. They identified 29 variants present in the affected relatives and not the unaffected relatives, one of which was HER2-G660D. Without a broader study
of this relative, we cannot be certain that another one of these variants underlies the inherited risk; however, the **HER2** mutation is most suspicious. As the use of next-generation sequencing increases in the care of NSCLC, there are certain to be many additional such germline variants identified, and pooling of these rare cases will be needed to truly understand their association with inherited risk.

Given the rarity of germline mutations in **EGFR** and **HER2**, we cannot at this time advocate for routine germline sequencing based solely on a family history of lung cancer. Rather, we recommend that never-smokers with lung cancer first undergo tumor genotyping, which routinely includes **EGFR** sequencing and increasingly includes **HER2** sequencing (22). If **EGFR-T790M**, **EGFR-V843I**, or **HER2-G660D** are found in the tumor, then referral for germline testing may be appropriate (11), particularly if there is a family history of lung cancer in nonsmokers and preferably as part of a clinical trial. An ongoing trial (NCT01754025) is evaluating this strategy (23), where probands are eligible for germline testing based on presence of **EGFR-T790M** in their cancer at diagnosis rather than based upon clinical characteristics, and relatives of carriers are then tested. This prospective cohort, for whom environmental, genetic, imaging, and follow-up data are collected, will attempt to understand the risk and natural history of lung and other cancers in the presence of germline **EGFR-T790M**. Similar efforts may be needed to better characterize lung cancer risk associated with **HER2-G660D** and other putative germline driver oncogene mutations.

**References**


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**Table 1. Driver oncogenes and inherited risk alleles for lung cancer associated with and independent of smoking**

<table>
<thead>
<tr>
<th>Somatic driver oncogenes (5,6)</th>
<th>Lung cancer associated with smoking</th>
<th>Lung cancer independent of smoking</th>
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<tbody>
<tr>
<td>KRAS mutations</td>
<td>EGFR mutations</td>
<td>ALK rearrangements</td>
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<tr>
<td>B-RAF mutations (non-V600E)</td>
<td>HER2 mutations</td>
<td>ROS1 rearrangements</td>
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<tr>
<td>PIK3CAMutations</td>
<td>B-RAF V600E mutation</td>
<td>RET rearrangements</td>
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</tbody>
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<tr>
<th>Genetic foci associated with inherited susceptibility (1–3,7,8,11,17)</th>
<th>Low relative risk</th>
<th>Low relative risk</th>
</tr>
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<tbody>
<tr>
<td>15q25.1 (CHRNA3, CHRNA4 and CHRNA9)</td>
<td>13q21.3 (GPSC)</td>
<td>10q25.2 (VTT1A)</td>
</tr>
<tr>
<td>High relative risk</td>
<td><strong>EGFR-T790M</strong> or V843I</td>
<td><strong>HER2-G660D</strong></td>
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<tr>
<td>TP53</td>
<td>8q21</td>
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* ALK, anaplastic lymphoma kinase; B-RAF, v-Raf murine sarcoma viral oncogene homolog B1 (also known as proto-oncogene B-Raf); CHRNA3, neuronal acetylcholine receptor subunit alpha 3; CHRNA4, neuronal acetylcholine receptor subunit beta 4; CHRNA5, neuronal acetylcholine receptor subunit alpha 5; EGFR, epidermal growth factor receptor; GPCS, glypican 5; HER2, human epidermal growth factor receptor 2 (also known as V-erb-b2 erythroblastic leukemia viral oncogene homolog 2 [ERBB2]); KRAS, K-Ras (also known as Kirsten rat sarcoma viral oncogene homolog, PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RB1, retinoblastoma 1; RET, rearranged during transfection (also known as RET proto-oncogene); ROS1, c-ros oncogene 1; TP53, tumor protein 53; VTT1A, vesicle transport interaction with t-SNAREs homolog 1A.

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**Affiliations of authors:** Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA (GRO); Department of Medicine, Division of Medical Oncology, Stanford University Medical Center, Palo Alto, CA (KSHN); Department of Medicine, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (DBC).